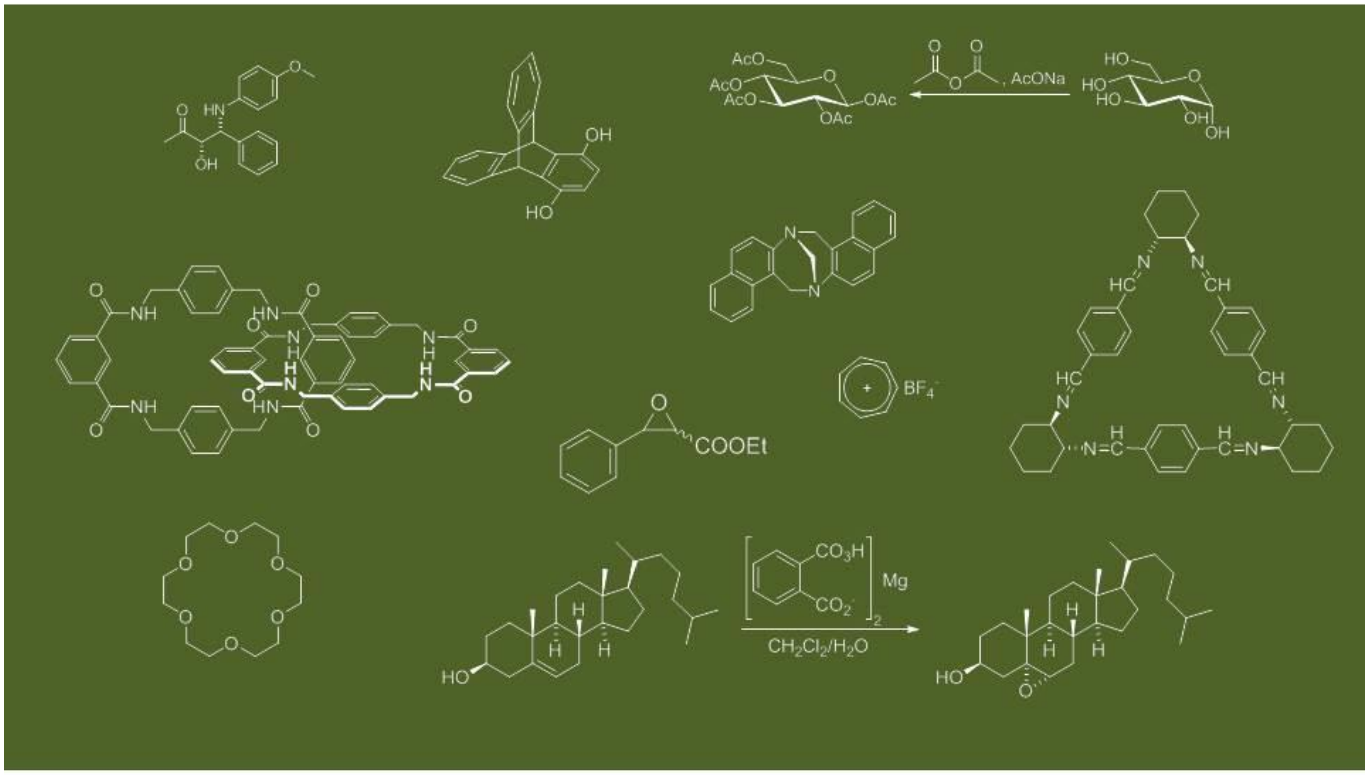
Organic chemistry

Laboratory methods



Bartosz Szyszko

Organic chemistry – laboratory methods

Description
This course deals with laboratory techniques in organic chemistry laboratory. Upon successful completion of this course students will posess practical skills required for work in modern chemical laboratory.

Website
http://do.chem.uni.wroc.pl/przedmiot/Metody-Laboratoryjne-laboratorium-ChOrg2

Language
English

Prerequisites
basic organic chemistry

Time commitment
90 hours; 5 preparatory sessions (30 hours) and 7 regular sessions (60 hours)

Learning objectives
1. Purification and drying organic solvents and reagents by distillation in an inert and moisture-free atmosphere.
2. Microscale synthesis.
3. Running a reaction for a long time (also under reflux).
4. Synthesis under moisture- and air-free condtions.
5. Running a reaction at low temperature.
6. Performing multi-step synthesis without isolation of the intemediates.
7. Isolation of the product from a mixture containing very reactive reagents.
8. Isolation of the product by distillation, crystallization and chromatography.
9. Using Schlenk line. Removing solvents with high vacuum. Performing a vacuum distillation (also fractional) and bulb-to-bulb distillation.

Calendar and class meetings
Before start of the course all the students will participate in the fire-fighting training provided by specialized Fire-Fighters. Date of the training will be provided in near future.

wednesday, 11^{00}-17^{00}

class	date	class	date
1	2 XI	7	14 XII 2016
2	9 XI	8	4 I 2017
3	16 XI	9	11 I 2017
4	23 XI	10	18 I 2017
5	30 XI	11	25 I 2017
6	7 XII	12	1 II 2017

Instructors

Dr. Bartosz Szyszko bartosz.szyszko@chem.uni.wroc.pl office 1066 (1st floor, Biotechnology Department) phone no. +48 71 375 7392	Dr. Halina Zhylitskaya halina.zhylitskaya@chem.uni.wroc.pl office 2035, 2043 (2nd floor, Biotechnology Department) +48 71 375 7637

Office hours
Bartosz Szyszko: Tuesday, Thursday 10^{15}-11^{15} or by appointment
Halina Zhylitskaya: Monday, Wednesday, Friday 11^{00}-12^{00} or by appointment

Grading and Rules of evaluation

The final grade will be weighted arithmetic mean of two grading elements: **(1)** lab work (60%) and **(2)** post-lab reports (40%)

- lab work will be graded twice – after 4th and 8th class; the lab work grade will be an arithmetic mean of those two grades
- post-lab reports will be graded seven times – every time the report will be sumbitted; the post-lab reports grade will be an arithmetic mean of those seven grades

The lab work grade will be based on:

- following the safety regulations and good work practices in chemical laboratory
- punctuality (starting and finishing the lab work on time)
- preparation for the class, theoretical knowledge of experimental techniques that will be used in the experiment
- a proper planning of the activities in time
- tidiness of the work space
- the proper use of glassware and equipment
- independence in the lab work
- knowledge of the proper disposal of chemical waste
- the proper conducting of notes from lab work

Please note that not-following the Safety Regulations will result in a low grade from the lab work!

The post-lab reports grade will be based on:

- punctuality – the report should be submitted maximum 14 days after the class; reports submitted after 14 days will be given 2.0 grade
- completeness of the report and correctness of the physicochemical data that must be provided for the characterization of each compound
- completeness and correctness of the answers provided for post-lab questions; correctness of literature citation
- each report will be graded only once

Preparation for the class

Before starting the class all students must:

- carefully **read the experimental procedure** for the experiment
- **identify** all the potential **hazards** that might appear during the experiment and find a way **to prevent them** and **deal with them**
- read the Material Safety Data Sheet (MSDS) for each reagent that will be used during the experiment
- **think of** and **prepare a sketch** of the **glassware set** and **equipment** that will be used during the experiment; this will be discussed with the Instructor and **should be modified according to Instructor's suggestions**
- **plan** all of the activities **in time** (and write them down in points)
- learn about a **proper way of disposal of chemical waste** generated during the experiment
- **get acquainted with instructional video materials** related to the experimental techniques that will be used in the experiment

Recommended textbooks

1. J. C. Gilbert, S. F. Martin, "Experimental Organic Chemistry. A Miniscale and Microscale Approach", Thomson 2006
2. A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996
3. J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
4. J. K. Swadesh (Ed.) "HPLC. Practical and Industrial Applications"
5. J. W. Zubrick "The Organic Chem Lab Survival Manual", Wiley 2010
6. L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
7. P. G. M. Wuts, T. W. Greene "Greene's Protective Groups in Organic Synthesis", any edition, Wiley & Sons
8. W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
9. C. F. Wilcox, „Experimental Organic Chemistry, A Small-Scale Approach", MacMillan Publishing Company, New York 1988

Safety Rules in the Organic Chemistry Laboratory

1. When working in the Organic Chemistry Laboratory you should remain calm and behave properly. All students are resposible for the tidiness of their work environment.

2. Wearing lab coat and the proper eye protection is obligatory. When working with corrosive reagent it is obligatory to wear protective gloves.

3. Wearing contact lenses during the lab work is not recommended. Pregnant women cannot take part in organic chemistry lab classes. Students who suffer from the chronic diseases like epilepsy or allergies are obligated to inform the Instructor about it.

4. All students need to have a lab book for making notes during experiments. All the products of syntheses should be given to the Instructor in the end of the class following by the post-lab report. This is obligatory for a successfull completion of the course.

5. Only diluted solutions of acids and bases might be disposed in a sink. The concentrated solutions of acids and bases should be diluted prior the disposal. All of the organic solvents have to be transferred into the appropriate container, which is located under the special fume hood. Students will be instructed how to dispose different types of liquid and solid waste. It is not allowed to put any solid waste into the sink.

6. All lab work with organic reagents and solvents must be performed under the fume hood.

7. Students must be extremely cautious when working with concentrated solutions of acids, bases, flammable liquids (diethyl ether, acetone, alcohols, benzene and other organic solvents), bromine and toxic reagents.

8. Any type of emmergency or dangerous situation should be immediately reported to the Instructor who will provide the first aid.

9. In the case of fire students should remain calm, switch off electricity sources and remove the flammable materials from the area covered with the fire. To fight the fire you should use a proper fire extinguisher or a fire blanket. Covering the burning area with a wet towel might stop small fire. In the case of any fire it is absolutely necessary to report the incident to the Instructor.

10. Burning people should be toppled to the floor and covered with a blanket fire or doused with water. You musn't use a fire extinguisher to fight a fire on a burning person.

11. It is not allowed to:

a) pipet with your mouth, b) use flammable solvents in the close proximity to the source of fire or heat, c) eat or taste chemicals, d) run the experiments that are not included in the lab schedule.

12. In the laboratory you mustn't:

a) smoke cigarettes, b) eat or drink, c) leave any apparatus unattended, d) leave the lab without informing the Instrutor, e) bring other people, f) bring the jackets, coats or bags of any type.

13. This is the obligation of a student on a duty (picked by the Instructor) to bring, take care and return the special equipment from the lab Technicians. This student is also responsible for taking care of the tidiness of the laboratory during the class and when the class finishes. The student on a duty will leave the laboratory, as the last person once the lab Technicians will approve the tidiness of the laboratory.

14. Students are financially responsible for the equipment and glassware.

15. Students will confirm that they have read and understood the Safety Rules by signing its copy.

Accidents in the lab and first aid

Burnings caused by heat, acids, anhydrides, alkalines and bromine
Affected area of the body should be thoroughly washed with a copious amount of running water (wash it for at least 30 minutes). Cover the area with a sterile bandage. If the chemical affected a large area of the body call the ambulance as soon as possible (phone no. 112 or 999).

Burnings caused by phenol and other organic reagents
If the chemical that caused the burning does not react with water the affected area of the body should be thoroughly washed with a copious amount of running water (wash it for at least 30 minutes).

Burnings caused by sodium
If there are still pieces of sodium on the skin they should be carefully removed with tweezers and then the affected area of the body should be thoroughly washed with a copious amount of running water (wash it for at least 30 minutes). Cover the area with a sterile bandage.

Acids, anhydrides, alkalines or bromine in the eye
The eye should be thoroughly washed with a copious amount of running water using an eye-wash (wash it for at least 30 minutes). The eye should be covered with a sterile bandage. Call the ambulance as soon as possible (phone no. 112 or 999).

Burning clothes
You shouldn't allow the burning person to run. Burning people should be toppled to the floor and tightly covered with a fire blanket or doused with water. You musn't use a fire exinguisher to fight a fire on a burning person.

Burning chemicals
Switch off all of the electricity and gas sources in the neighborhood of fire. Remove all the flammable materials from the area covered with fire. Covering the burning area with a wet towel might stop small fire. To fight the larger fire you should use a proper fire extinguisher or a fire blanket. In the case of any fire it is absolutely necessary to report the incident to the Instructor.

Emergency phone numbers

112	**Mobile phones**
999	**Emergency medical services**
998	**Fire Fighters**
+48 71 375 7298	**Concierge in Chemistry Department**

Instructional video materials

When preparing for the class all students must get acquainted with the experimental techniques that will be used during the experiment. The Instructor will evaluate theoretical knowledge of those techniques during the class.

In order to learn a new technique or to refresh knowledge of known method it is required to read a proper chapter in one of the recommended textbooks or, and **this is recommended solution**, to watch the proper video material.
Links to the appropriate materials are collected and linked below. Please let me know if any of those links do not work – in this case you will obtain the appropriate materials from the Instructor.

Using lab equipment and basic experimental techniques

Using a balance
https://www.youtube.com/watch?v=cG6QrqS4ruQ&index=11&list=PLB208D0FA80AD438F

Magnetic stirrers
https://www.youtube.com/watch?v=NeDgBuNoOAg&list=PLXmftzajsm91ExPowAJNOfXualOG4KAkV
https://www.youtube.com/watch?v=zTTbwFA_ftg
https://www.youtube.com/watch?v=jzzDixOGmgk
https://www.youtube.com/watch?v=4Fvpj_fN7zA
https://www.youtube.com/watch?v=jX36MWprjp4&list=PLBD8CDADC266F3BDC&index=6

Using an automatic pipette
https://www.youtube.com/watch?v=AcNtVgOp0bI&list=PLB208D0FA80AD438F&index=13

Using a rotary evaporator
https://www.youtube.com/watch?v=yDP5NycfCdc&index=19&list=PLjPjM_i9bhFTh_uzicV_oAbYTFCGp-8P-
https://www.youtube.com/watch?v=HSZJcv8fg5c
https://www.youtube.com/watch?v=ug2Qz-Y71jQ&list=PLnEQfEiSza7A2yiSG8sun5YGxJ1sg0Rwe
https://www.youtube.com/watch?v=3DQj4dibr78&index=6&list=PLB208D0FA80AD438F

Folding fluted filter paper
https://www.youtube.com/watch?v=hY3XuXa0YuE
https://www.youtube.com/watch?v=ykmTxRpRRCw

Gravity and vacuum filtration
https://www.youtube.com/watch?v=fFdvEgg1t14
https://www.youtube.com/watch?v=AiYnnpVUbyw

Extraction and using simple drying agents
https://www.youtube.com/watch?v=kdsZjeywrTk
https://www.youtube.com/watch?v=66QmPP0vluk
https://www.youtube.com/watch?v=DmvaOb1xb1o&list=PLB208D0FA80AD438F&index=5

Acid-base extraction
https://www.youtube.com/watch?v=Tn0P2x0X_vs

Crystallization, recrystallization
https://www.youtube.com/watch?v=7LBGQHjgHEw&list=PLB208D0FA80AD438F&index=9
https://www.youtube.com/watch?v=genmtAjsDzA

Sublimation
https://www.youtube.com/watch?v=dBNELFi5XiY&list=PLB208D0FA80AD438F&index=8

Simple distillation
https://www.youtube.com/watch?v=GtuMlWMajtw&index=15&list=PLB208D0FA80AD438F
https://www.youtube.com/watch?v=rpxtV2v2zuA

Fractional distillation
https://www.youtube.com/watch?v=iB6HHuzfadw

Vacuum distillation
https://www.youtube.com/watch?v=mn-u-7fRQv4

Microdistillation using a Hickmann still head
https://www.youtube.com/watch?v=46gqI90ELuU
https://www.youtube.com/watch?v=UT5mPJTpOyQ
https://www.youtube.com/watch?v=4k8Re3FlyuE

Reflux
https://www.youtube.com/watch?v=fHEk2WFgmXQ&index=17&list=PLB208D0FA80AD438F

Thin Layer Chromatography TLC
https://www.youtube.com/watch?v=iV1GfI_BbKE
https://www.youtube.com/watch?v=e99nsCAsJrw&index=3&list=PLB208D0FA80AD438F
https://www.youtube.com/watch?v=ml58GCq078o&index=4&list=PLB208D0FA80AD438F

Column chromatography
https://www.youtube.com/watch?v=B_QyhG2-VBI&index=10&list=PLB208D0FA80AD438F

Flash chromatography
https://www.youtube.com/watch?v=fF1gXUvyGb4
https://www.youtube.com/watch?v=ci2uu9Cuf5s

NMR sample preparation
https://www.youtube.com/watch?v=Sov0x9YdVfg
https://www.youtube.com/watch?v=3JxE_AwPD14

Air- and moisture-sensitive reagents, vacuum techniques

Drying glassware, using a heat-gun
https://www.youtube.com/watch?v=4O65iU0N89w
https://www.youtube.com/watch?v=9G7-Rc4lBcs

Drying molecular sieves
https://www.youtube.com/watch?v=CmKGt92oMYU

Using solvent still heads
https://www.youtube.com/watch?v=7IDlnuu-0QE

Vacuum distillation of solvent under moisture- and air-free conditions
https://www.youtube.com/watch?v=eVajSoZEr-k

Bulb-to-bulb distillation, using Kugelrohr
https://www.youtube.com/watch?v=o34psrncdB8

Using Solvents Purification System (SPS)
https://www.youtube.com/watch?v=n9Kfj8pmClA

Using a glove-box
https://www.youtube.com/watch?v=IpTc-qcNPgY

Using Schlenk line
https://www.youtube.com/watch?v=Eov60kI7yw8
https://www.youtube.com/watch?v=my1YR35W7Co
https://www.youtube.com/watch?v=-5xtZs3jPeg

Degassing solvent on the Schlenk line
https://www.youtube.com/watch?v=SEVzJp901no

Degassing solvents, freeze-pump-thaw method
https://www.youtube.com/watch?v=GpbXTk9VbBg

Inert atmosphere techniques, using cannula
https://www.youtube.com/watch?v=9npHPE6PhSI
https://www.youtube.com/watch?v=DSoFRyQTsHc

Working with pyrophoric liquids
https://www.youtube.com/watch?v=21iC4YEgOAs
https://www.youtube.com/watch?v=3_cBVfYVAC8
https://www.youtube.com/watch?v=WUHrzcEunNY

Working with reactive metals
https://www.youtube.com/watch?v=ozmddj0fIpk

Working with *n*-buthyllithium
https://www.youtube.com/watch?v=M3Av0UjSWpA
https://www.youtube.com/watch?v=ojBqqnqJals

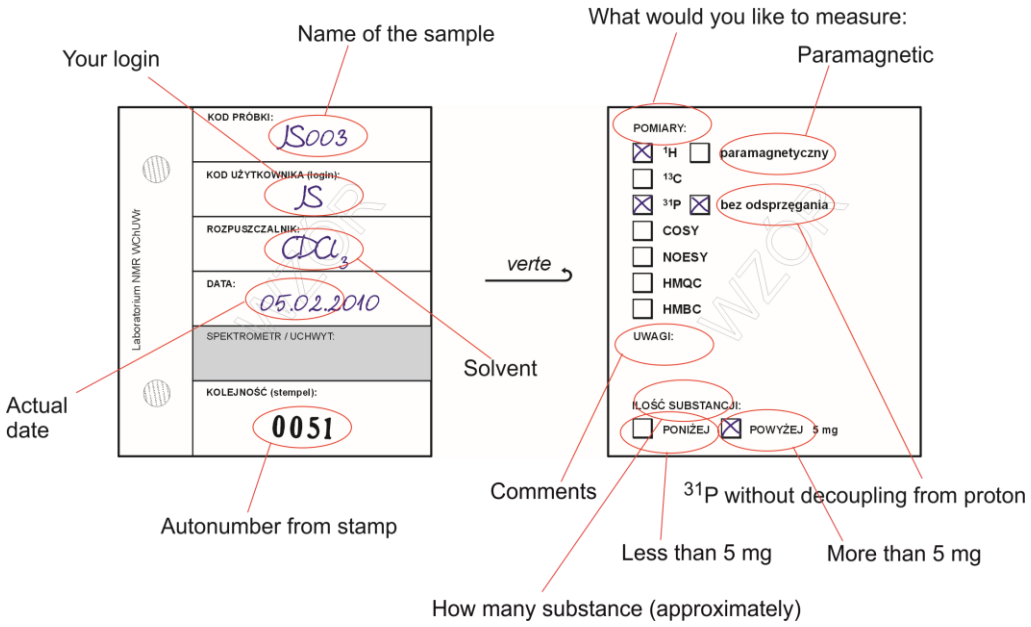
Working with Grignard reagents
https://www.youtube.com/watch?v=s3sShnm1ArM

Various vacuum techniques
https://www.youtube.com/watch?v=-5xtZs3jPeg
https://www.youtube.com/watch?v=quO0pwX56w8
https://www.youtube.com/watch?v=XIuIRdXsEw4

List of experiments

Labeling of NMR samples

Previously prepared NMR samples should be properly described using labels. The empty spots should be fulfilled following the example below.



In our case:
KOD UŻYTKOWNIKA: SO
KOD PRÓBKI: experiment number-initials-/fraction number.

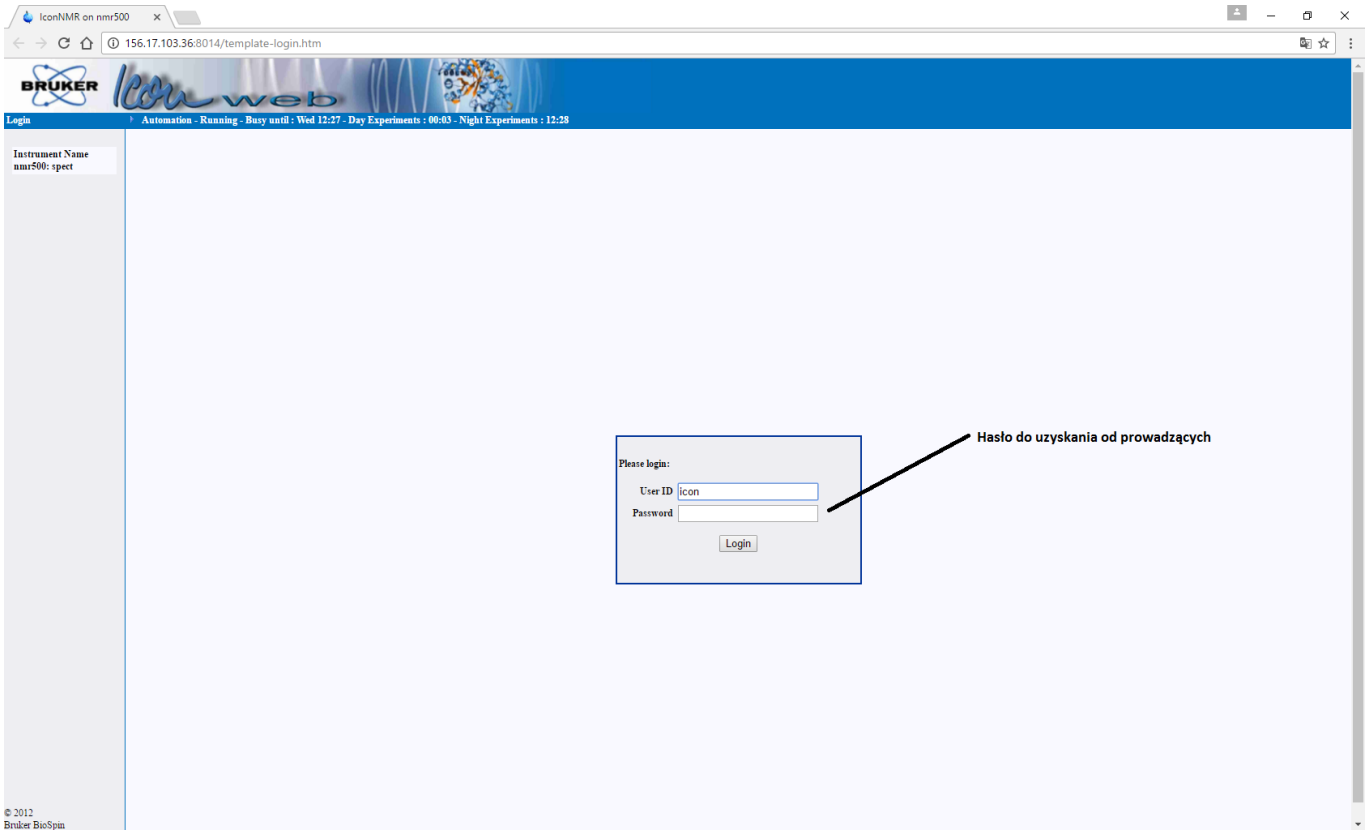
For example:
John/Joan Smith was running experiment no. 4.1D and obtained three fractions from fractional distillation. Their NMR samples should be labeled as follows:

4.1D-JS/1
4.1D-JS/2
4.1D-JS/3

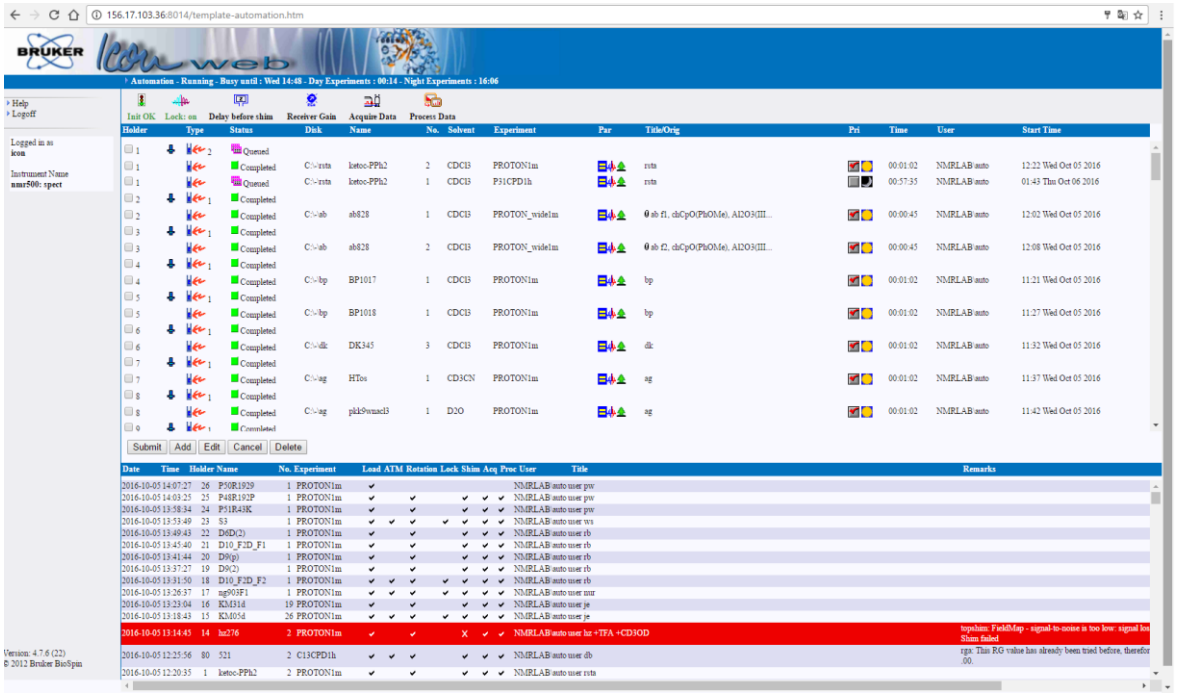
ROZPUSZCZALNIK: solvent used for sample preparation, in our case it will be most likely chloroform-*d* or dmso-d_6.
WIDMO: ^{1}H 1m for most samples, ^{1}H 15m when the product's concentration is very low

Checking the status of the sample

The NMR samples that have been submitted by the technician appear in the on-line version of NMR experiments queue. You can check the status of your experiment on the queue website:
http://156.17.103.36:8014/template-login.htm
using following informations: login – icon, password – will be provided by the Instructor



The queue interface looks as in the example below:



If the experiment that we are interested in has the Queued status, it means the sample is still waiting to be measured, while the Completed status, it means the spectrum has been collected and the sample was returned.

Analysis of the spectrum

Once the ^{1}H NMR spectrum has been recorded students need to analyze the data.
The TopSpin software is recommended for processing and analyzing the NMR data. The software is available on the computers in the computer room no. 16 (next to NMR lab) whenever the room is not occupied by other classes.
In order to access data you should log in to Windows using following informations:
login: so
password: Synteza1

Students might also use any other free software available in Internet, e.g. MestReNova (http://mestrelab.com/software/mnova/download/).

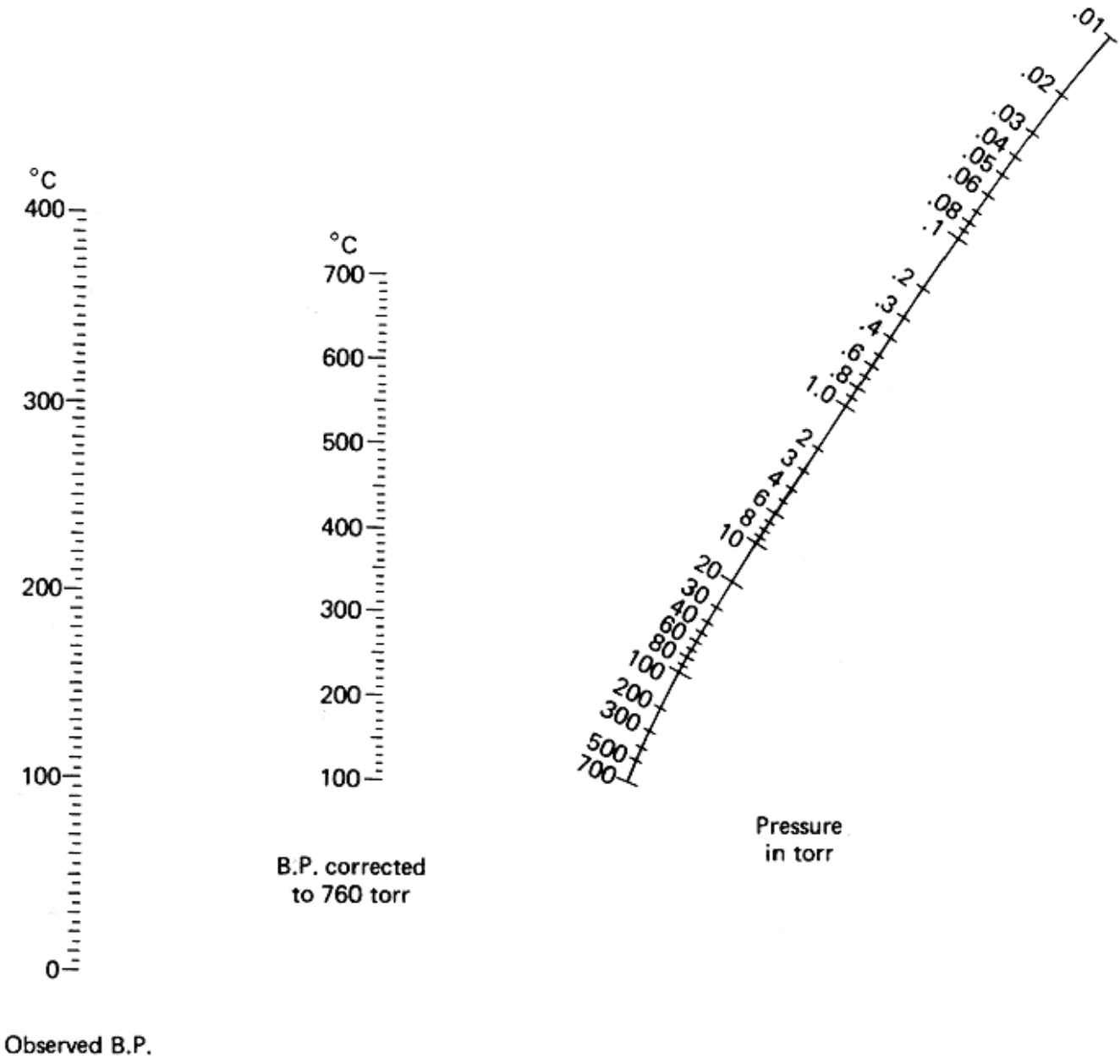
Before you start analyzing the spectrum you should identify and calibrate the residua solvent signal.
For chloroform-d: 7.24 ppm, dichloromethane-d_2: 5.32 ppm, dmso-d_6: 2.50 ppm.

The analysis of the spectrum should include:

1) Identification and assignment of the signals of the reaction product, including: multiplicity, coupling constants, chemical shifts, integrations, signals assignment
2) Identification of the main impurities present in the samples.
3) Evaluation of the purity of different fractions/batches of crystals, based on the comparison of their spectra
4) Suggestions on further separation/purification based on the type of impurities present in the samples.

The linked article discusses the spectroscopic data for most commonly present in organic samples impurities:
Zanieczyszczenia w próbkach NMR

Pressure-temperature nomograph



Web source: http://www.sanpedrofarmacia.com/modules/com_docman/nomograph-1931.html?nomograph-1931
Date of access : 4.10.2016

Table of properties for common solvents

rozpuszczalnik	Molecular weight	Boiling point (°C)	Melting point (°C)	Density (g/mL)	Solubility in water (g/100g)	Dielectric constant
acetic acid	60.052	118	16.6	1.0446	miscible	6.20
acetone	58.079	56.05	-94.7	0.7845	miscible	21.01
acetonitrile	41.052	81.65	-43.8	0.7857	miscible	36.64
benzene	78.11	80.1	5.5	0.8765	0.18	2.28
1-butanol	74.12	117.7	-88.6	0.8095	6.3	17.8
2-butanol	74.12	99.5	-88.5	0.8063	15	17.26
2-butanone	72.11	79.6	-86.6	0.7999	25.6	18.6
t-butyl alcohol	74.12	82.4	25.7	0.7887	miscible	12.5
carbon tetrachloride	153.82	76.8	-22.6	1.594	0.08	2.24
chlorobenzene	112.56	131.7	-45.3	1.1058	0.05	5.69
chloroform	119.38	61.2	-63.4	1.4788	0.795	4.81
cyclohexane	84.16	80.7	6.6	0.7739	<0.1	2.02
1,2-dichloroethane	98.96	83.5	-35.7	1.245	0.861	10.42
diethylene glycol	106.12	246	-10	1.1197	10	31.8
diethyl ether	74.12	34.5	-116.2	0.713	7.5	4.267
diglyme (diethylene glycol dimethyl ether)	134.17	162	-68	0.943	miscible	7.23
1,2-dimethoxy-ethane (glyme, DME)	90.12	84.5	-69.2	0.8637	miscible	7.3
dimethyl-formamide (DMF)	73.09	153	-60.48	0.9445	miscible	38.25
dimethyl sulfoxide (DMSO)	78.13	189	18.4	1.092	25.3	47
1,4-dioxane	88.11	101.1	11.8	1.033	miscible	2.21(25)
ethanol	46.07	78.5	-114.1	0.789	miscible	24.6
ethyl acetate	88.11	77	-83.6	0.895	8.7	6(25)
ethylene glycol	62.07	195	-13	1.115	miscible	37.7
glycerin	92.09	290	17.8	1.261	miscible	42.5
heptane	100.20	98	-90.6	0.684	0.01	1.92
Hexamethylphosphoramide (HMPA)	179.20	232.5	7.2	1.03	miscible	31.3
Hexamethylphosphorous triamide (HMPT)	163.20	150	-44	0.898	miscible	??
hexane	86.18	69	-95	0.659	0.014	1.89
methanol	32.04	64.6	-98	0.791	miscible	32.6(25)
methyl *t*-butyl ether (MTBE)	88.15	55.2	-109	0.741	5.1	??
methylene chloride	84.93	39.8	-96.7	1.326	1.32	9.08
N-methyl-2-pyrrolidinone (NMP)	99.13	202	-24	1.033	10	32
nitromethane	61.04	101.2	-29	1.382	9.50	35.9
pentane	72.15	36.1	-129.7	0.626	0.04	1.84
Petroleum ether (ligroine)	--	30-60	-40	0.656	--	--
1-propanol	88.15	97	-126	0.803	miscible	20.1(25)
2-propanol	88.15	82.4	-88.5	0.785	miscible	18.3(25)
pyridine	79.10	115.2	-41.6	0.982	miscible	12.3(25)
tetrahydrofuran (THF)	72.106	65	-108.4	0.8833	30	7.52
toluene	92.14	110.6	-93	0.867	0.05	2.38(25)
triethyl amine	101.19	88.9	-114.7	0.728	0.02	2.4
water	18.02	100.00	0.00	0.998	--	78.54
water, heavy	20.03	101.3	4	1.107	miscible	??
o-xylene	106.17	144	-25.2	0.897	insoluble	2.57
m-xylene	106.17	139.1	-47.8	0.868	insoluble	2.37
p-xylene	106.17	138.4	13.3	0.861	insoluble	2.27

Web source: http://murov.info/orgsolvents.htm#TABLE%202
Date of access: 4.10.2016

Eluotropic series of solvents

Solvent	Eluent strength
pentane	0.00
hexane	0.01
heptane	0.01
trichlorotrifluoroethane	0.02
toluene	0.22
chloroform	0.26
dichloromethane	0.30
diethyl ether	0.43
ethyl acetate	0.48
Methyl *t*-butyl ether	0.48
dioxane	0.51
acetonitrile	0.52
acetone	0.53
tetrahydrofuran	0.53
2-propanol	0.60
methanol	0.70

Introductory meeting

1A Organizational information

A brief description of the course, the lab schedule, the rules of evaluation and all details related to pre-lab assignments and post-lab reports will be provided.

1B Safety work practices in organic lab

This part of the class will take the form of workshops and a discussion about safe practices in a chemical laboratory.
We will discuss the Safety Regulations and good practices in running chemical experiments. We will also discuss how to choose a proper Personal Protective Equipment (PPE) for the experiment. Students will learn about localization and proper use of eye-washes, fire extinguishers, fire blankets and water courtains.

In order to prepare for the class all students need to watch the following, short video-materials related to safety in chemical laboratories. We will discuss them during the class.

General remarks
https://www.youtube.com/watch?v=kDxrQkOKUdI
https://www.youtube.com/watch?v=E836nc7SjiI

Common mistakes and prevention
https://www.youtube.com/watch?v=aA8mC5RIj5k
https://www.youtube.com/watch?v=YdYapyzJNsE
https://www.youtube.com/watch?v=3ELbwzqyuhs

The proper use of a fume hood
https://www.youtube.com/watch?v=nlAaEpWQdwA
https://www.youtube.com/watch?v=A4AHxLnByts

How to choose a proper Personal Protective Equipment (PPE)
https://www.youtube.com/watch?v=RXmG8mjUviI
https://www.youtube.com/watch?v=a6DrCdjedas
https://www.youtube.com/watch?v=GjAD83B4JaY
https://www.youtube.com/watch?v=aBVdGGml6bU
https://www.youtube.com/watch?v=aBVdGGml6bU

Measures to prevent fire
https://www.youtube.com/watch?v=IiHEYtnKfF0

The proper behavior in a chemical laboratory
https://www.youtube.com/watch?v=e7VkIuiT1kU
https://www.youtube.com/watch?v=VRWRmIEHr3A

Types of hazards in a chemical laboratory
https://www.youtube.com/watch?v=8queMM7VVfw
https://www.youtube.com/watch?v=q8UiamEWz4Q

Real-life accidents in chemical laboratories and their analyses
https://www.youtube.com/watch?v=P5VdbabPbvU&list=PL5eqYuJdjxdtxaAneyEmrLmq1avHppoaY
https://www.youtube.com/watch?v=sjDdl_d8br8
https://www.youtube.com/watch?v=F6NEdcZY2WY
https://www.youtube.com/watch?v=mrb896D2eMU

Students need to read and prepare answers for two following exercices:

Exercice 1

Please choose a topic from the list below and prepare a short talk about it. All of the topics should be covered during the class so please discuss your choice with the rest of the students in the group.

a) the proper choice of the personal protective equipment (PPE); hazards related to the lab coat of poor quality, improper gloves or protective glasses
b) the proper and safe use of a fumehood
c) the proper behavior in the case of a fire in the lab; the proper choice of a fire extinguisher; fighting different types of chemical fire
d) the proper behavior in the case of chemical burns caused by organometallic reagents or reactive metals; poisoning caused by extremely toxic chemicals (cyanides, organomercury compounds, heavy metals) and their prevention
e) hazards related to use of vacuum line and their prevention; hazards related to use of powdery substances (chromatography adsorbents: silica gel, alumina, celite) and their prevention
f) utilization of the reaction waste; decomposition of reagents and reactive drying agents (metal hydrides, sodium); a proper solid and liquid waste segregation (reasons); the compatibility of different types of liquid waste

Exercice 2

During this exercise we will discuss (all of us, including Instructors), our experience with dangerous situations during lab work. In order to prepare for this exercise, please think of any dangerous situation that you have caused, witnessed or taken part in during your work in laboratory environment (at university, during an internship or at work). Please think how you would change your work practice in order to avoid situations like that in future. You will give a short talk to the group about it.

1C Demonstration of lab equipment, assignment of students' cupboards

The last part of the class will take a form of a demonstration. The Instructor will show you the equipment listed below and briefly explain how to use it:

- magnetic stirrers with temperature controlers
- rotary evaporators
- chillers
- vacuum pumps
- special glassware
- Hamilton's syringes, automatic pipette
- polarimeter
- inert atmosphere bags
- Schlenk line
- Solvents Purification System (SPS)

Purification of solvents and reagents

2A Purification of *n*-hexane

References:

- ✓ W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
- ✓ A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ drying molecular sieves
- ✓ simple distillation
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ reactive drying agents – safe using and decomposition

Experimental procedure:

Place *n*-hexane in a separatory funnel and shake it with small portions of concentrated sulphuric acid. You should stop shaking when the lower layer (acid) becomes colorless. Remove the acid layer and wash the solvent in the separatory funnel with water, 10% aqeous sodium carbonate solution and water again (twice). Separate phases and transfer the organic layer into a bottle with a screw cap and shake it with a drying agent (use anhydrous magnesium sulfate or anhydrous sodium sulfate). Open the bottle from time to time to release the pressure.

After the initial purification, filter off the drying agent, and transfer the solvent into a round-bottom flask equipped with a magnetic stirrer bar. Add carefully, in small portions, calcium hydride. If the reaction that has started is too vigorous you should stop adding the drying agent.

Mount the flask to the lab stand and place it in the heating mantle placed on the magnetic stirrer Assemble the apparatus for distillation in an inert atmosphere with a chosen still head (consult it with your Instructor). Open the nitrogen valve, wash the equipment with nitrogen and start heating the solvent. Boil the solvent for 1.5 hours and start collecting the distillate. Collect the small portion of prerun and remove it. Collect the fractions distilling in the appropriate temperature range (write down the range) and transfer the fraction under nitrogen into the previously prepared clean and dry bottles charged with molecular sieves.

Once you collect the fraction close the bottle and protect the lid with a piece of parafilm.

Allow the equipment to cool down to room temperature and disassemble it.

Consult with your Instructor how to dispose the calcium hydride waste and only then dispose it.

Post-lab questions:

1. What are the main impurities that contaminate commercially available *n*-hexane?
2. Read the appropriate part in „Purification of Laboratory Chemicals" and give two other methods of purification of *n*-hexane. How to choose the appropriate method of purification?
3. List the most common drying agents that are useful for drying solvents and reagents. Point out their advantages and disadvantages. How to choose the appropriate drying agent?

2 B Distillation of thiophene

References:

- ✓ W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
- ✓ A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996.

Laboratory techniques:

- ✓ using simple drying agents
- ✓ reflux
- ✓ drying molecular sieves
- ✓ simple distillation
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ fractional distillation

Experimental procedure:

Place the reagent in a bottle with a screw cap equipped with a fresh portion of potassium hydroxide pellets. Close the bottle and leave it under the fume hood for one hour, shaking the bottle from time to time. Remember to release the pressure in the bottle once you finish shaking it.

After the initial drying, transfer the reagent with the drying agent into the round-bottom flask equipped with a magnetic stirrer bar. Mount the flask to the lab stand and place it in the heating mantle standing on the magnetic stirrer. Assemble the apparatus for the vacuum distillation in an inert atmosphere. Once you assemble the apparatus open the nitrogen valve, switch on the vacuum pump and start distillation. Collect and remove the prerun and start collecting the fractions (write down temperature range for each fraction you have collected). Transfer each fraction that you have collected into a bottle with a screw cap. Close the bottle and protect the lid with a piece of parafilm.

Allow the equipment to cool down to room temperature and disassemble it.

Consult with your Instructor how to dispose the chemical waste and only then dispose it.

Post-lab questions:

1. What are the main impurities that contaminate commercially available thiophene?
2. Read the appropriate part in „Purification of Laboratory Chemicals" and give two other methods of purification of thiophene. How to choose the appropriate method of purification?
3. List the most common drying agents that are useful for drying solvents and reagents. Point out their advantages and disadvantages. How to choose the appropriate drying agent?

2B Distillation of N,N,N',N'-tetramethylethylenediamine (TMEDA)

References:

- ✓ W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
- ✓ A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996.

Laboratory techniques:

- ✓ using simple drying agents
- ✓ reflux
- ✓ simple distillation
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)

Experimental procedure:

Transfer the reagent into a round-bottom flask equipped with a magnetic stirrer bar. Add carefully, in small portions fresh pellets of potassium hydroxide.

Mount the flask to the lab stand and place it in the heating mantle standing on the magnetic stirrer. Assemble the apparatus for distillation with a chosen still head (consult it with your Instructor). Open the nitrogen valve, wash the equipment with nitrogen and start heating the solvent. Boil the solvent for 2 hours and start collecting the distillate. Collect the small portion of prerun and remove it. Collect the fractions distilling in the appropriate temperature range (write down the range) and transfer the fraction under nitrogen into the previously prepared clean and dry bottle

Once you collect the last fraction close the bottle and protect the lid with a piece of parafilm.

Allow the equipment to cool down to room temperature and disassemble it.

Consult with your Instructor how to dispose the chemical waste and only then dispose it.

Post-lab questions:

1. What are the main impurities that contaminate commercially available N,N,N',N'-tetramethylethylenediamine?
2. Read the appropriate part in „Purification of Laboratory Chemicals" and give two other methods of purification of N,N,N',N'-tetramethylethylenediamine. How to choose the appropriate method of purification?
3. List the most common drying agents that are useful for drying solvents and reagents. Point out their advantages and disadvantages. How to choose the appropriate drying agent?

2C Distillation of pyridine

References:

- ✓ W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
- ✓ A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996.

Laboratory techniques:

- ✓ using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ drying molecular sieves
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ fractional distillation in inert atmosphere

Experimental procedure:

Transfer the reagent into a round-bottom flask equipped with a magnetic stirrer bar. Add carefully, in small portions fresh pellets of potassium hydroxide and pre-dried molecular sieves.

Mount the flask to the lab stand and place it in the heating mantle standing on the magnetic stirrer. Assemble the apparatus for fractional distillation in an inert atmosphere. Open the nitrogen valve, wash the equipment with nitrogen and start distillation. Collect the small portion of prerun and remove it. Collect the fractions distilling in the appropriate temperature range (write down the range) and transfer the fractions under nitrogen into the previously prepared clean and dry bottles equipped with molecular sieves. Once you collect the last fraction wash the solvent in the bottle with nitrogen and close it. Protect the lid with a piece of parafilm.

Allow the equipment to cool down to room temperature and disassemble it.

Consult with your Instructor how to dispose the chemical waste and only then dispose it.

Post-lab questions:

1. What are the main impurities that contaminate commercially available pyridine?
2. Read the appropriate part in „Purification of Laboratory Chemicals" and give two other methods of purification of pyridine. How to choose the appropriate method of purification?
3. List the most common drying agents that are useful for drying solvents and reagents. Point out their advantages and disadvantages. How to choose the appropriate drying agent?

2D Distillation of triethylamine

References:

- ✓ W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
- ✓ A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996

Laboratory techniques:

- ✓ using simple drying agents
- ✓ reactive drying agents – safe using and decomposition
- ✓ reflux
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ fractional distillation in inert atmosphere

Experimental procedure:

Place the reagent in a screw cap bottle with a fresh portion of potassium hydroxide pellets. Close the bottle and leave it under the fume hood for one hour, shaking the bottle from time to time. Remember to release the pressure in the bottle once you finish shaking it.

After the initial drying, decant the reagent (without the drying agent) to the round-bottom flask equipped with a magnetic stirrer bar. Add carefully, in small portions calcium hydride. If the reaction that has started is too vigorous you should stop adding the drying agent.

Mount the flask to the lab stand and place it in the heating mantle standing on the magnetic stirrer.

Assemble the apparatus for distillation in inert atmosphere with a chosen still head (consult it with your Instructor). Open the nitrogen valve, wash the equipment with nitrogen and start heating the solvent. Boil the solvent for 1 hour and after this period of time start collecting the distillate. Collect the small portion of prerun and remove it. Collect the fractions distilling in the appropriate temperature range (write down the range) and transfer the fractions under nitrogen into the previously prepared clean and dry bottles. Once you collect the fractions close the bottle and protect the lid with a piece of parafilm.

Allow the equipment to cool down to room temperature and disassemble it.

Consult with your Instructor how to dispose the calcium hydride waste and only then dispose it.

Post-lab questions:

1. What are the main impurities that contaminate commercially available triethylamine?
2. Read the appropriate part in „Purification of Laboratory Chemicals" and give two other methods of purification of triethylamine. How to choose the appropriate method of purification?
3. List the most common drying agents that are useful for drying solvents and reagents. Point out their advantages and disadvantages. How to choose the appropriate drying agent?

2D Distillation of methanol

References:

- ✓ W. L. G. Armarego, C. L. L. Chai, "Purification of Laboratory Chemicals" any edition, Elsevier
- ✓ A. I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996

Laboratory techniques:

- ✓ reactive drying agents – safe using and decomposition
- ✓ fractional distillation in inert atmosphere
- ✓ using solvent still heads
- ✓ reflux
- ✓ Solvent Purification System (SPS)

Experimental procedure:

Place clean magnesium turnings, iodine and 50–75 mL of anhydrous methanol in a round-bottom flask equipped with a magnetic stirrer bar. Mount the flask to the lab stand and place it in the heating mantle standing on the magnetic stirrer.

Assemble the apparatus for distillation in inert atmosphere with a chosen still head (consult it with your Instructor). Open the nitrogen valve, wash the equipment with nitrogen and start heating the solvent. Boil the mixture as long as it will take for the iodine color to disappear. You should also observe that magnesium turnings have reacted with methanol forming white solid.

Add the methanol which you need to purify and boil the solvent for 2 hours. After this period of time start collecting the distillate. Collect the small portion of prerun and remove it. Collect the fractions distilling in the appropriate temperature range (write down the range) and transfer the fractions under nitrogen into the previously prepared clean and dry bottles. Once you collect the fractions close the bottle and protect the lid with a piece of parafilm.

Allow the equipment to cool down to room temperature and disassemble it.

Consult with your Instructor how to dispose the chemical waste and only then dispose it.

Post-lab questions:

1. What are the main impurities that contaminate commercially available methanol?
2. Read the appropriate part in „Purification of Laboratory Chemicals" and give two other methods of purification of methanol. How to choose the appropriate method of purification?
3. List the most common drying agents that are useful for drying solvents and reagents. Point out their advantages and disadvantages. How to choose the appropriate drying agent?

Syntheses of catalysts

2A Synthesis of the catalyst for Glaser-Eglington-Hay coupling

$$2\ CuSO_4 + Na_2SO_3 + 2\ NaOH + 2\ NaCl \xrightarrow{\Delta} 2\ CuCl + 3\ Na_2SO_4 + H_2O$$

References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, "Advanced Inorganic Chemistry", any edition, Wiley

Laboratory Techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux

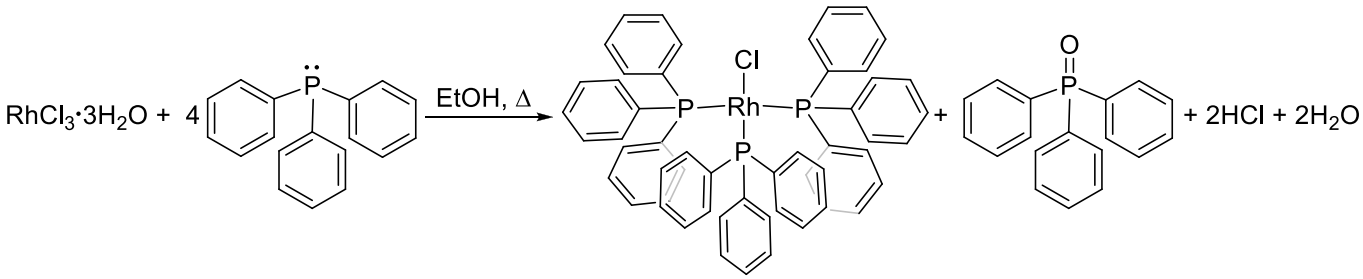
Experimental Procedure:

In a 25 mL round-bottom flask, prepare a solution of powdered copper(II) sulfate pentahydrate crystals (1.2 g, 0.004 mol) and sodium chloride (0.38 g) in hot water (5 mL). In an Erlenmeyer flask prepare a solution of solid sodium hydroxide (0.9 g) in water (1.4 mL). Transfer 0.3 mL of the hydroxide solution to a small beaker and add sodium bisulfite (0.28 g). Add this solution with swirling to the hot copper sulfate solution. Chill the mixture in an ice bath and collect the precipitated cuprous chloride on a Hirsch funnel. Wash the solid with small portions (2–3 mL each) of water and acetone. Transfer the solid to a filter paper and allow it to dry for 5 minutes. It is best to use the material immediately, but it can be stored for several days. Place the product in a dry bottle and store under a layer of degassed acetone.

Post-lab questions:

1. Using scientific database systems (SciFinder or Google Scholar) search for other coupling reactions catalyzed by copper(I) chloride. Give three examples of such reactions that have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
2. Which other copper(I) compounds are being used in organic synthesis? Which reactions they catalyze? Give at least three examples. Use scientific database systems (SciFinder or Google Scholar) for literature search. Provide the proper citation (with DOI number) for all those reactions.

2C Synthesis of Wilkinson's catalyst



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ F. A. Cotton, G. Wilkinson, C. A. Murillo, M. Bochmann, "Advanced Inorganic Chemistry", any edition, Wiley

Laboratory techniques:

- ✓ degassing of solvents and reagents
- ✓ synthesis under moisture- and air-free condtions
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ gravity and vacuum filtration

Experimental procedure:

Dissolve the triphenylphosphine (0.26 g, 1 mmol) in hot ethanol (10 mL) in a 50 mL three-neck flask and buble nitrogen through the solution for 10 minutes. Meanwhile, dissolve the rhodium(III) chloride trihydrate (0.04 g, 0.15 mmol) in ethanol (2 mL) in a test tube and bubble nitrogen through this until the triphenylphosphine solution has been degassed. Add the solution in the test tube to the content of the flask and rinse with a further 1 mL of ethanol, adding this to the flask. Set up the apparatus for reflux under nitrogen, flush out the apparatus with nitrogen for 5 minutes and reflux the mixture for 90 minutes. After this period of time, allow the mixture to cool and filter off the crystalline precipitate with suction using a glass sinter funnel. Record the yield and prepare the sample for NMR. Place the product in a screw cap vial from which the air has been displaced by nitrogen. If you have not obtained sufficient material the filtrate may be refluxed for a further period of time to obtain a second crop of crystals. However, if this is necessary it must be carried out immediately as the solution is not stable for extended periods.

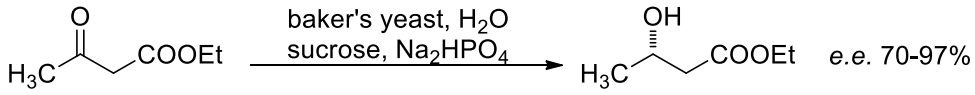
Post-lab questions:

1. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by Wilkinson's catalyst that have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
2. Which other rhodium(I)-based catalysts are being used in organic synthesis? Which reactions they catalyze? Give at least three examples. Use scientific database systems (SciFinder or Google Scholar) for literature search. Provide the proper citation (with DOI number) for all those reactions.

Various catalytic methods in organic chemistry

3.1 Biocatalysis

3.1A Asymmetric synthesis of ethyl (S)-3-hydroxybutanoate with the use of baker's yeast – fermentation method



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ Y. Naoshima et al., *Chem. Commun.* **1990**, 964
- ✓ D. Seebach et al., *Org. Synth.* **1984**, *63*, 1
- ✓ "Biocatalysts for Fine Chemicals Synthesis" (red. S. Roberts), Wiley, Chichester **1999**

Laboratory techniques:

- ✓ using temperature controller
- ✓ running a reaction for a long time
- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ bulb-to-bulb distillation
- ✓ using Kugelrohr
- ✓ determination of specific rotation

Experimental procedure:

Dissolve sucrose (80 g) and sodium dihydrogenphosphate (Na_2HPO4, 0.5 g) in warm (35 °C) water (350 mL) in a 1 L Erlenmeyer flask equipped with a magnetic stirrer and an oil bath. Add dry (16 g) or fresh (50 g) baker's yeast and stir it until the homogenous mixture will be obtained. After 15–30 minutes, when the fermentation has started, add distilled ethyl acetylacetate (4.9 mL, 38.4 mmol). Stir the mixture for at least 48 hours at 30–35 °C. After this period of time filter baker's yeast and wash them with water (50 mL). Add Celite to suspension (20 g) to make the filtration easier. Saturate the filtrate with sodium chloride. Extract the solution with diethyl ether (50 mL) five times (250 mL of solvent in total). Formation of an emulsion should be avoided. In the case an emulsion was formed add small amount of methanol to the solution. Instead of using diethyl ether you can use ethyl acetate, which forms emulsions less easily. Collect the organic phase and dry it over magnesium sulfate. Filter the suspension with suction into a 500 mL round-bottom flask and evaporate the filtrate on a rotary evaporator.

Run the tests for the presence of ethyl acetylacetate. The product should give negative results in both of them.

1) Dissolve a sample of the product (15 mg) in water (0.5 mL) in a test tube and add 1–2 drops of 1% iron(III) chloride solution. If the solution turns green, blue or red it indicates the presence of enol form of ethyl acetylacetate.
2) Determine the purity of your product running a TLC plate (dichloromethane as eluant) with samples of the reactant and the product. Compare the retention factors (R_f) for both compounds. Use *p*-methoxybenzaldehyde to visualize the spots.

Purify the product by *bulb-to-bulb* distillation using Kugelrohr. B.p. equals 71–73 °C (12 mmHg). Typical yield of this reaction is 3–4 g (59–78%).

Record the yield and prepare the sample for NMR.

Prepare a solution of the product (1 g per 100 mL of solvent) in chloroform and measure optical rotation. Use this value to determine the specific rotation and enantiomeric excess (e.e.) of your product. Specific

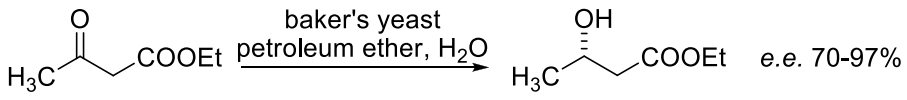
rotation for pure (*S*)-ethyl 3-hydroxybutanoate equals $[\alpha]_D^{25}$ = +43.7 (c = 1, $CHCl_3$).

Post-lab questions:

1. What is biocatalysis? What are advantages and disadvantages of this catalytic method? Give three examples of commercially available biocatalysts (provide links to suppliers' websites).
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by enzymes, that have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
3. Using scientific database systems (SciFinder or Google Scholar) search for three types of reactions catalyzed by baker's yeast. Provide the proper citation (with DOI number) for all those reactions.

Is the selectivity of this catalyst high enough to reduce carbonyl group (with high yield) in the presence of other functional groups (multiple bonds, ester group and others)?

3.1B Asymmetric synthesis of ethyl (*S*)-3-hydroxybutanoate with the use of baker's yeast – synthesis in organic solvent



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ C. Meson et al., *Tetrahedron: Asymmetry* **1997**, *8*, 1049
- ✓ O. Rotthaus et al., Tetrahedron, **1997**, 53, 935

Laboratory techniques:

- ✓ running a reaction for a long time
- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ bulb-to-bulb distillation
- ✓ using Kugelrohr
- ✓ determination of specific rotation

Experimental procedure:

Place distilled acetyl acetate (1 g, 7.68 mmol), petroleum ether (250 mL) and water (12 mL) in a 500 mL round-bottom flask equipped with a large (4–5 cm) magnetic stirrer bar. Add dry baker's yeast (15 g). Close the neck of the flask with a stopper made of wool. Run the reaction for 24 hours in room temperature. After this time filter the solution with suction on a Büchner funnel and wash baker's yeast with ethyl acetate (30 mL) three times (90 mL in total). Dry organic extracts over magnesium sulfate. Filter the solution into round-bottom flask and evaporate the solvents using rotary evaporator until you obtain a thick oil. Purify the product by *bulb-to-bulb* distillation using Kugelrohr. B.p. equals 71–73 °C (12 mmHg). Typical yield of this reaction is 3–4 g (59–78%).

Record the yield and prepare the sample for NMR.

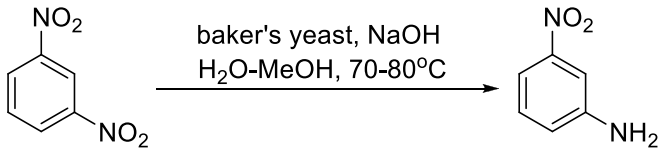
Prepare a solution of the product (1 g per 100 mL of solvent) in chloroform and measure optical rotation. Use this value to determin the specific rotation and enantiomeric excess (e.e.) of your product. Specific rotation for pure (*S*)-ethyl 3-hydroxybutanoate equals $[\alpha]_D^{25}$ = +43.7 (c = 1, $CHCl_3$).

Post-lab questions:

1. What is biocatalysis? What are advantages and disadvantages of this catalytic method? Give three examples of commercially available biocatalysts (provide links to suppliers' websites).
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by enzymes, that have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
3. Using scientific database systems (SciFinder or Google Scholar) search for three types of reactions catalyzed by baker's yeast. Provide the proper citation (with DOI number) for all those reactions.

Is the selectivity of this catalyst high enough to reduce carbonyl group (with high yield) in the presence of other functional groups (multiple bonds, ester group and others)?

3.1C Synthesis of 1-amino-3-nitrobenzene with the use of baker's yeast



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ W. Baik et al., *Tetrahedron Lett.* **1994**, *35*, 3965

Laboratory techniques:

- ✓ using temperature controller
- ✓ running a reaction for a long time
- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ column chromatography
- ✓ thin layer chromatography TLC

Experimental procedure:

Place baker's yeast (30 g) and water (80 mL) in a 250 mL round-bottom flask. Warm the mixture to 70 °C in 5 minutes. Add the solution of 1,3-dinitrobenzene (500 mg, 3 mmol) dissolved in methanol (40 mL) and aqeous solution of sodium hydroxide (4 g of NaOH dissolved in 10 mL of water). Stir the suspension vigorously at 70–80 °C for 2 hours. Cool the solution to room temperature and add dichloromethane (50 mL). After the phase separation, filter the organic layer through a Celite placed in a Schott funnel. Dry the extract over anhydrous magnesium sulfate and filter it. Evaporate the solvents using a rotary evaporator. Purify the crude product on chromatography column with silica gel. In order to find a proper solvent system for the chromatography, run several TLC plates with different mixtures of dichloromethane and *n*-hexane as eluant. Typical yield of this reaction is 393 mg (95%).
Prepare the NMR sample of the purified compound.

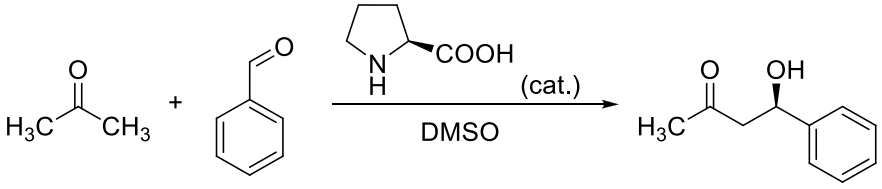
Post-lab questions:

1. What is biocatalysis? What are advantages and disadvantages of this catalytic method? Give three examples of commercially available biocatalysts (provide links to suppliers' websites).
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by enzymes, that have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
3. Using scientific database systems (SciFinder or Google Scholar) search for three types of reactions catalyzed by baker's yeast. Provide the proper citation (with DOI number) for all those reactions.

Is the selectivity of this catalyst high enough to reduce carbonyl group (with high yield) in the presence of other functional groups (multiple bonds, ester group and others)?

3.2 Organocatalysis

3.2A L-Proline catalysed asymmetric synthesis of aldoles from acetone



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ B. List et al., *J. Am. Chem. Soc.* **2000**, *122*, 2395
- ✓ K. Sakthivel et al., *J. Am. Chem. Soc.* **2001**, *123*, 5260

Laboratory techniques:

- ✓ running a reaction for a long time
- ✓ extraction and using simple drying agents
- ✓ microscale synthesis
- ✓ gravity and vacuum filtration
- ✓ column chromatography

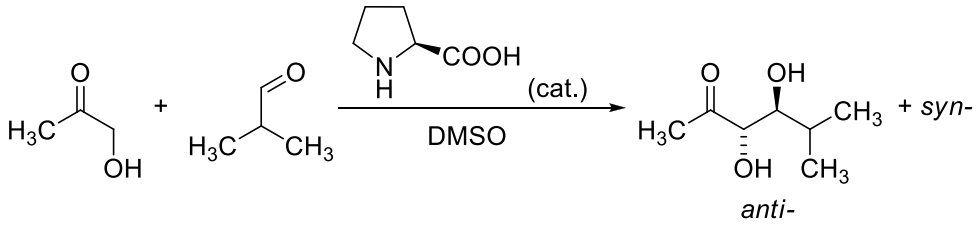
Experimental procedure:

Place L-proline (35 mg, 0.3 mmol) and 10 mL of DMSO–acetone (4:1) solution in a 25 mL round-bottom flask equipped with a magnetic stirrer. Stir the solution for 15 minutes and then add benzaldehyde (102 μL, 1 mmol) and seal the flask with a septum. Stir the mixture for at least 48 hours in room temperature (write down time of the reaction). After this period of time add saturated solution of ammonium chloride (10 mL) and extract the product three times with ethyl acetate (three 15 mL portions). Combine the extracts and dry them over magnesium sulfate. Filter the solution and evaporate the solvent using a rotary evaporator. Purify the product on chromatography column with silica gel. Use a mixture of hexane–ethyl acetate (3:1) as an eluant. Prepare the NMR sample of the purified product.

Post-lab questions:

1. What is organocatalysis? What are advantages and disadvantages of this catalytic method? Give three examples of commercially available organocatalysts (provide links to suppliers' websites). Read the article: https://www.dropbox.com/s/ilyj36vdaz9i3lh/Chemenzymes.pdf?dl=0 and explain the term "chemzymes".
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by organocatalysts, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
3. Read the articles listed in the References section (*JACS* 2000, *JACS* 2001), draw the mechanism of catalytic cycle and explain the role of L-proline in the aldol reaction.

3.2B L-Proline catalysed asymmetric synthesis of aldoles from hydroxyacetone



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ W. Notz et al., *J. Am. Chem. Soc.* **2000**, *122*, 7386

Laboratory techniques:

- ✓ microscale synthesis
- ✓ running a reaction for a long time
- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ column chromatography

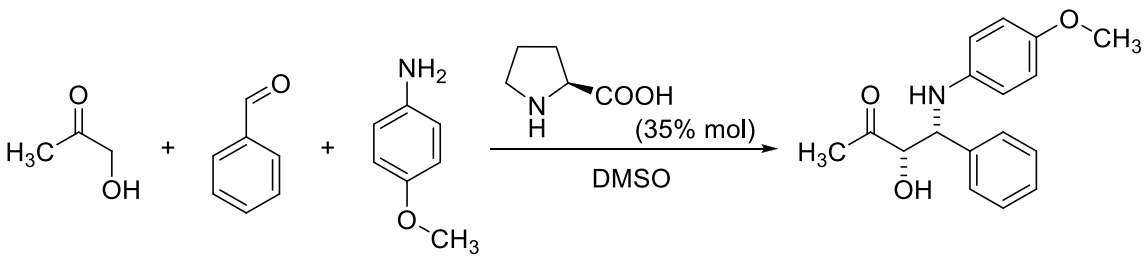
Experimental procedure:

Place 10 mL of DMSO–hydroxyacetone mixture (4:1) in a 25 mL round-bottom flask equipped with a magnetic stirrer and add L-proline (28 mg, 0.25 mmol). Stir the solution for 15 minutes and then add isobutyraldehyde (91 μL, 72 mg, 1 mmol) and seal the flask with a septum. Stir the mixture for at least 60 hours in room temperature (write down time of the reaction). After this period of time add saturated solution of ammonium chloride (2 mL) and extract the product three times with ethyl acetate (three 10 mL portions). Combine the extracts and dry them over magnesium sulfate. Filter the solution and evaporate the solvent using a rotary evaporator. Purify the product on chromatography column with silica gel. Use a mixture of hexane–ethyl acetate (1:1) as an eluant. Prepare the NMR sample of the purified product.

Post-lab questions:

1. What is organocatalysis? What are advantages and disadvantages of this catalytic method? Give three examples of commercially available organocatalysts (provide links to suppliers' websites). Read the article: https://www.dropbox.com/s/ilyj36vdaz9i3lh/Chemenzymes.pdf?dl=0 and explain the term "chemzymes".
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by organocatalysts, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
3. Read the articles listed in the References section of experiment **3.2A** (*JACS* 2000, *JACS* 2001), draw the mechanism of catalytic cycle and explain the role of L-proline in the aldol reaction.

3.2C L-Proline catalysed synthesis of Mannich's bases from hydroxyacetone



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ B. List et al., *J. Am. Chem. Soc.* **2002**, *124*, 827

Laboratory techniques:

- ✓ microscale synthesis
- ✓ running a reaction for a long time
- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ column chromatography

Experimental procedure:

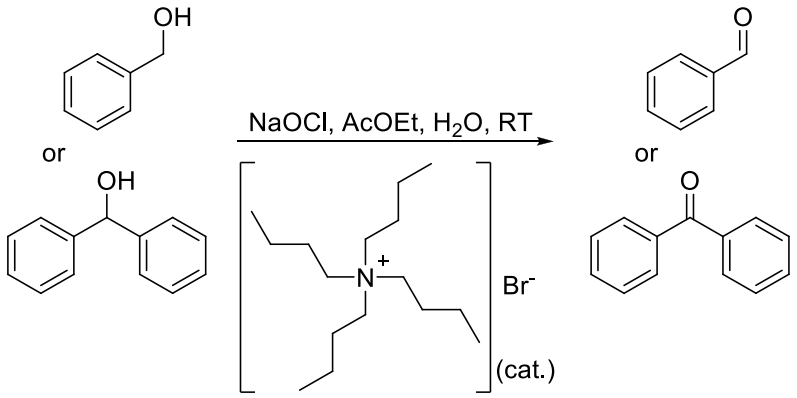
Place L-proline (23 mg, 0.2 mmol), *p*-anisidine (135 mg, 1.1 mmol), benzaldehyde (102 μL, 1 mmol) and the DMSO–hydroxyacetone solution (9 mL, 9:1) in a 20 mL round-bottom flask equipped with a magnetic stirrer. Seal the flask with a septum and stir the mixture for at least 16 hours (write down time of the reaction). After this period of time add saturated solution of ammonium chloride (2 mL) and extract the product with two portions (15 mL each) of hexane–ethyl acetate (2:3) solution. Wash the organic phase with water (15 mL) and dry it over magnesium sulfate. Filter the solution and evaporate the solvents on rotary evaporator. Purify the product on chromatography column with silica gel. Use a mixture of hexane–ethyl acetate (3:1) as an eluant. Prepare the NMR sample of a purified, oily product.

Post-lab questions:

1. What is organocatalysis? What are advantages and disadvantages of this catalytic method? Give three examples of commercially available organocatalysts (provide links to suppliers' websites). Read the article: https://www.dropbox.com/s/ilyj36vdaz9i3lh/Chemenzymes.pdf?dl=0 and explain the term "chemzymes".
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions catalyzed by organocatalysts, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.
3. Explain the term "domino reactions" and give three examples of such reactions that have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

3.3 Phase Transfer Catalysis (PTC)

3.3A Interphase oxidation of alcohols with NaOCl catalysed by quaternary ammonium salts



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ G. A. Mirafzal et al., *Tetrahedron Lett.* **1998**, *39*, 7263

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ simple distillation
- ✓ crystallization and recrystallization

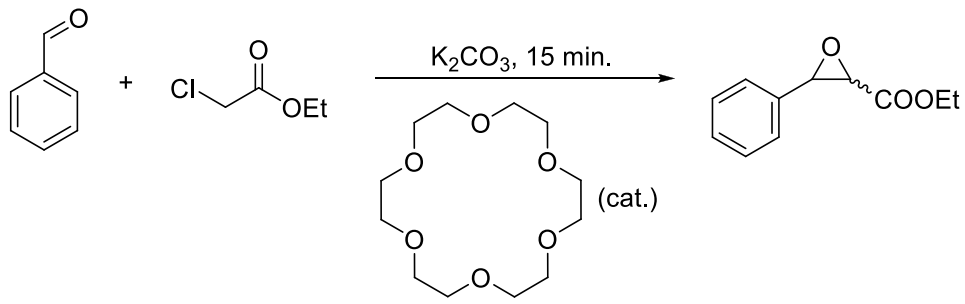
Experimental procedure:

Place ethyl acetate (15 mL) and benzyl alcohol (577 μL, 600 mg, 5.56 mmol) or diphenylmethanol (1.02 g, 5.56 mmol) in a 50 mL round-bottom flask equipped with a magnetic stirrer. Stir the mixture vigorously and add the solution of sodium(I) chlorate (5%, 15 mL) and the catalyst – tetrabutylammonium bromide (TBAB, 300 mg, 0.93 mmol). The oxidation is usually finished after 30–60 minutes of stirring. After this period of time transfer the mixture into a separatory funnel and separate phases. Collect the organic phase and re-extract the water phase with additional portion of ethyl acetate (20 mL). Wash the combined extracts with water and dry them over anhydrous magnesium sulfate. Filter the solution and evaporate the solvents on rotary evaporator. Purify the product of oxidation of benzyl alcohol by a simple distillation. In the case of the reaction with diphenylmethanol purify the product by crystallization from hexane. Prepare the NMR sample for the purified product.

Post-lab questions:

1. What is phase transfer catalysis? What are advantages and disadvantages of this catalytic method? Give three types of commercially available phase transfer catalysts (provide links to suppliers' websites).
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions running under phase transfer catalysis conditions, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

3.3B Interphase Darzens reaction – synthesis of ethyl 3-phenyloxirane-2-carboxylate catalysed by crown ether



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ M. Fedoryński et al., *J. Org. Chem.* **1978**, *43*, 4682

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ using temperature controller
- ✓ removal of solvents with high vacuum
- ✓ bulb-to-bulb distillation
- ✓ using Kugelrohr

Experimental procedure:

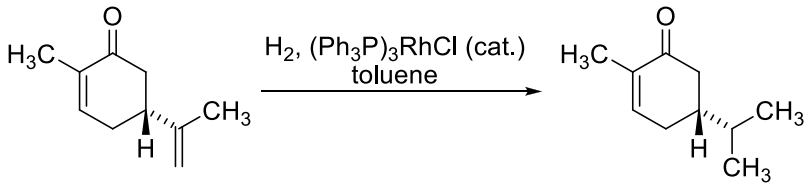
Place distilled benzaldehyde (5.1 mL, 50 mmol), anhydrous potassium carbonate (8.3 g, 60 mmol) and crown ether 18-crown-6 (0.13 g, 0.5 mmol) in a 50 mL three-neck round-bottom flask equipped with a magnetic stirrer, a reflux condenser, a dropping funnel and a thermometer. Stir the suspension vigorously and heat it to 125–130 °C and add dropwise, over 30 minutes, distilled ethyl chloroacetate (9.2 g, 75 mmol). Stir the solution for further 10 minutes and cool it to room temperature. Add water (30 mL) and transfer the solution to a separatory funnel. Separate phases and collect the organic layer. Wash the organic phase with water and dry it over anhydrous magnesium sulfate. Filter the solution and isolate the product by bulb-to-bulb distillation using Kugelrohr. B.p. of the product equals 99–107 °C at 0.5 mmHg. Typical yield of this reaction is 6.95 g (72%). The product exists as a mixture of *cis* and *trans* isomers in a 1:1 molar ratio. Prepare the NMR sample of the purified product.

Post-lab questions:

1. What is phase transfer catalysis? What are advantages and disadvantages of this catalytic method? Give three types of commercially available phase transfer catalysts (provide links to suppliers' websites).
2. Using scientific database systems (SciFinder or Google Scholar) search for three reactions running under phase transfer catalysis conditions, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

3.4 Reactions catalysed by metal complexes

3.4A Reduction of carvone to 7,8-dihydrocarvone catalysed by Wilkinson's catalyst



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ Encyclopedia of Reagents for Organic Synthesis, EROS, 1253
- ✓ S. G. Davies, "Organotransition Metal Chemistry: Applications to Organic Synthesis", Pergamon, Oxford 1982

Laboratory techniques:

- ✓ reactive drying agents – safe using and decomposition
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ degassing of solvents and reagents
- ✓ fractional distillation
- ✓ removal of solvents with high vacuum
- ✓ bulb-to-bulb distillation
- ✓ using Kugelrohr
- ✓ working with compressed gases

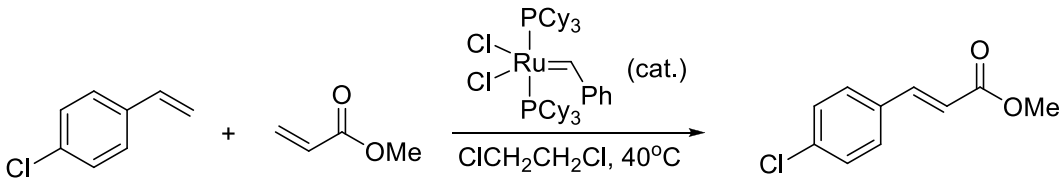
Experimental procedure:

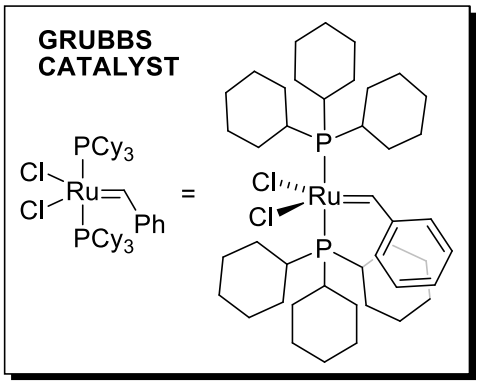
Degas dry toluene (35 mL) by bubbling nitrogen through it for 10 minutes. In the meantime, weigh the carvone (1.50 g, 10 mmol) and Wilkinson's catalyst (0.2 g) into a hydrogenation flask containing a magnetic stirrer bar. Add the toluene and bubble nitrogen through the mixture for a further 5 minutes. Attach the flask to the gas burette and evacuate the flask. Flush out the system totally with hydrogen by repeated evacuation and filling (at least four times). The more care you take at this stage, the faster will be the rate of hydrogenation. Fill the apparatus with hydrogen, commence stirring and follow the uptake with time. Stop the reaction when the theoretical volume has been reached (or possibly slightly exceeded due to leakage) and the reaction rate appears to plateau. Filter the solution through the silica contained in a sinter funnel and wash the residual silica with 100 mL of diethyl ether. Remove the solvent on a rotary evaporator with moderate heating (*ca.* 40 °C) and distil the product in a short path distillation apparatus under reduced pressure using a water aspirator, collecting the fraction boiling at a bath temperature of 90–110 °C. Record the yield and prepare the NMR sample of the purified product.

Post-lab questions:

1. Explain the term "18 electrons rule" in the context of coordination compounds of transition metals. Explain why Wilkinson's catalyst is an exception from this rule.
2. Draw and describe the catalytic cycle of alkene reduction with the use of Wilkinson's catalyst. Write down the number of valence electrons of rhodium on each step of the cycle.

3.4B Olefin metathesis – synthesis of methyl ester of (*E*)-methyl 3-(4-chlorophenyl)acrylate





References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ J. Louie et al., *J. Am. Chem. Soc.* **2001**, *123*, 11312

Laboratory techniques:

- ✓ using a glovebox
- ✓ Solvent Purification System (SPS)
- ✓ degassing of solvents and reagents
- ✓ microscale synthesis
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ synthesis with very reactive reagents
- ✓ column chromatography

Experimental procedure:

Conduct the synthetic part of the experiment in a Glove-box.

Place methyl acrylate (210 µL, 2.3 mmol), 4-chlorostyrene (140 µL, 1.2 mmol) and 1st generation Grubbs catalyst (35 µmol) in a pre-dried 1 mL round-bottom flask equipped with a magnetic stirrer. Add 1,2-dichloroethane (5 mL) and seal the flask with a septum. Stir the mixture for at least 1 hour at 40 °C. After this period of time cool the solution to room temperature and separate the crude product on column chromatography with silica gel. Use *n*-hexane as eluant. Typical yield of this reaction is 216 mg (92%). Purify the product by recrystallization from the methanol–water mixture. Prepare the NMR sample of the pure product.

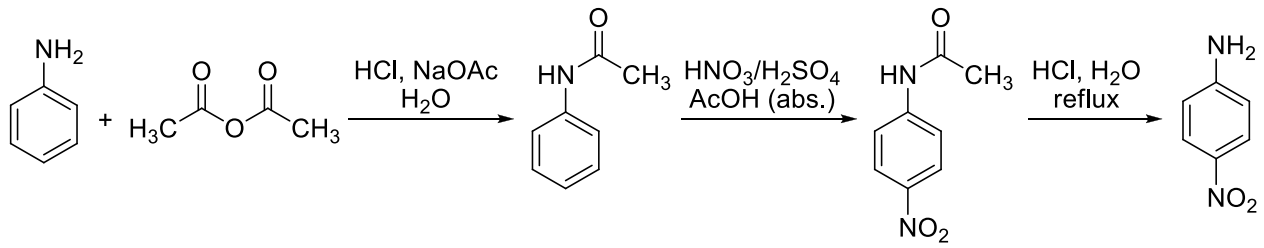
Post-lab questions:

1. What is the alkene metathesis reaction? Draw the general mechanism for this process. List and describe the subtypes of this reaction.
2. Give the examples of catalystys for alkene metathesis reaction. Discuss advantages and disadvantages of Schrock, Schrock-Hoveyda and Grubbs catalysts.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of alkene metathesis, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

Protecting groups and umpolung

4.1 Representative methods of functional groups' protection

4.1A Synthesis of *p*-nitroaniline from aniline based on protection/deprotection of amine group



References:

- ✓ C. F. Wilcox, „Experimental Organic Chemistry, A Small-Scale Approach", MacMillan Publishing Company, New York 1988
- ✓ P. G. M. Wuts, T. W. Greene "Greene's Protective Groups in Organic Synthesis", any edition, Wiley & Sons

Laboratory techniques:

- ✓ multi-step synthesis
- ✓ using temperature controller
- ✓ synthesis at low temperature
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization

Experimental procedure:

Protection of amine group – Lumière-Barbier method

Dissolve aniline (1.1 mL, 0.012 mol) in 30 mL of water to which 1 mL (0.012 mol) of concentrated hydrochloric acid has been added. If the amine is discolored, add 0.2–0.4 g of decolorizing carbon, stir the solution for a few minutes, and filter it with suction. Meanwhile, prepare for use in the next step a solution of 1.8 g (0.013 mol) of sodium acetate trihydrate crystals in 4 mL of water; if any insoluble particles are present, filter the solution.

Transfer the solution of aniline hydrochloride to a 50 mL flask. Add 1.6 mL (1.66 g, 0.03 mol) of acetic anhydride and swirl the contents to dissolve the anhydride. Add at once the previously prepared sodium acetate solution and mix the reactants thoroughly by swirling. Cool the reaction mixture to an ice bath and stir vigorously while the product crystallizes. Collect the crystals on a suction filter, wash with cold water, and allow them to dry. The yield is 1.0–1.4 g. The material obtained by this acetylation procedure is usually quite pure and of better quality that prepared by the acetylation in acetic acid. If necessary, the product may be recrystallized from water, with addition of about 0.2 g of decolorizing carbon. Prepare the NMR sample of the product.

Nitration of acetanilide

In a 50 mL Erlenmeyer flask dissolve 1.36 g (0.01 mol) of pure acetanilide in 1.6 mL of glacial acetic acid by warming it gently. Cool the warm solution until crystals begin to form and then add slowly, while swirling the solution, 2 mL of ice-cold concentrated sulfuric acid. Prepare a nitrating mixture by adding 0.7 mL (1 g, 0.012 mol) of concentrated nitric acid to 1 mL of cold, concentrated sulfuric acid; cool the solution to room temperature and transfer it to a small dropping funnel.

Cool the acetanilide solution to 5 °C in an ice bath, remove the flask from the bath, and add the nitrating mixture slowly, drop by drop. Swirl the reaction mixture to obtain good mixing in the viscous solution and

do not permit the temperature to rise above 20–25 °C. After all of the nitrating mixture has been added, allow the solution to stand at room temperature for about 40 minutes (but no longer than 1 hour) to complete the reaction. Pour the solution slowly with stirring into a mixture of 20 mL of water and 4–5 g of chipped ice. Collect the product with suction, press it firmly on the filter, and wash thoroughly with more water to form a thin paste, return it to the suction filter, and wash thoroughly with more water to remove the nitric and sulfuric acids. Dry the material as much as possible. The crude, moist *p*-nitroacetanilide is sufficiently pure to be used directly for hydrolysis to *p*-nitroaniline. The moist product is equivalent to about 1.2 g of dry material. Prepare the NMR sample.

Deprotection of amine group

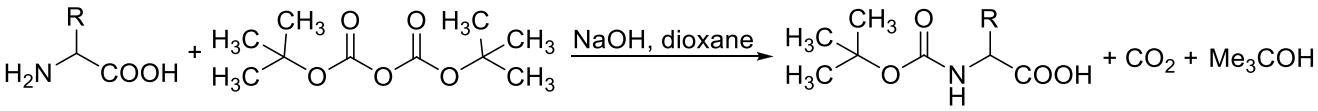
In a 50 mL Erlenmeyer flask mix the moist, crude *p*-nitroacetanilide with 3 mL of water and 4 mL of concentrated hydrochloric acid. Reflux the mixture gently for 15–20 minutes. The material gradually dissolves and an orange-colored solution is formed. When the hydrolysis is completed, add 6 mL of cold water and cool the mixture to room temperature. Crystals of the product may separate.

Pour the *p*-nitroaniline hydrochloride slowly, stirring thoroughly, into a mixture of 4 mL of concentrated aqueous ammonia, 15 mL of water, and 5–6 g of chipped ice. The mixture must be distinctly alkaline at the time of the mixing; test with indicator papers, and add a little more ammonia if necessary. Collect the orange-yellow precipitate of *p*-nitroaniline with suction and wash it with cold water. Recrystallize the product from a large volume of hot water; about 30 mL of water will be required per gram of material. The yield is 0.5–0.8 g. Prepare a sample of the purified product.

Post-lab questions:

1. Give three examples of protecting groups that might be used for the protection of amines. For each of those groups provide two methods of incorporation and cleavage. Explain the compatibility of the chosen protection/deprotection methods with the presence of other functional groups in a molecule.
2. Using scientific database systems (SciFinder or Google Scholar) search for two examples of natural product or drug synthesis, which rely on the protection/deprotection of amine group. Provide the proper citation (with DOI number) for all those reactions.

4.1B BOC-protection of amine group of aminoacid



References:

- ✓ I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996.
- ✓ Z. Jerzmanowska, "Analiza Jakościowa Związków Organicznych", PZWL, Warszawa 1975

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ crystallization and recrystallization
- ✓ synthesis at low temperature

Experimental procedure:

Place the appropriate aminoacid (10 mmol), 1,4-dioxane (20 mL), water (10 mL), and 1 M sodium hydroxide solution (10 mL) in a 100 mL round-bottom flask equipped with a magnetic stirrer bar. Cool the reagents in water–ice cooling bath and stir the solution vigorously. Add di-*tert*-butyl dicarbonate (2.4 g, 11 mmol) to the solution and stir it for 30 minutes at room temperature. After this period of time concentrate the solution to 10–15 mL using a rotary evaporator (temperature of the water bath shouldn't be higher than 40 °C), and then cool it in an ice–water cooling bath. Add ethyl acetate (30 mL) and acidify a mixture with aqueous solution of potassium bisulfite ($KHSO_4$) to pH 2–3.

Transfer the solution into a separating funnel and extract the product with two portions of ethyl acetate (15 mL each). Collect the organic phase and wash it twice with water (30 mL per portion), dry over anhydrous magnesium sulfate and filter. Evaporate the solvents using a rotary evaporator. Purify the crude product by recrystallization from ethyl acetate–*n*-hexane. Prepare the NMR sample of the purified compound.

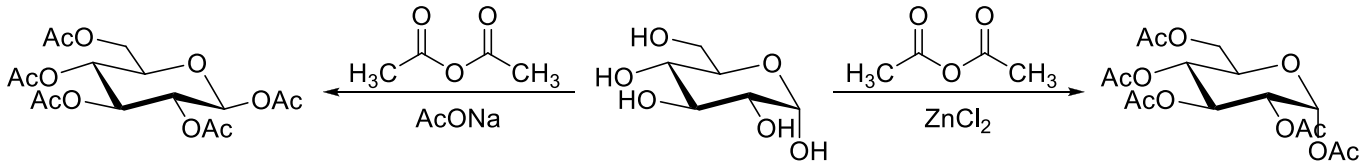
In order to confirm the protection of amino group of aminoacid run a reaction with ninhydrin.

In two clean and dry test tubes place unprotected aminoacid (reactant) and the purified product of the reaction. Add water (1–5 mL) and 4–5 drops of aqeous 1% solution of ninhydrin to each tube. Boil the mixtures for 1–2 minutes using a hot water bath. Coloration of the solution indicates the presence of free amino group.

Post-lab questions:

1. Give three examples of protecting groups that might be used for the protection of the amine group of aminoacid. For each of those groups provide two methods of incorporation and cleavage. Explain the compatibility of the chosen protection/deprotection methods with the presence of other functional groups in a molecule.
2. Using scientific database systems (SciFinder or Google Scholar) search for two examples of natural product or drug synthesis, which rely on the protection/deprotection of the amine group. Provide the proper citation (with DOI number) for all those reactions.

4.1C Protection of hydroxyl groups of carbohydrate – syntheses of 1,2,3,4,6-penta-*O*-acetyl-α-D-glucopyranose and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose



References:

- ✓ I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996.

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization

Experimental procedure:

Synthesis of 1,2,3,4,6-penta-O-acetyl-α-D-glucopyranose

Place the anhydrous zinc(II) chloride (0.5 g) and acetic anhydride (12.5 mL, 13.5 g, 0.13 mol) in a 100 mL round-bottom flask equipped with a reflux condenser and a magnetic stirrer. Zinc(II) chloride is extremely hygroscopic. Powder a couple of its crystals in a mortar and weigh the appropriate amount as fast as possible. Heat the mixture for 5–10 minutes on a boiling water bath, swirling the flask periodically until the reagents dissolve. Add slowly, in portions D-glucose (2.5 g, 0.014 mol), swirling the flask to make sure the reaction is not too vigorous. Boil the reagents for 1 hour on a hot water bath. After this period of time pour the mixture into water–ice mixture (125 mL) contained in a beaker, and stir it vigorously to decompose the unreacted anhydride. After 30 minutes the initially oily product should form a solid. Filter the product with suction, wash it thoroughly with cold water and recrystallize it from ethanol. Typical yield of this reaction is 3.5 g (63%). Prepare the NMR sample of the purified compound.

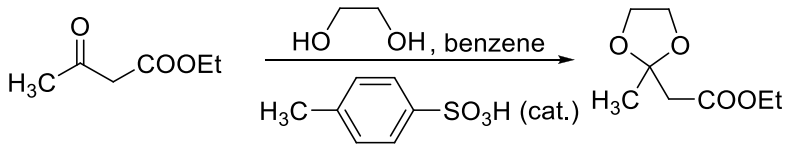
Synthesis of 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose

Powder the anhydrous sodium acetate (4 g) with α-D-glucose (5 g, 0.028 mol) in a mortar and transfer the mixture into a 200 mL round-bottom flask equipped with an efficient reflux condenser. Add acetic anhydride (25 mL, 27 g, 0.26 mol) and boil the mixture in a hot water bath swirling the flask periodically in order to obtain a clear solution. Heat the reagents under reflux for next 2 hours. After this period of time pour the solution onto chipped ice (250 mL) contained in a large beaker. Left the product in ice for 1 hour during which it should crystallize. Swirl the flask periodically to avoid the formation of large clods. Filter the product with suction, wash it with a copious amount of cold water and recrystallize it from ethanol. Typical yield of this reaction is 6.2 g (56%). Prepare the NMR sample of the purified compound.

Post-lab questions:

1. Give three examples of protecting groups that might be used for the protection of a hydroxyl group. For each of those groups provide two methods of incorporation and cleavage. Explain the compatibility of the chosen protection/deprotection methods with the presence of other functional groups in a molecule.
2. Using scientific database systems (SciFinder or Google Scholar) search for two examples of natural product or drug synthesis, which rely on the protection/deprotection of hydroxy group. Provide the proper citation (with DOI number) for all those reactions.

4.1D Protection of carbonyl group – synthesis of 1,3-dioxolane from ethyl acetylacetate



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ D. R. Paulson et al., *J. Chem. Educ.* **1973**, *50*, 216
- ✓ I. Vogel, A. R. Tatchell, B. S. Furnis, A. J. Hannaford , P. W. G. Smith "Vogel's Textbook of practical organic chemistry", Prentice Hall 1996.

Laboratory techniques:

- ✓ reflux
- ✓ fractional distillation
- ✓ vacuum distillation

Experimental procedure:

Place ethyl acetylacetate (30 g, 0.23 mol), ethane-1,2-diol (16 g, 0.25 mol), a small crystal of *p*-toluenesulfonic acid and benzene (50 mL) in a 250 mL round-bottom flask equipped with a Dean-Stark adapter, a reflux condenser and a magnetic stirrer bar. Boil the reagents under reflux as long as water is being formed. Purify the product of the reaction by fractional distillation under reduced pressure. Boiling point of the product is 99–101 °C (17–18 mmHg). Typical yield of the reaction is 35 g (87%). Prepare the NMR sample of the purified compound.

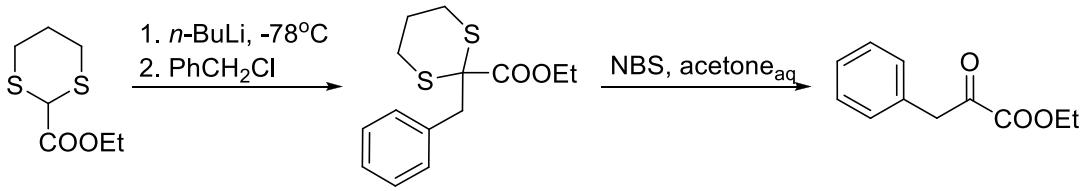
Transfer the purified product of the synthesis into a dry and clean container. Fill the container with nitrogen, seal it and protect with a piece of parafilm. Store the compound in a fridge – it will be used for the synthesis during the experiment **7A**.

Post-lab questions:

1. Give three examples of protecting groups that might be used for the protection of a carbonyl group. For each of those groups provide two methods of incorporation and cleavage. Explain the compatibility of the chosen protection/deprotection methods with the presence of other functional groups in a molecule.
2. Using scientific database systems (SciFinder or Google Scholar) search for two examples of natural product or drug synthesis, which rely on the protection/deprotection of carbonyl group. Provide the proper citation (with DOI number) for all those reactions.

4.2 Umpolung

4.2A Synthesis of ethyl phenylpyruvate by alkylation of ethyl 1,3-dithiane-2-carboxylate and following oxidative hydrolysis with NBS



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ G. Wittig et al., *Chem. Ber.* **1951**, *84*, 627
- ✓ D. Seebach, *Angew. Chem. Int. Ed.* **1979**, *18*, 239
- ✓ D. Seebach, *Synthesis* **1969**, 17

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ degassing of solvents and reagents
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ synthesis at low temperature
- ✓ multi-step synthesis
- ✓ synthesis with very reactive reagents
- ✓ using Schlenk line
- ✓ bulb-to-bulb distillation
- ✓ using Kugelrohr
- ✓ working with pyrophoric liquids

Experimental procedure:
All apparatus must be thoroughly dried in a hot (>120 °C) oven before use

Synthesis of ethyl 2-benzyl-1,3-dithiane-2-carboxylate
Measure the ethyl 1,3-dithiane-2-carboxylate (1.64 mL, 2.00 g, 10.5 mmol) into a 100 mL three-neck flask containing a magnetic stirrer bar and equip it with a gas bubbler, a septum and a low temperature thermometer. Introduce a nitrogen atmosphere to the flask, add 30 mL anhydrous tetrahydrofuran and cool the solution to –78 °C with stirring. Add the solution of *n*-butyllithium (6.9 mL of 1.6 M solution in hexane, 11 mmol) dropwise by syringe and then allow the temperature of the mixture to reach 0 °C by raising the flask almost totally out of the cooling bath. Stir at this temperature for 1 hour and then lower the flask back into the cooling bath. Stir at this temperature for 1 hour and then lower the flask back into the cooling bath to return the temperature of the reaction mixture to –78 °C. Add the benzyl chloride (1.05 mL, 1.25 g, 10 mmol) dropwise by syringe and again raise the temperature, quench the reaction by adding 20 mL of saturated aqeuous ammonium chloride. Separate the organic phase and re-extract the aqeous phase with 25 mL of diethyl ether. Dry the combined organic extracts with anhydrous magnesium sulfate, filter and remove the solvents on a rotary evaporator with gentle heating. Purify the residue by short path distillation at reduced pressure (bath temperature ca. 160–200 °C/0.1 mmHg) and record the yield of the purified product. Prepare the sample for NMR.

Synthesis of ethyl phenylpyruvate
Dissolve the N-bromocuccinimide (2.85 g, 16 mmol) in 50 mL of water contained in a 100 mL round-bottom flask containing a magnetic stirrer bar. Add 1.5 mL of acetone, stir the mixture, and then cool to

–5 °C in an ice–salt cooling bath. Whilst the mixture is cooling, prepare a solution of the ethyl 2-benzyl-1,3-dithiane-2-carboxylate (0.54 g, 2 mmol) in 10 mL of acetone and add it in one amount to the reaction flask with vigorous stirring. After 5 minutes pour the reaction into a mixture of 10 mL of dichloromethane, 10 mL of light petroleum and 10 mL of 5% aqeous sodium bicarbonate contained in a 250 mL Erlenmeyer flask, and stir the mixture vigorously for a further 5 minutes. Allow the mixture to settle and separate the organic phase, re-extracting the aqeous phase with a further 15 mL of diethyl ether. Wash the combined organic phases with 15 mL of water and dry over anhydrous magnesium sulfate. Filter the solution and remove the solvents on a rotary evaporator to furnish the crude product, which may be purified by short path distillation at reduced pressure (bath temperature ca. 150–200 °C at water aspirator pressure). Record the yield of the product and prepare the sample for NMR.

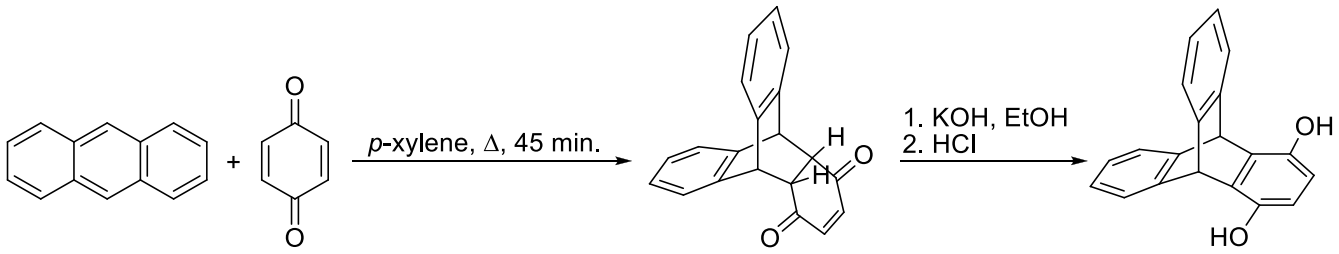
Post-lab questions:

1. Explain the term *umpolung*. Give three, other than described in the instruction, applications of *umpolung* for changing the reactivity of different classes of organic compounds.
2. Using scientific database systems (SciFinder or Google Scholar) search for three examples of syntheses that apply *umpolung* methodology, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

Pericyclic reactions and synthesis with reactive reagents (carbenes, radicals, benzyne)

5.1 Pericyclic reactions

5.1A Diels-Alder reaction – synthesis of dihydroxytriptycene



References:

- ✓ C. F. Wilcox, „Experimental Organic Chemistry, A Small-Scale Approach", MacMillan Publishing Company, New York 1988

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ multi-step synthesis

Experimental procedure:

Synthesis of p-benzoquinone-anthracene adduct

In a 25 mL round-bottom flask dissolve, in 2 mL of *p*-xylene, 0.36 g (0.002 mole) of anthracene and 0.22 g (0.002 mole) of *p*-benzoquinone. Attach a water-cooled reflux condenser and boil the solution for 45 minutes. Cool the solution to 15–20 °C and allow the adduct to crystallize. Collect the pale yellow crystals with suction and press them firmly on the filter. The yield of adduct is about 0.5 g. the crude product is sufficiently pure for the conversion to dihydroxytriptycene. Record the yield of the product and prepare the sample for NMR.

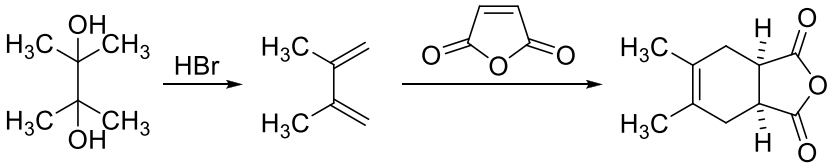
Synthesis of 1,4-dihydroxytriptycene

Place the *p*-benzoquinone–anthracene adduct (about 0.5 g) in a 50 mL round-bottom flask and add a solution of 0.1 g of potassium hydroxide pellets in 10 mL of ethanol. Warm the flask on a water bath for about 5 minutes, or until the adduct has dissolved. Dilute the ethanolic solution with 20 mL of water, cool the flask in an ice–water bath, and carefully neutralize the base by adding 20% hydrochloric acid, drop by drop with swirling, until the liquid is acidic to pH paper. Collect the precipitated dihydroxytriptycene by suction filtraction, wash it well with water, and spread it to dry in the air. The yield is about 0.4 g. The crude product is almost colourless. To obtain pure dihydroxytriptycene, you may crystallize the crude material from 95% ethanol or from ethanol–water mixture. Record the yield of the product and prepare the sample for NMR.

Post-lab questions:

1. What are pericyclic reactions? List the types of pericyclic reactions. Provide the examples for all types.
2. What are *retro*-Diels-Alder and *hetero*-Diels-Alder reactions? Give two examples for each of them. Provide the proper citation (with DOI number) for all those reactions.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of pericyclic reactions other than Diels-Alder reaction, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

5.1B Diels-Alder reaction – synthesis of 2,3-dimethyl-buta-1,3-diene and its reaction with maleic anhydride



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999

Laboratory techniques:

- ✓ multi-step synthesis
- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ simple distillation
- ✓ microdistillation
- ✓ crystallization and recrystallization

Experimental procedure:

Synthesis of 2,3-dimethylbuta-1,3-diene

Weigh the 2,3-dimethylbutane-2,3-diol (11.8 g, 0.1 mol) into a 100 mL round-bottom flask containing a magnetic stirrer bar, add the hydrobromic acid (48% solution, 1.5 mL) and stir the mixture for 1 hour. If the diol dissolves slowly, this can be speeded up by gentle heating. After this time, remove the stirrer bar and equip the flask for distillation with a –10 to 110 °C range thermometer. Distil the mixture slowly and collect the product which distils, until the temperature recorded by the thermometer reaches 95 °C. Transfer the distillate, which consists of two phases, to a 25 mL separatory funnel. Remove the lower aqueous layer, wash the organic layer twice more with 3 mL portions of water, and dry the organic phase for 5–10 minutes over magnesium sulfate. Filter the mixture into a 10 mL round-bottom flask through a small filter funnel plugged lightly with glass wool. Set the apparatus for distillation as before and distil slowly, collecting two fractions with boiling ranges of 65–75 °C and 75–100 °C. The first fraction is 65–90% pure diene, whilst the second fraction is about 65% pure. The major impurity in both fractions is 3,3-dimethylbutan-2-one. Record the quantity of each fraction. Prepare the sample for NMR.

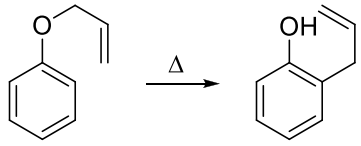
Diels-Alder reaction with maleic anhydride

Place the butenedioic anhydride (0.3 g, 3 mmol) in a test tube, powder it finely with a glass rod and clamp the tube vertically. Add 0.5 mL of fraction 1 of redistilled 2,3-dimethylbuta-1,3-diene and heat the mixture to 50 °C in a water bath, stirring with a 0–250 °C thermometer. After a short period of time an exothermic reaction begins and the temperature should rise to 100 °C in several seconds, causing excess diene to boil off. When the reaction has subsided, remove the test tube from the heating bath and allow the mixture to cool to about 40 °C. Add 15 mL hexane to the pasty product, warm the mixture in a hot water bath and stir until no more solid dissolves. Remove the thermometer, allow the test tube to stand undisturbed for 1 minute, and transfer the clear supernatant carefully to a 10 mL Erlenmeyer flask with a pipette, making sure to leave the insoluble residue of unreacted butenedioic anhydride behind. Leave the solution to cool for 10 minutes and filter off the crystals of the adduct with suction, washing them with a small quantity (2 mL) of cold hexane, and dry them with suction. Record yield based on the quantity of butenedioic anhydride used. Prepare the sample for NMR.

Post-lab questions:

1. What are pericyclic reactions? List the types of pericyclic reactions. Provide the examples for all types.
2. What are *retro*-Diels-Alder and *hetero*-Diels-Alder reactions? Give two examples for each of them. Provide the proper citation (with DOI number) for all those reactions.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of pericyclic reactions other than Diels-Alder reaction, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

5.1C Claisen rearrangement – synthesis of 2-allylphenol



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ S. J. Rhoads et al., *Org. Reactions* **1971**, *22*, 1

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ simple distillation
- ✓ microdistillation

Experimental procedure:

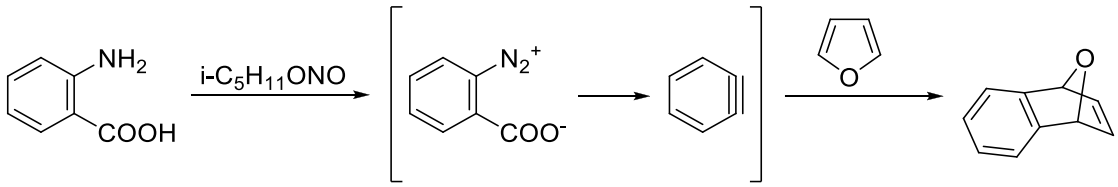
Place 5.37 g (40 mmol) of allyl phenyl ether in a 10 mL round-bottom flask. Add a boiling stone, fit an air reflux condenser, and heat the material under reflux for about 3 hours. The rearrangement can be conveniently followed by measuring the refractive index of the mixture at 30 minutes intervals; the reaction is completed when the refractive index has risen from 1.520 to 1.544. After cooling dissolve the product in 10 mL sodium hydroxide solution (5 M), and extract the solution with two portions (5 mL each) of petroleum ether. Acidify the aqueous solution with hydrochloric acid (6 M), and extract the product with three portions of diethyl ether (5 mL each). Dry the combined ether extracts over magnesium sulfate. Filter off the drying agent by suction, and evaporate the filtrate on a rotary evaporator. Distill the residue at atmospheric pressure in a small distillation set. Record the bp, yield and prepare the sample for NMR.

Post-lab questions:

1. What are pericyclic reactions? List the types of pericyclic reactions. Provide the examples for all types.
2. What are possible modifications of the basic Claisen rearrangement? Give three examples of such variations and provide the appropriate reaction scheme for each of them. Explain, what's the difference between modified and basic version of the reaction.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of pericyclic reactions other than Claisen rearrangement, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

5.2 Syntheses with very reactive reagents

5.2A Synthesis of benzyne and its reaction with furan



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ L. F. Fieser et al., *Can. J. Chem.* **1965**, *43*, 1599

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ synthesis with very reactive reagents

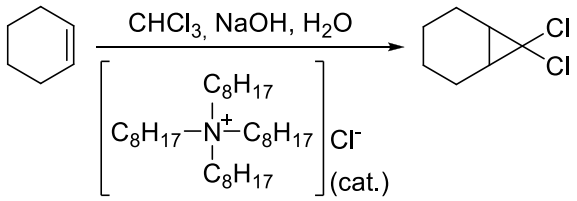
Experimental procedure:

Place the furan (10 mL, 9.4 g, 0.14 mmol), a few boiling stones, and 10 mL 1,2-dimethoxyethane (DME) in a 100 mL round-bottom flask. Fit an efficient reflux condenser to the flask, and heat the solution to reflux on a water bath. In two separate 25 mL Erlenmeyer flasks, make up a solution of the isoamyl nitrite (4 mL, 30 mmol) in 10 mL DME, and a solution of the anthranilic acid (2.74 g, 20 mmol) in 10 mL DME. At 8–10 minutes intervals, add 2 mL of each of these solutions simultaneously to the flask through the condenser, using two separate Pasteur pipettes. When the additions are complete, heat the mixture under reflux for a further 30 minutes. During this period, prepare a solution of the sodium hydroxide (0.5 g) in 25 mL water. Allow the brown reaction mixture to cool to room temperature, and add the sodium hydroxide solution. Transfer the mixture to a 100 mL separatory funnel, and extract the product with three portions of petroleum ether (15 mL each). Wash the organic layer with three portions of water (15 mL each), and then dry it over magnesium sulfate. Filter off the drying agent by suction, and evaporate the filtrate on a rotary evaporator to leave an almost colourless crystalline solid. Slurry the crystals with a very small quantity of ice-cold petroleum ether, and rapidly filter them by suction through a pre-cooled filter funnel. Dry the crystals by suction for a few minutes. Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Search and write down two, other than presented in the instruction, methods of benzyne synthesis. Provide the proper citation (with DOI number) for all those reactions.
2. In the absence of other reagents benzyne forms a dimer. Write down the reaction scheme presenting formation of this compound.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of reactions with benzyne playing a role of the reagent, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

5.2B Addition of carbene to alkene under PTC conditions – synthesis of 7,7-dichlorobicyclo-[4.1.0]heptane



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References:

- ✓ C. F. Wilcox, „Experimental Organic Chemistry, A Small-Scale Approach", MacMillan Publishing Company, New York 1988

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ simple distillation
- ✓ microdistillation
- ✓ synthesis with very reactive reagents

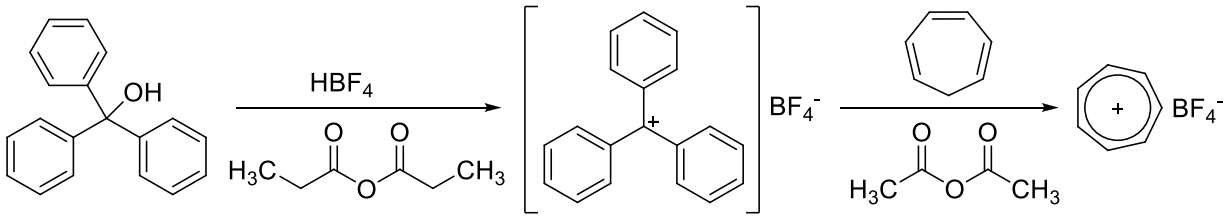
Experimental procedure:

Place 2.0 g of sodium hydroxide pellets (0.05 mole) in a 125 mL Erlenmeyer flask and add 2.0 mL of cold water. Swirl the flask to dissolve the base. Considerable heat will develop as the sodium hydroxide dissolves and the solution should be cooled in an ice-bath to bring it down to room temperature. Add 10 drops (0.4 g, 0.001 mole) of tricaprylmethylammonium chloride to the aqueous base followed by a solution of 2.0 mL (1.62 g, 0.02 mole) of cyclohexene in 2.0 mL (2.98 g, 0.025 mole) of chloroform. Swirl the solution vigorously for about 20 minutes; the idea is to form a thick emulsion. During this time the solution will become warm as the reaction proceeds. Transfer the reaction mixture to a separatory funnel with the aid of about 15 mL of water, rinse the flask with 4 mL of methylene chloride, and add the rinse to the funnel. Shake the funnel and draw off the lower organic layer into a 50 mL Erlenmeyer flask. Extract the aqueous layer remaining in the funnel with a second 4 mL portion of methylene chloride. Combine the two organic extracts and wash them with a fresh 5 mL portion of water. Dry the extract over a little anhydrous magnesium sulfate, filter the drying agent, transfer the filtrate into 50 mL Erlenmeyer flask, and evaporate the bulk of the methylene chloride on a water bath in the hood. Transfer the residue with a Pasteur pipette into a 50 mL round-bottom flask; attach a Hickmann still with a thermometer to the flask. Distill slowly and collect the distillate in the well of the still. Withdraw from the well and discard any material that boils below 100° and save the fraction that collects between 180 and 200 °C. Typical yields are in the range of 0.5–1.0 g. Record the yield of the reaction and prepare the sample for NMR.

Post-lab questions:

1. What is the source of dichlorocarbene in this reaction? Write the reaction in which this reactive species is being formed.
2. What are carbenoids? Give three examples of those compounds.

5.2C Synthesis and properties of stabilized carbocations – synthesis of triphenylmethyl fluoroborate and tropylium fluoroborate



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ crystallization and recrystallization
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ synthesis at low temperature
- ✓ multi-step synthesis
- ✓ synthesis with very reactive reagents
- ✓ degassing of solvents and reagents
- ✓ drying glassware, using heat-gun

Experimental procedure:

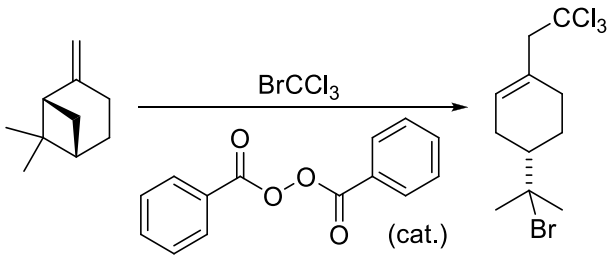
Set up a 100 mL three-neck flask containing a magnetic stirrer bar with a thermometer, nitrogen bubbler and septum. Connect the apparatus to the nitrogen source and add the triphenylmethanol (2.6 g, 10 mmol) and propanoic anhydride (25 mL) to the flask. Warm the contents to 45 °C using a water bath with stirring until all of the solid has dissolved and then cool the contents to 0 °C by partially immersing the flask in a –20 °C cooling bath. Add the fluoboric acid (60% solution, 2.0 mL, 13.7 mmol) dropwise to the stirred solution by syringe, keeping the temperature of the reaction mixture below 10 °C, and then allow the mixture to cool to 0 °C for 15 minutes. Filter off the orange precipitate on a sinter funnel with suction and wash the residue with sodium-dried diethyl ether until the washings are colourless. Dry the crystals briefly by suction and then transfer them rapidly to the vacuum dessicator. Record the yield.

Dissolve dry triphenylmethyl fluoborate (1.0 g, 3 mmol) in 25 mL ethanoic anhydride in a pre-dried 200 mL Erlenmeyer flask containing a magnetic stirrer bar and add the cycloheptatriene (0.5 mL, 0.45 g, 5 mmol) with stirring. Note any colour changes and then add 100 mL of diethyl ether and filter off the white precipitate on a sinter funnel with suction. Wash the solid on the sinter with diethyl ether and dry briefly in a vacuum dessicator. Record the yield of your material and prepare the sample for NMR.

Post-lab questions:

1. Explain the reason of high stability of the carbocations obtained in the experiment. Give examples of other stable carbocations.
2. The homologue of tropylium cation – homotropylium cation is an example of an interesting type of conjugated compounds, which are called homoaromatic. Explain the term homoaromaticity and give other examples of homoaromatic compounds.

5.2D Free radical addition to *β*-pinene – synthesis of 7-trichloromethyl-8-bromo-Δ^1-*p*-menthane



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ T. A. Kaye et al., *J. Chem. Educ.* **1976**, *53*, 60

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ synthesis with very reactive reagents

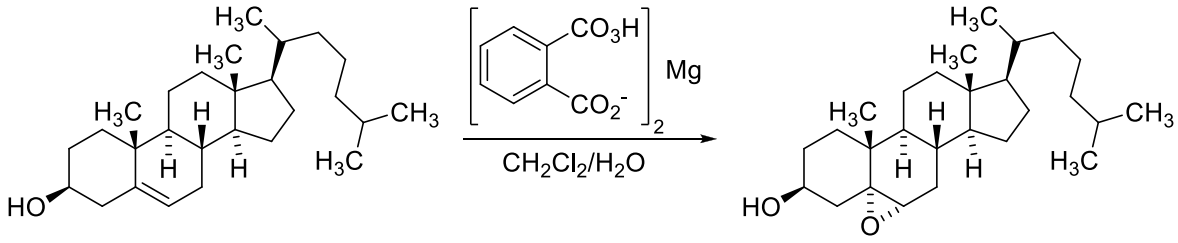
Experimental procedure:

Place the β-pinene (1.2 mL, 1.02 g, 7.5 mmol), bromotrichloromethane (0.85 mL, 8.2 mmol) and benzoyl peroxide (*ca.* 5 mg, catalytic amount) in a 100 mL three-neck flask equipped with a reflux condenser with nitrogen bubbler and nitrogen inlet. The third neck id stoppered. Add 30 mL cyclohexane, taking care to wash down all the material that may be adhering to the walls of the flask. Heat the mixture under a nitrogen atmosphere under reflux for 40 minutes. Add 5 mL of water to the mixture and remove the solvent and excess bromotrichloromethane on a rotary evaporator, heating with a hot water bath. If bumping is a problem, transfer the mixture to a large flask using a further 5 mL of water. Cool the aqueous residue in an ice bath until the oil solidifies (*ca*. 15 minutes), break up the solid with a spatula and filter it with suction. Powder the solid on the funnel and wash it with 10 mL of water followed by three 5 mL portions of ice-cold methanol. Dry the residue with suction, and record the yield of the crude product. The material is fairly pure but, if time permits, it may be recrystallized from methanol. However take care not to expose the material to prolonged heating as this causes decomposition. Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Write down the sequence of radical reactions that result in the formation of the product.
2. Explain which structural features of benzoyl peroxide make it a convenient source of radicals.

5.2E Peracid epoxidation of alkene – synthesis of 3β-hydroxy-5α,6α-epoxycholestane from cholesterol



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ P. Brougham et al., *Synthesis* **1987**, 1015
- ✓ Encyclopedia of Reagents for Organic Synthesis EROS, 3663

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ thin layer chromatography TLC
- ✓ synthesis with very reactive reagents

Experimental procedure:

Place the cholesterol (1.93 g, 5 mmol), 20 mL dichloromethane and a magnetic stirrer bar in a 100 mL two-neck flask equipped with a reflux condenser and an addition funnel. Charge the addition funnel with a solution of the magnesium monoperoxyphthalate (90%, 3.0 g, 5.5 mmol) in 15 mL water and add this dropwise to the **vigorously** stirred reaction at reflux (about 10 minutes). When the addition is complete, maintain stirring and heating for a further 90 minutes, maintaining the pH in the range 4.5–5.0 by adding 5% sodium hydroxide solution dropwise as necessary down the condenser. After this period, allow the mixture to cool and destroy the excess peracid by adding sodium sulfite solution a few drops at a time until the mixture gives a negative starch-iodide test. Transfer the mixture to a separatory funnel, and wash the organic solution with two portions of sodium bicarbonate solution (10 mL each), two portions of water (10 mL each), and finally 5 mL saturated sodium chloride solution. Emulsions frequently form during the extraction. This is best dealt with as follows: add a little more dichloromethane and sodium chloride solution to the emulsion. If, after shaking, the layers do not separates add more sodium chloride solution. Dry the solution over magnesium sulfate. Filter off the drying agent by suction, and evaporate the filtrate to dryness on a rotary evaporator. Recrystallize the residue from 90% aqueous acetone. Record the yield of your product and prepare the sample for NMR.

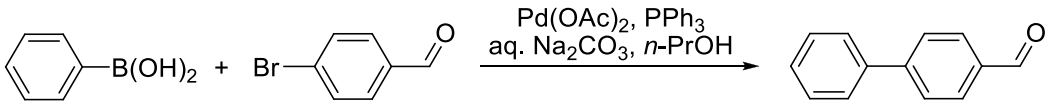
Run a TLC of your product before and after recrystallization; use a silica gel TLC plate and diethyl ether–petroleum ether (1:1) as the eluting solvent. Run the product against a sample of cholesterol to determine if all the starting material has been consumed.

Post-lab questions:

1. Write the mechanism of alkene epoxidation with the use of peracids. What side products are formed in this reaction?
2. What are advantages of magnesium monoperoxyphthalate (MMPP) in a comparison with *m*-chloroperoxybenzoic acid (MCPBA)?

Selective formation of carbon–carbon bonds

6A Suzuki cross-coupling – synthesis of unsymmetrical biaryls



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ C. S. Callam et al., *J. Chem. Educ.* **2001**, *78*, 947

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ crystallization and recrystallization
- ✓ thin layer chromatography TLC
- ✓ synthesis under moisture- and air-free condtions
- ✓ degassing of solvents and reagents
- ✓ using Schlenk line
- ✓ drying glassware, using heat-gun
- ✓ working with pyrophoric liquids
- ✓ working with compressed gases

Experimental procedure:

Place 4-bromobenzaldehyde (1.00 g, 5.4 mmol) and phenylboronic acid (0.692 g, 5.68 mmol) in a 100 mL three-neck round-bottom flask equipped with a magnetic stirrer bar, a reflux condenser sealed with a septum and a balloon, and an adapter connected with a vacuum line. Seal the remaining side neck with a septum. After a discussion with the Instructor open the nitrogen valve and start the vacuum pump. Open the appropriate stopcock on the vacuum line and evacuate the flask. Ater ca. 3 minutes change the position of the stopcock and fill the flask with nitrogen. Repeat the *evacuation–gas filling* cycle three times. The flask should be filled with nitrogen in the end.

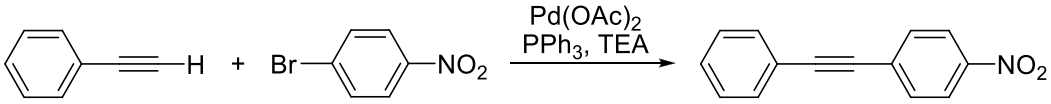
Prepare the degassed *n*-propanol. Place *n*-propanol (10 mL) in a small Schlenk flask and seal the neck with a septum. Mount the flask to the lab stand and connect its side tube with a vacuum line. Close the stopcock in the Schlenk flask and make sure that the appropriate stopcock on the vacuum line is also closed. Place the Schlenk flask in a Dewar flask filled with liquid nitrogen and allow the alcohol to freeze (ca. 5 minutes). Change the position of the stopcock on the vacuum line and remove the air from the tubing. Open the stopcock in the Schlenk flask and evacuate the flask for 3–5 minutes. Close the stopcock in the Schlenk flask and gently remove it from Dewar flask. Slowly put the Schlenk flask into a beaker with water. Protect the apparatus with a protecting screen and lower the sash of the fumehood. When the alcohol melts the bubbles of the air show up. When alcohol in the flask will reach room temperature remove the beaker with water and clean the Schlenk flask with a paper towel. Place the flask in the Dewar flask again and allow it to freeze (ca. 5 minutes). Change the position of the stopcock in the vacuum line and remove the air from the tubing. Open the stopcock in the Schlenk flask and evacuate it (ca. 3–5 minutes). Close the stopcock in the Schlenk line and remove the flask from the Dewar flask. Slowly place the Schlenk flask in a beaker with water. Protect the apparatus with a protecting screen and lower the sash of the fumehood. Repeat the freeze–pump–thaw cycle three times. In the last cycle the Schlenk flask should be filled with nitrogen. Transfer the degassed solvent into the flask with reagents. In order to do it place a cannula in the flask (break the septum). Place the opposite end of the cannula in the Schlenk flask with *n*-propanol (cannula should reach the bottom of the flask). Fill the Schlenk flask with nitrogen, and close the nitrogen flow in the flask with reagents. Place the nitrogen-outlet needle in the septum.

Transfer the solvent from the Schlenk flask into the flask with reagents regulating the pressure of nitrogen. Once the solvent is transferred remove the nitrogen-outlet needle, fill the flask with nitrogen and remove the cannula.
Stir the mixture for 15 minutes, until complete dissolution. With nitrogen flowing, remove the septum and add fast palladium(II) acetate (3.6 mg, 16.0 µmol), triphenylphosphine (12.8 mg, 48.8 µmol) and re-seal the neck with the septum.
In two 10 mL round-bottom flasks place 2 M solution of sodium carbonate (5 mL) and water (5 mL). Degass the liquids purging them with nitrogen for 15 minutes. Using 5 mL syringes trasfer 3.25 mL of sodium carbonate solution and 2 mL of water into the flask with reagents. Heat the mixture under reflux for 1 hour. Monitor the progress of the reaction with TLC (use hexanes–ethyl acetate 4:1 as the eluant).
After this time cool the reaction mixture to room temperature, add water (7 mL) and stir the reagents open to the air for 5 minutes. Dilute the mixture with ethyl acetate (10 mL) and transfer it to a separatory funnel. Collect the organic phase, re-extract the water phase with ethyl acetate (10 mL).
Combine organic extracts and place them in a separatory funnel. Wash the solution with 5% aqueous solution of sodium carbonate (two 10 mL portions) and brine (two 10 mL portions). Transfer the organic phase into a 150 mL conical flask and add active carbon (0.5 g) and sodium sulfate (1 g). Stir the mixture fo 10 minutes. Filter the suspension with suction through a 1 cm layer of Celite. Wash the celite several times with ethyl acetate. Evaporate the solvent using rotary evaporator. Transfer the solid product to a round-bottom flask and add *n*-hexane (5 mL). Heat the solution to reflux and add methanol (2 mL). When the solid will dissolve remove the heating and allow the mixture to cool to room temperature. Filter off the crystals with suction and wash them on the Schott funnel with cold hexane. Dry the product on the Schott funnel. Record the yield of your product and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction. Briefly describe all steps.
2. Give at least three examples of other, than boronic acids, types of organoboronic compounds that might be used in Suzuki couplings. Which of them are commercially available? What are their advantages and disadvantages?
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of Suzuki coupling, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

6B Sonogashira coupling – synthesis of 1-nitro-4-(phenylethynyl)benzene



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- ✓ http://www.ch.ic.ac.uk/local/organic/0405Expt4.pdf
- ✓ J. P. Collman, L. S. Hegedus, J. R. Norton, R. G. Finke, "Principles and Applications of Organotransition Metal Chemistry", University Science Books/UOP 1987
- ✓ R. F. Heck, "Palladium Reagents in Organic Synthesis", Academic Press 1985
- ✓ B. M. Trost, T. R. Verhoeven in "Comprehensive Organometallic Chemistry", Pergamon Press 1982, vol. 8, 799-938
- ✓ T. Hayashi et al., Tetrahedron Lett. 1979, 1871
- ✓ J. K. Stille, *Angew. Chem. Int. Ed.* **1986**, *25*, 508
- ✓ N. Miyaura et al., *J. Am. Chem. Soc.* **1985**, *107*, 972
- ✓ G. Wu et al., *J. Org. Chem.* **1991**, *56*, 6506

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ sublimation
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ degassing of solvents and reagents
- ✓ using Schlenk line
- ✓ drying glassware, using heat-gun
- ✓ working with pyrophoric liquids
- ✓ working with compressed gases

Experimental procedure:

Place 4-bromonitrobenzene (2.02 g 10 mmol), phenylethyne (1.53 g, 1.65 mL, 1.5 eq.), palladium (II) acetate (2.8 mg, 0.12 mol%), triphenylphosphine (6.6mg, 0.25 mol%) and triethylamine (20 mL) in a 100 mL three-neck flask equipped with a magnetic stirrer bar, a reflux condenser sealed with a septum with a balloon, a magnetic stirrer bar and an adapter connected to the vacuum line. Seal the third neck with a septum.

After a discussion with the Instructor open the nitrogen valve and start the vacuum pump. Open the appropriate stopcock on the vacuum line and evacuate the flask. Ater ca. 3 minutes change the position of the stopcock and fill the flask with nitrogen. Repeat the *evacuation–gas filling* cycle three times. The flask should be filled with nitrogen in the end.

In the other, 50 mL round-bottom flask place distilled triethylamine (20 mL) and seal the flask with a septum. Break the septum with two needles – one will be an inlet, the other one an outlet of nitrogen. Fill the flask with nitrogen from the vacuum line. Purge the amine with gas for 15 minutes. After this time transfer the amine into the flask with reagents using a cannula. In order to do it place a cannula in the flask with reagents (break the septum). Place the opposite end of the cannula in the flask with triethylamine (cannula should reach the bottom of the flask). Fill the flask with nitrogen, and close the nitrogen flow in the flask with reagents. Place the nitrogen-outlet needle in the septum. Transfer the amine regulating the pressure of nitrogen. Once the triethylamine is transferred remove the nitrogen-outlet needle, fill the flask with inert gas and remove the cannula.

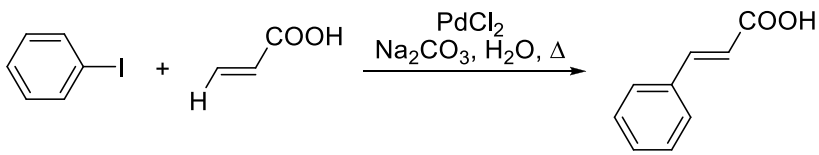
Place the flask in an oil bath and heat it under nitrogen at 100 °C for 75 minutes. The exotermic reaction will make the boiling vigorous but its intensity will be decreasing with time. After 75 minutes of heating remove the flask from the oil bath and cool allow the solution to cool to room temperature. Open the solution to the air and add 2 M solution of hydrochloric acid (42 mL). Filter off the solid with suction and dry it for a week in a vacuum dessicator. Purify the product by vacuum sublimation (s.p. 115 °C at 2–3

mmHg). Record the yield of your product and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction, including the conversion of palladium(II) to palladium(0). Search for analogous transformations using scientific database systems (SciFinder or Google Scholar). Provide the proper citation (with DOI number) for all those reactions.
2. Many examples of Sonogashira coupling requires the presence of two catalysts based on palladium and copper. Read the discussion about possible mechanistic pathways in the review article http://pubs.acs.org/doi/abs/10.1021/cr050992x and write down the the general catalytic cycle of Sonogashira coupling co-catalyzed by copper(I). Briefly describe every step and mark the oxidation state of both metals in the cycle.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of Sonogashira coupling, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

6C Heck coupling – synthesis of cynammic acid



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ N. A. Bumagin et al., *J. Organometal. Chem.* **1995**, *486*, 259

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ microscale synthesis

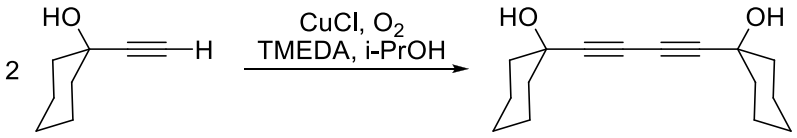
Experimental procedure:

Place acrylic acid (108 mg, 1.5 mmol) and de-ionized water (5 mL) in a 25 mL round-bottom flask equipped with a magnetic stirrer bar. While stirring, add reagents as follows: sodium carbonate (315 mg, 3.0 mmol), palladium(II) chloride (4 mg, 0.02 mmol) and iodobenzene (204 mg, 1.0 mmol). Stir the mixture vigorously for 15 minutes at room temperature and then boil it for 3 hours. Cool the solution to room temperature and acidify it with 10% hydrochloric acid. Filter off the crystals of the product with suction, and wash it with water. Dissolve the crude product in the smallest possible amount of dimethylsulfoxide and filter it through a small piece of wool. Heat the solution and crystallize the product by slow, dropwise addition of water or 10% hydrochloric acid. Cool the suspension to room temperature, filter off the product with suction and wash it with water. Dry the product in a vacuum dessicator over calcium chloride. Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction. Desribe briefly all steps.
2. Using scientific database systems (SciFinder or Google Scholar) search for three examples of Heck coupling, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

6D Glaser-Eglington-Hay coupling – synthesis of 1,1'-(buta-1,3-diyn-1,4-diyl)dicyclohexanol



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- ✓ C. F. Wilcox, „Experimental Organic Chemistry, A Small-Scale Approach", MacMillan Publishing Company, New York 1988
- ✓ K. M. Doxsee, J. E. Hutchison, "Green Organic Chemistry – Strategies, Tools, and Laboratory Experiments", Thompson Brooks/Cole 2004
- ✓ http://greenchem.uoregon.edu/Pages/Overview.php?WhereFrom=ResultsAll&ID=67

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ crystallization and recrystallization
- ✓ thin layer chromatography TLC
- ✓ working with compressed gases

Experimental procedure:

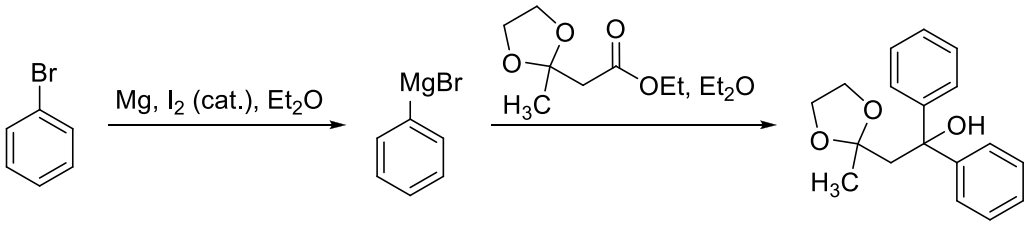
To a 100 mL round-bottom two-neck flask containing a magnetic stirrer bar, add 30 mL of 2-propanol, 100 mg of cuprous chloride, and 20 drops of tetramethylethylenediamine. Stir with a magnetic stir bar.
Seal the side neck of the flask with a septum and attach a ballon with air through a needle. Add 2 g of 1-ethynylcyclohexanol to the reaction flask, then heat the reaction to a gentle reflux. After about 30 minutes, spot a sample of the reaction mixture on a silica gel TLC plate. Spot the starting material in a separate lane on the same plate for comparison. Elute with a 70:30 mixture of hexanes/ethyl acetate, then use both ultraviolet light and iodine staining to visualize your TLC plate. If your reaction mixture still contains starting material, continue to heat the reaction at reflux until your TLC analysis shows that the reaction is complete. When the reaction is complete, evaporate the 2-propanol on a rotary evaporator. Ensure that all the 2-propanol has been removed – gentle warming will help to drive off the last traces. Add 20 mL of water containing 1 mL of 12 M hydrochloric acid to the material remaining in the flask. Collect the solid by vacuum filtration and pull air through it until it is dry.
If your crude product is still blue or green, add 20 mL of water containing 1 mL of 12 M hydrochloric acid to the material remaining in the flask. Collect the solid by vacuum filtration and pull air through it until it is dry.
If the product is brown or black in color, decolorize it according to the following procedure:
dissolve the crude product in about 20 mL of ethyl acetate and add approximately 0.25 g of decolorizing carbon. Heat the mixture gently for about 1 minute, then remove the carbon by filtration. Evaporate some of the solvent on a rotary evaporator. It should not be necessary to remove all of the solvent in order to cause the white crystalline product to separate.
If the product is white or off-white, go directly to recrystallization procedure.
Recrystallize the crude product by dissolving it in less than 20 mL of hot ethyl acetate, then allowing the solution to cool to room temperature. Collect the product by vacuum filtration and pull air through it until it is dry (if time allows, cool the solution in an ice bath for 10 minutes or so before isolating the product). Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction. Briefly desribe all steps.
2. Name of the reaction in this experiment is a generalization. In reality Glaser coupling, Hay coupling and Eglington coupling are simillar but not identical reactions. Describe differences between all those three reactions and compare them with Cadiot-Chodkiewicz coupling.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of acetylene coupling reactions, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions.

Organometallic and organophosphorus reagents in synthesis

7A Grignard reagents – synthesis of phenylmagnesium bromide and its reaction with ethyl 3-oxobutanoate ethylene ketal



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ D. R. Paulson et al., *J. Chem. Educ.* **1973**, *50*, 216

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ reactive drying agents – safe using and decomposition
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ crystallization and recrystallization
- ✓ synthesis under moisture- and air-free condtions
- ✓ multi-step synthesis
- ✓ synthesis with very reactive reagents
- ✓ degassing of solvents and reagents
- ✓ using Schlenk line
- ✓ drying glassware, using heat-gun
- ✓ working with pyrophoric liquids

Experimental procedure:

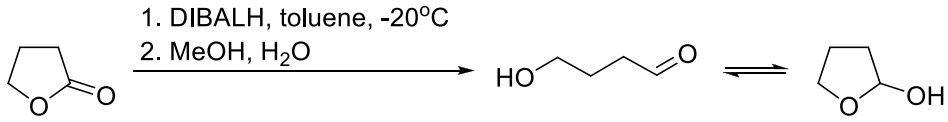
Set up a 100 mL round-bottom flask with an addition funnel, a magnetic stirrer bar and a reflux condenser carrying a calcium chloride guard tube. Add the magnesium turnings (1.34 g, 55 mmol), 10 mL dry diethyl ether and crystal of iodine to the flask. Place 10 mL dry diethyl ether and the bromobenzene (1.34 g, 55 mmol) in the addition funnel, and add a few drops of this solution to the magnesium. Start the stirrer, and wait until the formation of the Grignard reagent starts. Add the remaining bromobenzene solution diluted with an extra 20 mL diethyl ether at such a rate as to maintain gentle reflux. After the addition is complete, reflux the mixture with stirring on a hot water bath for about 10 minutes. Cool the flask in an ice bath, and then add a solution of the ethyl 3-oxobutanoate ketal (4.35 g, 25 mmol) in 10 mL dry diethyl ether dropwise. After the addition is complete, stir the mixture for a further 30 minutes at room temperature, and then add 20 mL ice–water to the flask. When the ice has melted, add further 10 mL diethyl ether, and stir the mixture until the gummy solid dissolves. Transfer the mixture to a separatory funnel, and separate the layers. Extract the aqueous layer with 10 mL diethyl ether, combine the ether layers, wash them with 10 mL water, and dry them over magnesium sulfate. Filter off the drying agent by suction, and evaporate the filtrate on a rotary evaporator to leave yellow-orange oil, which crystallizes, on cooling. Recrystallize the crude product from diethyl ether. Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction. Desribe briefly all steps.

2. Is the structure of Grignard reagents in the solution state as simple as it is suggested by their structural formula? Explain the term “Schlenk equilibrium”
3. There is a transformation similar to Grignard reaction, which is called Barbier reaction. What is this reaction? Show similarities and differences between Grignard and Barbier reactions.

7B Diisobutylaluminium hydride (DIBAL-H) – reduction of butyrolactone and estimation by NMR of the relative proportions of 4-hydroxybutanal and its cyclic isomer



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ Encyclopedia of Reagents for Organic Synthesis, EROS, 1908

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ bulb-to-bulb distillation
- ✓ using Kugelrohr
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ synthesis at low temperature
- ✓ synthesis with very reactive reagents
- ✓ degassing of solvents and reagents
- ✓ using Schlenk line
- ✓ drying glassware, using heat-gun
- ✓ working with pyrophoric liquids

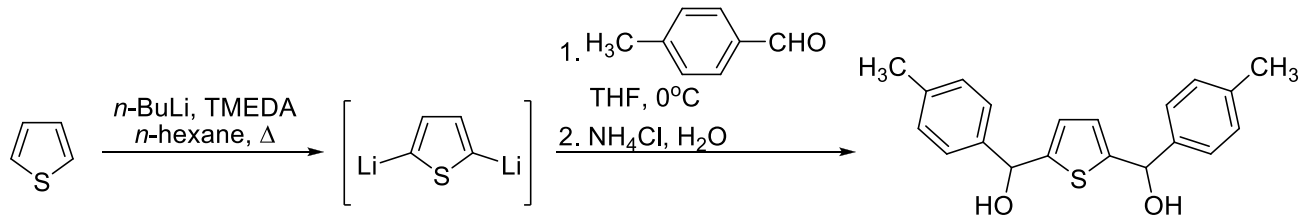
Experimental procedure:
All apparatus must be thoroughly dried in a hot (>120 °C) oven before use.

Weigh out the γ-butyrolactone (2.15 g, 25 mmol) in a pre-dried 25 mL Erlenmeyer flask, dissolve it in 15 mL of anhydrous toluene and rapidly transfer it to a dry 100 mL three-neck reaction flask containing a magnetic stirrer bar and fitted with a septum, a nitrogen bubbler and –100 to +30 °C thermometer. Seal the remaining neck with a septum. Rinse the Erlenmeyer flask with a further 15 mL of dry toluene and transfer these washings to the flask as well. Place the reaction flask in a solid CO_2–ethylene glycol cooling bath and stir the solution until the thermometer registers ca. –15 °C.
Mount the bottle with diisobutylaluminium hydride to the lab stand. Insert the needle connected through the tubing to the vacuum line into the bottle and open the nitrogen valve. Wash the 25 mL syringe with nitrogen gas and insert the needle into the bottle with DIBALH. Collect the solution of reducing agent from the bottle (18.4 mL, 27.5 mmol, 1.1 equiv., 1.5 M toluene solution). Be careful collecting the reagent – **it might catch fire if treated not carefully**. Place the needle above the surface of the solution in the bottle and collect nitrogen gas. Remove the needle with the reagent from the bottle according to the Instructor's suggestion. You should apply this procedure every time when working with water- and air-sensitive reagents.
Add the diisobutylaluminium hydride dropwise by syringe to the stirred mixture at such a rate that the temperature does not rise above –10 °C and then allow the mixture to stir for 90 minutes at –15 °C. Quench the reaction at –15 °C by adding 10 mL of methanol by syringe and allow it to warm to room temperature with stirring. Add 2 mL of water and transfer the gelatinous mixture to a 1 L round-bottom flask, rinsing several times with 5 mL portions of methanol. Remove the solvents on a rotary evaporator with gentle warming (40 °C) and triturate the solid residue with five 50 mL portions of diethyl ether, warming the flask carefully in a water bath. Dry the combined extracts over magnesium sulfate, filter and remove the solvent to yield the crude reduction product as an orange oil. Purify this material by short path distillation at reduced pressure (32–36 °C/2 mmHg, or 40–55 °C/5 mmHg, or 80–95 °C/20 mmHg). Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction. Briefly describe all steps.
2. Is the structure of DIBALH in the solution state as simple as it is suggested by its structural formula? Read the article https://www.dropbox.com/sh/0n59lyhtpc86h84/AADs1p4yyn69-Iic_JQTCYBba?dl=0 and write down what is the structure of DIBALH suggested by the authors of this paper.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of reactions with DIBALH, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions. What are the advantages of this reducing agent?

7C Organolithium reagents – synthesis of 2,5-bis(tolylhydroxymethyl)thiophene



References:

- ✓ A. Ulman, J. J. Manassen, *J. Chem. Soc.*, *Perkin Trans. 1* **1979**, 1066
- ✓ Porphyrins and Metalloporphyrins Chemistry Group's materials

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ crystallization and recrystallization
- ✓ synthesis under moisture- and air-free condtions
- ✓ using temperature controller
- ✓ multi-step synthesis
- ✓ synthesis with very reactive reagents
- ✓ degassing of solvents and reagents
- ✓ using Schlenk line
- ✓ drying glassware, using heat-gun
- ✓ working with pyrophoric liquids

Experimental procedure:
The synthesis needs to be carried-out in water- and air-free conditons.

Place dry *n*-hexane (200 mL), N,N,N',N'-tetramethylethylenediamine (TMEDA, 19.0 mL, 14.5 g, 0.13 mol) and thiophene (4 mL, 4.2 g, 0.05 mol) in a 500 mL three-neck flask equipped with a magnetic stirrer bar and a reflux condenser with a gas adapter. Seal the side necks of the flask with septa. Insert the long needle connected to the vacuum line through one of the necks and degas the solution purging it for 15 minutes with nitrogen.
Mount the bottle with *n*-BuLi to the lab stand. Insert the needle connected through the tubing to the vacuum line into the bottle and open the nitrogen valve. Wash the 25 mL syringe with nitrogen gas and insert the needle into the bottle. Collect the reagent from the bottle (50 mL, 0.13 mol, 2.5 M solution in *n*-hexane). Be careful collecting the reagent – **it might catch fire if treated not carefully**. Place the needle above the surface of the solution in the bottle and collect nitrogen gas. Remove the needle with the reagent from the bottle according to the Instructor's suggestion. You should follow this procedure every time when working with water- and air-sensitive reagents.
Add dropwise the solution of DIBALH to the degassed mixture in the flask. Heat the solution under nitrogen to reflux and boil it for 1 hour. After this time allow it to cool to room temperature (still under nitrogen).
Meanwhile, prepare the solution of the aldehyde. Place *p*-methylbenzaldehyde (7.4 mL, 7.5 g, 0.063 mol) and anhydrous tetrahydrofurane (THF, 125 mL) in a 1 L round-bottom flask equipped with a magnetic stirrer bar and a gas adapter. Place the needle connected through the tubing with the vacuum line and open the appropriate stopcock. Degas the solvent purging nitrogen through it for 15 minutes. During degassing place the flask in an ice–water bath and cool the solution to ca. 0 °C. Using a syringe with a large needle or a cannula transfer the cold solution of 2,5-dilithiothiophene into a cold solution of aldehyde. Stir the solution and allow it to warm to room temperature. Transfer the mixture to a large separatory funnel and add 1 M solution of ammonium chloride (130 mL). You should't seal the separatory funnel with a stopper. Instead swirl the solution in an open separatory funnel. After phase separation collect the

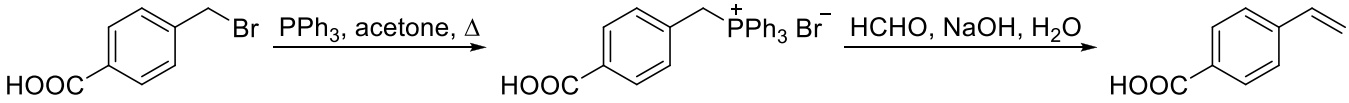
organic phase and re-extract the water phase with two portions of diethyl ether (130 mL each). Combine the organic extracts, place them in a separatory funnel and wash with water and brine (100 mL each). Dry the organic phase over magnesium sulfate and filter off the drying agent. Evaporate the solvents using a rotary evaporator.

Dissolve the obtained, orange oil in the smallest possible amount of boiling chloroform. To a boiling solution add, in small portions, *n*-hexane until the precipitate start forming. Place the flask in a cold water cooling bath and allow it to reach room temperature or put the flask into the fridge for 30 minutes or more. Collect the precipitate by vacuum filtration and wash it with *n*-hexane on a Schott funnel. Transfer the solid into a round-bottom flask and dry it using a vacuum pump. Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Write the mechanism of the reaction.
2. Is the structure of *n*-BuLi in the solution state as simple as it is suggested by its structural formula? Read the part of the article http://pubs.acs.org/doi/abs/10.1021/cr400187u describing structures of alkyllithium reagents and write down what is the structure of *n*-BuLi in different solvents.
3. Using scientific database systems (SciFinder or Google Scholar) search for three examples of reactions with *n*-BuLi, which have been published in last two years. Provide the proper citation (with DOI number) for all those reactions. What are the advantages of this reducing agent?

7D Organophosphorus reagents – 4-vinylbenzoic acid from Wittig reaction in aqueous medium



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ thin layer chromatography TLC
- ✓ multi-step synthesis

Experimental procedure:

Synthesis of 4-carboxybenzyltriphenylphosphonium bromide

Dissolve the bromomethylbenzoic acid (4.30 g, 20 mmol) and the triphenylphosphine (5.20 g, 20 mmol) in 60 mL acetone in a 100 mL round-bottom flask and reflux the mixture for 45 minutes. After this time, cool the reaction mixture and filter off the precipitated phosphonium salt with suction. Wash the solid with two portions of diethyl ether (20 mL each) on the sinter and dry it with suction. Record the yield and prepare the sample for NMR. The product is sufficiently pure to use directly in the next stage.

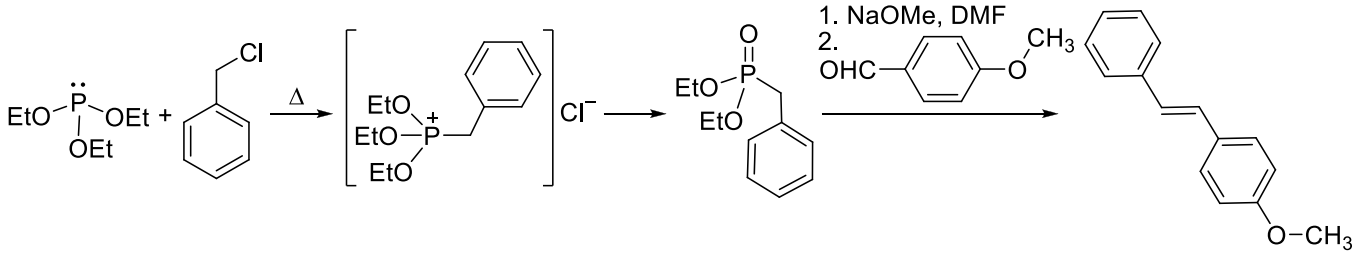
Synthesis of 4-vinylbenzoic acid

Place the 4-carboxybenzyltriphenylphosphonium bromide (3.76 g, 8 mmol), aqueous formaldehyde (32 mL, an excess) and 15 mL water in a 250 mL Erlenmeyer flask equipped with a magnetic stirrer bar. Clamp the flask, stir vigorously and add a solution of the sodium hydroxide (2.5 g) in 15 mL water over *ca.* 10 minutes. Stir the mixture for an additional 45 minutes, filter off the precipitate with suction, washing it with water. Acidify the combined filtrate and washings with concentrated hydrochloric acid and filter off the resultant precipitate of crude product with suction. Recrystallize the product from aqueous ethanol and record the yield. Prepare the sample for NMR and run a TLC of the product (silica gel, dichloromethane–ethyl acetate(1:1)) and compare its R_f with that of the starting material.

Post-lab questions:

1. What is ylide? Give three examples of ylides other than phosphorous ylide.
2. What would be the geometry of a double bond (cis-trans?) in the product if in the reaction the formaldehyde would be replaced with other aldehyde? Explain.

7E Organophosphorus reagents – *p*-methoxystilbene from Horner-Wadswarth-Emmons reaction



References:

- ✓ C. F. Wilcox, „Experimental Organic Chemistry, A Small-Scale Approach", MacMillan Publishing Company, New York 1988

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ running a reaction for a long time
- ✓ using temperature controller
- ✓ multi-step synthesis

Experimental procedure:

Avoid contact of phosphorous compounds with the skin. Wash off any spilled material thoroughly with soap and water.

Synthesis of diethyl benzylphosphonate

In a 25 mL round-bottom flask place 1.8 mL (1.66g, 0.01 mol) of triethyl phosphite and 1.2 mL (1.26 g, 0.01 mol) of benzyl chloride. Add a boiling chip, attach a condenser, and heat the mixture gently for 1 hour. When the temperature reaches 130–140 °C, evolution of ethyl chloride begins. The internal temperature continues to rise and attains about 190 °C by the end of the hour. Allow the product to cool, remove the condenser, and add 2 mL of dimethylformamide with swirling to dissolve the phosphonate ester. Record the yield and prepare the sample for NMR.

Synthesis of p-methoxystilbene

To the cooled phosphonate ester solution prepared above, add 0.56 g (0.0104 mol) of fresh sodium methoxide. Handle sodium methoxide carefully. Any material spilled on the hands should be washed off promptly with a large quantity of water.

Swirl the mixture, and add drop by drop a solution of 1.2 mL (1.36 g, 0.01 mol) of *p*-methoxybenzaldehyde in 8 mL of dimethylformamide with intermittent cooling in an ice bath so that the temperature of the reaction mixture is maintained between 30 and 40 °C. Allow the reaction mixture to stand overnight or longer.

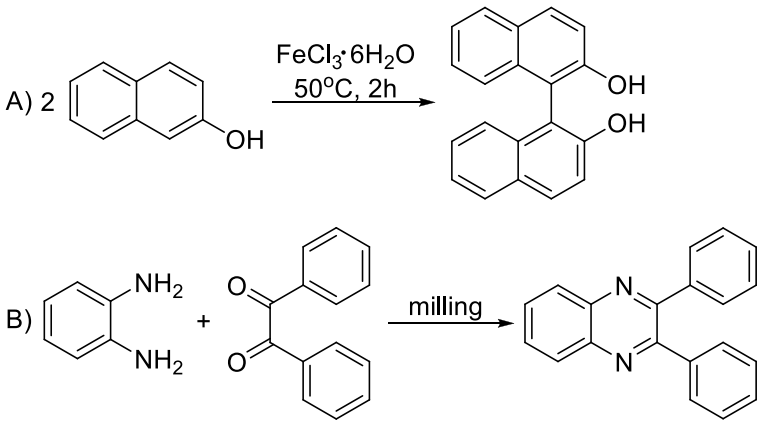
Pour the reaction mixture into about 10 mL of water, while stirring it and collect the product on a suction filter. After washing thoroughly with water, recrystallize the product from ethanol. Record the yield and prepare the sample for NMR.

Post-lab questions:

1. What is ylide? Give three examples of ylides other than phosphorous ylide.
2. What is the name of the reaction between benzyl chloride and triethyl phosphite? What is the mechanism of this reaction?

Various modern synthetic methods

8A Mechanochemical synthesis of racemic 1,1'-bi-2-naphthol and 2,3-diphenylquinoxaline



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ F. Toda et al., *J. Org. Chem.* **1989**, *54*, 3007
- ✓ G. Kaupp et al., *Eur. J. Org. Chem.* **2002**, 1368

Laboratory techniques:

- ✓ solid-phase synthesis
- ✓ using ball-mill
- ✓ gravity and vacuum filtration
- ✓ crystallization and recrystallization

Experimental procedure:

Synthesis of racemic 1,1'-bi-2-naphthol

Place a mixture of 2-naphthol (1 g, 7 mmol) and iron(III) trichloride hexahydrate (3.8 g, 14 mmol) in a mortar, powder it thoroughly and transfer to a test tube. Heat the tube at 50 °C for 2 hours. Cool the reagents to room temperature, mix them with a diluted hydrochloric acid and filter with suction. Wash the solid on the sinter with diluted hydrochloric acid and water and dry it. Recrystallize the crude product from ethanol. Typical yield of the reaction is 0.95 g (95%). Record the yield and prepare the sample for NMR.

Synthesis of 2,3-diphenylquinoxaline

Place a mixture of *o*-phenylenediamine (324 mg, 3 mmol) and benzil (630 mg, 3 mmol) in the ball mill and stir the reagents for 1 hour at room temperature.

Alternatively, powder the reagents in a mortar and transfer them into a beaker equipped with a magnertic stirrer bar. Stir the reagents for 1 hour.

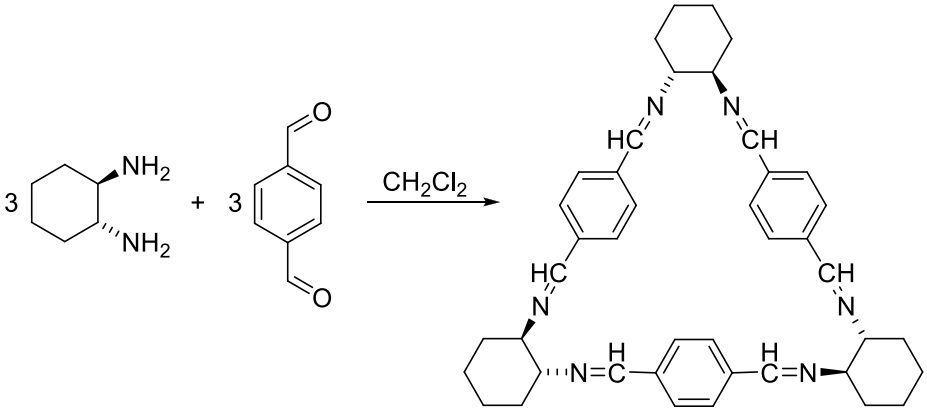
Typical yield of this reacion is 846 mg (100%).

Record the yield of the reaction and prepare the sample for NMR.

Post-lab questions:

1. The above described reactions belong to the group called „green organic reactions". Explain why. Calculate atom economy (E) for the synthesis of 2,3-diphenylquinoxaline.
2. Read the articles listed in the Refences section (*JOC* 1989, *EJOC* 2002) and explain how the authors proves that the reaction takes place in the solid state?

8B Macrocyclic compounds – synthesis of trianglimine



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ J. Gawroński et al., *J. Org. Chem.* **2000**, *65*, 5768

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ crystallization and recrystallization
- ✓ microscale synthesis
- ✓ using temperature controller
- ✓ synthesis at low temperature

Experimental procedure:

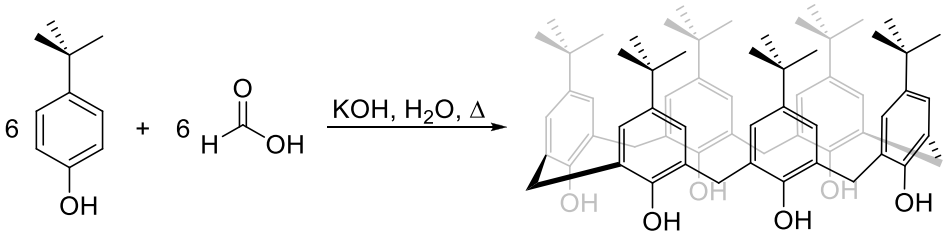
Place a solution of (*1R,2R*)-1,2-diaminocyclohexane (114 mg, 1 mmol) in dichloromethane (1 mL) in a 5 mL round-bottom flask equipped with a magnetic stirrer bar. Close the flask with a septum. Cool the solution to 0 °C in an ice–water cooling bath and add the solution of terephthalaldehyde (134 mg, 1 mmol) in dichloromethane (1.5 mL). Stir the reagents at room temperature for 2–3 hours and evaporate the solvent in a stream of nitrogen.

Recrystallize the crude product from a mixture of benzene–hexane or ethyl acetate. The compound gives several bathes of crystals with a total yield *ca.* 190 mg (90%). Record the yield and prepare the sample for NMR.

Post-lab questions:

1. Read the appropriate definitions in IUPAC glossary http://pac.iupac.org/publications/pac/pdf/1996/pdf/6812x2287.pdf and explain what the difference between a macrocycle and a macromolecule is.
2. Draw and name five examples of macrocyclic compounds other than trianglimine.
3. Read the article mentioned in the References section (*JOC* 2000) and explain why the trianglimine is the favoured product of the reaction, instead of acyclic oligomers or polymers.

8C Macrocyclic compounds – synthesis of *p*-tert-butylcalix[6]arene



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ C. D. Gutsche et al., *Org. Synth.* **1990**, *68*, 238
- ✓ V. Percec et al., *J. Org. Chem.* **2001**, *66*, 2104

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ using temperature controller

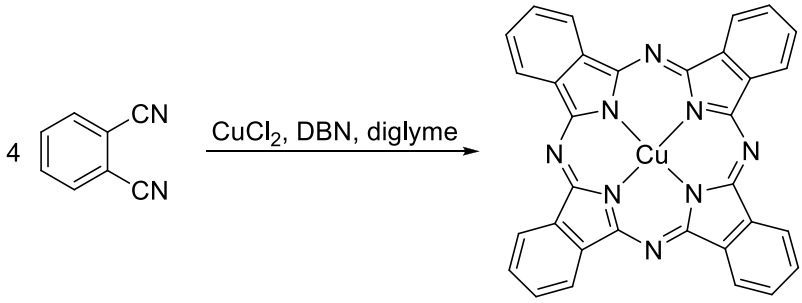
Experimental procedure:

Place 37% aqeuous solution of formaldehyde (3.0 mL, 0.1 mol) in a 50 mL three-neck round-bottom flask equipped with a magnetic stirrer bar and then add *p*-tert-buthylphenol (2.4 g, 16 mmol) and potassium hydroxide (0.36 g, 6.3 mmol). Heat the flask at 120 °C in an oil bath for 2 hours with the rapid flow of nitrogen. The reaction mixture, which is clear and colorless at the beginning, becomes light yellow after 30 minutes, a somewhat deeper yellow after 2 hours, and eventually changing to a thick slurry as the water evaporates and finally turning to a deep yellow or brown-yellow very viscous mass. During this period there is a considerable frothing, and the reaction mixture fills most of the flask before shrinking back to the original volume. After this period of time allow the reaction mixture to cool to room temperature. Dissolve the viscous solid in *p*-xylene (25 mL) and boil it for 2–3 hours. Upon cooling of the resulting solution the product crystallizes in a form of colorless crystals. Filter off the product and partially dissolve it in chloroform (60 mL). Add 1 M hydrochloric acid (20 mL) and stir it for 20 minutes. Transfer the solution to a separatory funnel and collect the organic phase. Re-extract the water phase with an additional portion of chloroform (20 mL). Combine the extracts, wash them with water and dry over anhydrous magnesium sulfate. Filter off the drying agent with suction and concentrate the filtrate to 40 mL by boiling it in an open flask, under the fume hood. To a boiling solution add hot acetone (25 mL). Cool the solution to room temperature, filter off the crystals of the product with suction and dry them on sinter. Record the yield and prepare the sample for NMR. Typical yield of this synthesis is 1.67 g (65%).

Post-lab questions:

1. Explain the origin of the term „calixarenes".
2. What structural features should characterize the synthetic precursor in order to form a calixarene instead of bakelite-type polymers?
3. The product of this synthesis – *p*-tert-buthylcalix[6]arene might be transformed into unsubstituted derivative (calix[6]arene) in the course of the reaction with aluminium trichloride. What is the mechanism of this transformation? To correctly answer the question it might be useful to search for similar reactions (de-tert-butylations) using scientific database systems (SciFinder or Google Scholar).

8D Templated synthesis – synthesis of copper(II) phthalocyanine



References:

- ✓ L. M. Harwood, C. J. Moody, J. M. Percy "Experimental Organic Chemistry, Standard and Microscale", 2nd ed., Blackwell Science 1999
- ✓ R. P. Linstead et al., *J. Chem. Soc* **1934**, 1016; 1017; 1022; 1027; 1031; 1033
- ✓ P. Sayer et al., *Acc. Chem. Res.* **1982**, *15*, 73

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization

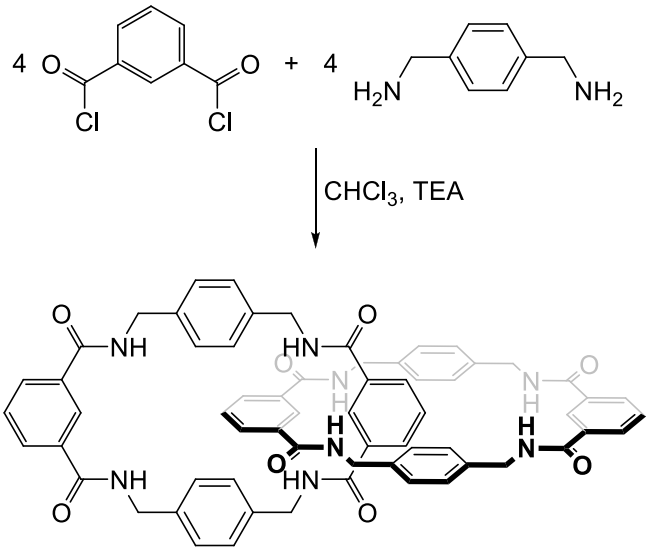
Experimental procedure:

Place phthalonitrile (3.2 g, 25 mmol), anhydrous copper(II) chloride (2.0 g, 16 mmol), 1,5-diazabicyclo[4.3.0]non-5-en (DBN, 2.5 g, 20 mmol) and bis(2-methoxyethyl ether) (diglyme, 10 mL) in a 100 mL round-bottom flask and heat until the solvent boils (160 °C). Continue to reflux for about 2 hours, then cool and pour the contents into water. Bring the water to the boil briefly in order to dissolve unreacted copper compounds, then cool, acidify to remove the base, and filter off the copper phthalocyaine. Dry the blue powder in the air. If the copper phthalcyanine is obtained as a brown solid it can be purified as follows: dissolve the finely ground product in concentrated sulfuric acid (ca. 5 mL acid per 1 g product). Leave for about 30 minutes, and then carefully pour the acid solution onto 100 g of crushed ice in a beaker. Allow the blue flocculent precipitate to coalesce, and collect it by suction filtration. Finally, wash the product thoroughly with hot water, and dry it at 100 °C.

Post-lab questions:

1. What is templated reaction? Give three other examples of templated synthesis that have been published in last two years. What whas the templation mechanism in those reactions? Provide the proper citation (with DOI number) for all those reactions.
2. Phthalocyanines, as many others oligopyrrolic macrocycles, might be modified in many ways. Go through the review article http://pubs.acs.org/doi/pdf/10.1021/cr400088w, find, draw and name phthalocyanines that differ from the basic one by the number of benzopyrrole units in the molecule.
3. What templates are most commonly used in syntheses of phthalocyanines that posess only three benzopyrrole units in their molecules?

8E Mechanically interlocked molecules – synthesis of [2]catenane



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ H. Johnston et al., *Angew. Chem. Int. Ed.* **1995**, *34*, 1209

Laboratory techniques:

- ✓ extraction and using simple drying agents
- ✓ gravity and vacuum filtration
- ✓ using solvent still heads
- ✓ Solvent Purification System (SPS)
- ✓ crystallization and recrystallization
- ✓ running a reaction for a long time
- ✓ microscale synthesis
- ✓ synthesis under moisture- and air-free condtions
- ✓ using Schlenk line
- ✓ drying glassware, using heat-gun

Experimental procedure:

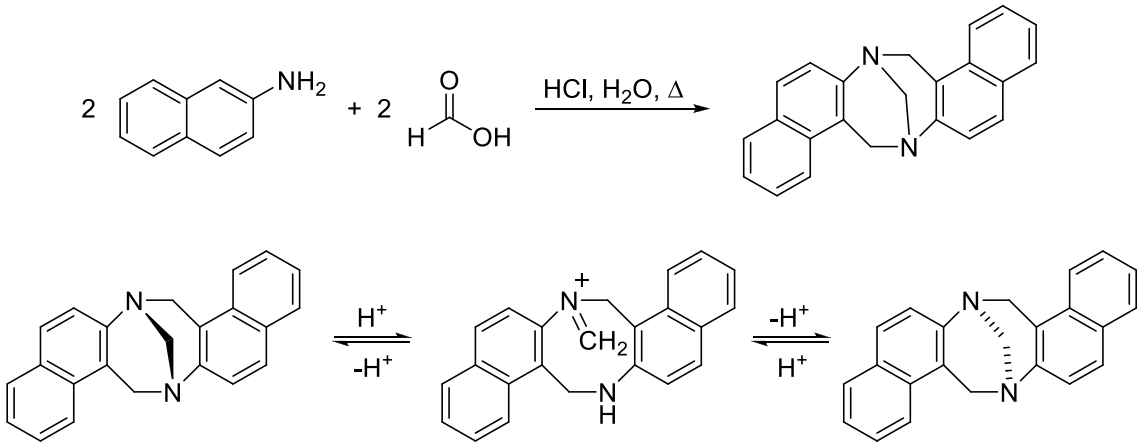
Place a solution of distilled triethylamine (0.8 mL, 9 mmol) in anhydrous chloroform (65 mL) in a 250 mL three-neck round-bottom flask equipped with a magnetic stirrer bar and two dropping funnels. Seal the third neck with a septum and insert an inlet and an outlet of nitrogen gas. Purge the solution with nitrogen for 10 minutes. Stir the solution and add simultaneously, dropwise, over 30 minutes, solutions of isophtaloyl dichloride (0.44 g, 2 mmol) in anhydrous chloroform (65 mL) and 1,3-phenylenedimethanamine (0.29 g, 2.2 mmol) in anhydrous chloroform (65 mL). Stir the reaction mixture for 12 hours. Filter off the formed precipitate with suction and transfer the filtrate to a separatory funnel. Wash the filtrate with 1 M hydrochloric acid (three 100 mL portions), 5% sodium hydroxide solution (three 100 mL portions) and water (three 100 mL portions). Dry the organic phase over magnesium sulfate, filter off the drying agent and evaporate the filtrate using a rotary evaporator. Typical yield of the reaction is 115 mg (20%).

Record the yield of the synthesis and prepare the sample for NMR.

Post-lab questions:

1. Explain the term „mechanically interlocked molecules" Give other examples of such compounds.
2. Go through the review article http://pubs.rsc.org/en/content/articlepdf/2009/cs/b819333a and give the definition of "mechanical bond".

8F Chiral compounds – synthesis and deracemization of Tröger's base controlled by optical rotation measurements



References:

- ✓ J. Gawroński, K. Gawrońska, K. Kacprzak, M. Kwit "Współczesna synteza organiczna – wybór eksperymentów", Wydawnictwo Naukowe PWN 2004
- ✓ E. Tálas et al., *Tetrahedron: Asymmetry* **1998**, *9*, 4151
- ✓ R. G. Kostyanowski et al., *Mendeleev Commun.* **2003**, 111

Laboratory techniques:

- ✓ gravity and vacuum filtration
- ✓ reflux
- ✓ crystallization and recrystallization
- ✓ determination of specific rotation
- ✓ using temperature controller

Experimental procedure:

Racemic naphthyl Tröger's base

Place 2-naphthylamine (1.45 g, 10 mmol), concentrated hydrochloric acid (1 mL) and 37% solution of formaldehyde (1.3 mL) in a 5 mL round-bottom flask equipped with a magnetic stirrer bar and a reflux condenser. Heat the mixture in an oil bath at 100 °C for 20 minutes. Separate the resulting, gummy product from the solution and boil it with methanol. Filter the methanol solution and neutralize it with aqeous ammonia. Collect the precipitate with suction, wash it with cold methanol on a sinter and dry in a vacuum dessicator. Typical yield of the reaction is 1.0 g (65%). Purify the crude, racemic product by recrystallization from methanol. Record the yield of the reaction and prepare the sample for NMR.

Deracemization

Place the prepared in the first step compound (200 mg) in a 10 mL round-bottom flask equipped with a magnetic stirrer bar and dissolve it in anhydrous methanol (4 mL). Add trifluoroacetic acid (1 mL) to the solution and stir it in an open flask under the fumehood until the solvents evaporate.

Dissolve the resulting crystals in methanol containing the amount of sodium methoxide equal the amount of trifluoroacetic acid in the reactant and leave the solution for crystallization. Filter off the crystals of the product with suction, wash them with methanol on sinter and dry. Record the yield and prepare the sample for NMR.

Prepare a solution of the product (1 g per 100 mL of solvent) in chloroform and measure optical rotation. Use this value to determine the specific rotation and enantiomeric excess (e.e.) of your product. Specific rotation for enantiomerically pure product equals $[\alpha]_D^{24}$ = +(–) 1160 (c = 0.1, $CHCl_3$).

Post-lab questions:

1. What structural features of Tröger's base make it possible to obtain this compound in the enantiomerically pure form?
2. What is deracemization (asymmetric transformation)?