Chem 135: Experimental Synthetic Chemistry

Website
https://canvas.harvard.edu/courses/1428

Textbook

Software
iNMR, NMR data processing software (instructions for download and licensure will be provided during the first two weeks of class)

Instructors
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In Brief
- rigorous preparation for research in organic chemistry
- flexible scheduling
- realistic conditions: repeat experiments without penalty until they work
- modern techniques and experiments chosen from Chem 30 course material

Prerequisites
Permission of instructors. Enrollment is limited.

Schedule
- typical workload: 15 hours per week, lab starts week 3
- mandatory: Block A; choice: two contiguous B/C/D/E blocks (fixed time each week); if necessary: additional blocks

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Lab Safety

We take lab safety very seriously. You must wear a lab coat and eye protection at all times while in the lab. You will receive extensive safety training during the course where you will be informed of our other regulations. Failure to follow regulations or obey the instructions of course staff will be considered grounds for immediate suspension or expulsion from the class.

Detailed Scheduling Regulations

1. Everyone will attend a lecture/lab briefing on Mondays (1-3 pm, Mallinckrodt 217).

2. Regular slots: during week 2, you will choose two contiguous B, C, D, or E blocks. From week 3 onwards, you will go to lab (NW 158) at this time each week. You will be assigned a supervising TF.

3. During week 2, you will attend mandatory lab safety training, receive a lab orientation, and familiarize yourself with our departmental nuclear magnetic resonance and mass spectrometry facilities.

4. Flexible slots: if you require more time, you may schedule more time on a weekly basis. Scheduling will be conducted via Google Spreadsheet. Reservations must be made the previous day and cannot be changed once made. You are expected to show up for all scheduled blocks (see attendance policy). You may not attend any lab period you are not signed up for.

5. The course staff will collect your preferences for regular slots and apportion them as fairly as possible. Students with academic or athletic commitments will receive special consideration. Flexible slots will be assigned on a first-come, first-served basis.

6. Scheduling must obey the limits set forth below:
   - B, C, or D blocks: six people in regular slots, two people in flexible slots
   - E blocks: four people in regular slots, four people in flexible slots

7. The 11 weeks of lab are apportioned by experiment: 3-5 (9-BBN); 6-7 (cross-coupling); 9-11 (pseudoephedrine); 12-14 (Dess–Martin periodinane). Lab hours will be restricted during week 8 for Spring Break. If you complete an experiment early, please speak to the course staff. You will generally be given permission to leave early or skip a scheduled lab period in this case. Conversely, you should not start the next experiment early.

8. Experiments often involve several hours of waiting. Consult the experimental manual to get a sense of the expected timeline. Your TF will also give you guidance on how to best allocate your time. Tables are provided in the Northwest building to let you do other work during these periods. Alternatively, you may ask your TF for permission to leave for a certain time period during your scheduled lab block. For example, it is customary for students to schedule time for dinner this way.
Chem 135 institutes a very strict attendance policy for two important reasons. From an educational perspective, this is a practical course in which consistent participation is essential for success. The learning curve is simply too steep and the schedule too short to accommodate any absences. Practically, the course is very expensive to run, and no-shows make it difficult to allocate resources effectively. It is typical for the schedule to be very full during some weeks, and an absence means that another student is denied the opportunity to complete work. Therefore, the following three strikes policy is in effect:

- one unexcused absence: warning with no penalty
- two unexcused absences: exclusion warning and a 5% penalty on the final course grade
- three unexcused absences: automatic exclusion

The three strikes policy comes into effect the third week of class. Attendance will be taken during each lab briefing, regular slot, and flexible slot. A student is considered to have missed a class if he or she is not present after 22 minutes past the start of the scheduled time have elapsed (7 minutes travel time + 15 minutes leeway). After this point, the student is not permitted to attend and no make-up periods will be possible.

A student who has missed two scheduled classes or lab periods runs the risk of exclusion. The Harvard College Handbook defines this extremely serious measure as the following:

“A student who neglects any course may, after written warning by the instructor, be excluded from the course by the instructor with the approval of the Administrative Board. The warning should specify the steps the student must take in order to be allowed to continue in the course...Exclusion from a course is equivalent in all respects to failing it and in and of itself makes the student’s record for the term unsatisfactory. A notation of EXLD (excluded) on the transcript indicates that the student was not permitted to continue in the course and received no credit. A student may not withdraw from a course from which he or she has been excluded. Students excluded from a course are denied any right to further course evaluation, including final and makeup examinations.”

After one missed class or lab period, the student will receive a warning but no penalty. After two missed periods, the student will receive a written warning by e-mail and a five percent penalty on his or her final course grade. (This is usually sufficient to decrease his or her final grade by one or even two fractional letter grades!) The student need only appear at all subsequent scheduled periods to avoid exclusion. If the student misses a third lab period, he or she will be subject to automatic exclusion with no exceptions.

It is understood that from time to time, illness, conflicting academic activities (e.g., a test), or athletics will preclude a student from attending. In general, the Chem 135 philosophy is not to penalize a student for such absences. Accordingly, the following policy is in effect:

- Unforeseen Events: these include illness, a death in the family, etc. Please e-mail Dr. Kwan and Dr. Scharf as soon as possible. You will be also asked to provide written documentation from Harvard University Health Services or its equivalent. There are no “make-up” lab periods; you will simply have to schedule more flexible slots as they become available. Please note that any extended absence (greater than one week) may require
more extensive discussions; unfortunately, it may make it impossible for you to continue in
the course.

- Planned Absences: these include tests, athletic practices or meets, etc. For a weekly
commitment, you are expected to try and schedule your regular slots in such a way that they
do not conflict. Athletes will have priority for Saturday blocks. We will make every effort to
accommodate you on a good faith basis. For a one-time conflict, please inform your TF at
least three days in advance. In general, failure to inform the course staff of a planned
absence at least three days in advance shall be construed to be unexcused. We reserve
the right to deny any request for an excused absence.

Grading Philosophy

Because the primary goal of this class is to prepare you for undergraduate research in organic
chemistry, its philosophy may be different from courses you have taken in the past. The focus is on
“getting it right”: you will be asked to repeat experiments without penalty until certain goals are met.
Accordingly, there is extra time in the schedule to let you troubleshoot without feeling pressured.

Academic Integrity and Collaboration

Written work: No collaboration is permitted on the problem sets or midterm. You may discuss
the lab reports with your classmates. However, in all cases, all work should be entirely your own.
You must use appropriate citation practices to acknowledge the use of any books, articles, websites,
lectures, discussions, etc., that you have consulted.

Lab work: Every student is expected to perform each experiment individually. However, in
multi-step sequences, a student may use starting materials from another student with permission.
The person receiving the material will only be granted credit for the products going forward. For
example, experiment 2 involves the synthesis of a pre-catalyst, which is then used to perform a cross-
coupling. If Jane is given the pre-catalyst and performs a successful cross-coupling, then she will
only receive credit for the cross-coupling. However, there is no penalty for goals that have been
achieved already: if Jane has already synthesized the pre-catalyst, used all of it in attempts to
perform the cross-coupling, receives more pre-catalyst, and then succeeds in the cross-coupling, she
will be awarded full credit. No one is obligated to share material. Discussions or helping classmates
in other ways like setting up apparatus is encouraged. Students should avoid disturbing the
apparatus or samples of others; if in doubt, please consult a member of the course staff for guidance.
Grading Scheme (100 points)

Note: if an experiment is successful on the first attempt, then you will receive full credit for attempts. You can receive partial credit for yield goals. Goals are also counted cumulatively. For example, if the target is 1.0 g and you make 0.3 g on the first attempt and 0.8 g on your second, you will receive full credit. However, you may not change the scale from the given procedure. Doing so will disqualify your attempt! Purity will be judged on your cleanest attempt.

Classroom Component

- Problem set 1 (2.5 points)
- Problem set 2 (2.5 points)
- Midterm (15 points)

Laboratory Component

Lab 1: 9-BBN (13 points practical)

- First attempt of complete sequence (+3)
- Second attempt of complete sequence (+1)
- Obtain >5.0 g of 9-BBN (+2)
- Obtain >6.7 g of 9-BBN (+1)
- Crystallinity of 9-BBN (+3)
- Obtain >1.3 g of pure 1-decanol (+1)
- Obtain >3.0 g of pure 1-decanol (+2)

Lab 2: Cross-Coupling (9 points practical)

- First attempt of complete sequence (+3)
- Second attempt of complete sequence (+1)
- Obtain >0.6 g of pre-catalyst (+2)
- Obtain >0.9 g of pre-catalyst (+1)
- Obtain >0.15 g of pure product (+1)
- Obtain >0.20 g of pure product (+1)

Lab 3: Pseudoephedrine (11 points practical)

- First attempt of complete sequence (+3)
- Second attempt of complete sequence (+1)
- Obtain >1.5 g of acylated auxiliary (+1)
- Obtain >1.0 g of benzylated product (+2)
- Obtain >0.15 g of methyl ketone (+3)
- Perform clean Mosher derivatization (+1)

Lab 4: Dess–Martin (11 points practical)

- First attempt of complete sequence (+2)
- Second attempt of complete sequence (+2)
- Obtain >20 g of dry, pure DMP (+2)
- Successfully used own DMP for oxidation (+2)
- Obtain >1.0 g of pure olefin (+2)
- Obtain >2.0 g of pure olefin (+1)

Record Keeping

Lab notebook (+1)
Lab report:
- Experimental procedures (+1)
- Characterization data (+2)
- Lab questions (+1)
Lab stewardship (+2)

Lab notebook (+2)
Lab report:
- Experimental procedures (+2)
- Characterization data (+3)
- Lab questions (+1)
Lab stewardship (+1)

Lab notebook (+2)
Lab report:
- Experimental procedures (+2)
- Characterization data (+4)
- Lab questions (+2)
Lab stewardship (+2)

Lab notebook (+1)
Lab report:
- Experimental procedures (+2)
- Characterization data (+2)
- Lab questions (+1)
Lab stewardship (+2)
Lab Stewardship

Chem 135 operates in a state-of-the-art, multi-million dollar facility in the Northwest Building. We share this space with many other researchers. As such, we have an important obligation to keep the lab and its apparatus in clean and good working order at all times. Every student will receive a lab stewardship grade for each experiment. Students are expected to:

- keep all the glassware you use clean
- dispose of chemical waste, including your own samples, promptly and properly
- remove samples from apparatus promptly (e.g., vacuum line, NMR instruments)
- keep work surfaces clean and tidy
- inform the teaching staff if we are running low on any reagents or if any equipment is broken
- clearly and indelibly label your samples

Lab Notebook Grading Scheme (20 points total)

- every reaction shown with starting materials, products, reagents, and conditions (3 points)
- reagent table present with compound name, number of equivalents, number of moles, density (if applicable), concentration (if applicable), and source (e.g. Aldrich) (3 points)
- procedure written in standard style with enough detail to allow another scientist to repeat the same experiment, including reaction setup, workup, and purification (4 points)
- summaries of data obtained during experiment are present: TLC drawings, key NMR/IR/MS data, color changes, times when reagents added, etc. (4 points)
- neat and legible (6 points)

Lab Report Grading Scheme

Each experiment has its own set of instructions that will include a grading scheme for the experiment and a characterization checklist. You must use your own material for characterization. In general, you should hand in a typed report to your TF. Follow standard ACS guidelines. If in doubt, please consult the Journal of Organic Chemistry Guidelines for Authors:

pubs.acs.org/paragonplus/submission/ joceah/ joceah_authguide.pdf

Points will be deducted for a failure to adhere to proper style.

Grading Accuracy

Clerical errors sometimes happen. We will provide a Google Survey for you to verify your yields with us so we can ensure you receive proper credit for your work. Please bring any errors to our attention promptly.

Lateness Policy

Problem sets, notebooks, and lab reports must be handed in promptly. For every day they are late, you will incur a 10% penalty. For example, if a lab report is out of 4 and is late by two days, you will lose 0.8 points. Weekends and holidays count. Once the solutions are posted, you automatically receive a zero. Exceptions can be made within reason, particularly if discussed in advance.
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| 1    | 1/26/2015 (M)    | 1-3pm              | Mallinckrodt (M217) | **BEGINNING OF LECTURES**  
  
  **Part 1:** Course administration  
  (Dr. E. Kwan)  
  **Part 2:** Overview of experiments, lab notebooks, calculations  
  (Dr. A. Scharf) |
| 2    | 2/2/2015 (M)     | 1-3pm              | Mallinckrodt (M217) | Laboratory Essentials (AS)                                           |
|      | 2/4/2015 (W)     | 2-4pm              | Northwest 158      | Mandatory Lab Safety Training                                       |
| 3    | 2/9/2015 (M)     | 1-3pm              | Mallinckrodt (M217) | Introduction to Structural Elucidation (EEK)                         |
|      | 2/10/2015 (T);  | 12pm-8pm (T, W, Th)| Northwest 158      | **BEGINNING OF LABORATORY RESEARCH**  
  10am-8pm (Sa)  
  9-BBN; Hydroboration |
|      | 2/11/2015 (W);  |                     |                   |                                                                      |
|      | 2/12/2015 (Th);  |                     |                   |                                                                      |
|      | 2/14/2015 (Sa)   |                     |                   |                                                                      |
| 4    | 2/16/2015 (M)    | 1-3pm              | Mallinckrodt (M217) | **PRESIDENTS’ DAY**  
  9-BBN; Hydroboration |
<p>|      | 2/17/2015 (T);   | 12pm-8pm (T, W, Th)| Northwest 158      |                                                                      |
|      | 2/18/2015 (W);   | 10am-8pm (Sa)      |                   |                                                                      |
|      | 2/19/2015 (Th);  |                     |                   |                                                                      |
|      | 2/21/2015 (Sa)   |                     |                   |                                                                      |
| 5    | 2/23/2015 (M)    | 1-3pm              | Mallinckrodt (M217) | <strong>Chemical Shifts and Coupling Constants (EEK)</strong>                      |
|      | 2/24/2015 (T);   | 12pm-8pm (T, W, Th)| Northwest 158      |                                                                      |
|      | 2/25/2015 (W);   | 10am-8pm (Sa)      |                   |                                                                      |
|      | 2/26/2015 (Th);  |                     |                   |                                                                      |
|      | 2/28/2015 (Sa)   |                     |                   |                                                                      |
| 6    | 3/2/2015 (M)     | 1-3pm              | Mallinckrodt (M217) | <strong>Solving NMR Problems (EEK)</strong>                                        |</p>
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<td>Cross-Coupling</td>
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<td>Problem Set 1 Due</td>
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<td>Mallinckrodt (M217)</td>
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(1) Preparation of 9-BBN (Soderquist)


\[
\text{cyclooctadiene} + \text{BH}_3\text{SMe}_2 \rightarrow \text{product}
\]

This experiment will involve the slow addition of 1,5-cyclooctadiene to an air-sensitive reagent (borane) in 1,2-dimethoxyethane (glyme). The excess DMS will be removed by distillation. Upon slow cooling, 9-BBN will crystallize from the hot glyme solution under inert atmosphere. The mother liquor will be removed by cannula, and a subsequent recrystallization will be performed. Care is needed to produce high quality crystals. The resulting 9-BBN will be used to prepare 1-decanol via the anti-Markovnikov hydroboration/oxidation of 1-decene.

(2) Palladium-Catalyzed Cross Couplings with a Buchwald Precatalyst


\[
\text{aryl amine} + \text{Pd(OAc)}_2 \rightarrow \text{aryl Pd complex} \rightarrow \text{precatalyst}
\]

This experiment will involve the preparation of XPhos-precatalyst, which is a palladium(II) species that is poised to undergo rapid reductive elimination to a catalytically active palladium(0) species upon treatment with weak base. This allows relatively unstable boronic acids to be coupled quickly at ambient temperatures. This will require crystallizations under inert atmosphere, the removal of solvent from a suspension, and a column chromatographic purification.
This experiment will involve the diastereoselective alkylation of a chiral amide with benzyl bromide, followed by auxiliary cleavage with methyllithium. This is a general method for the preparation of α-chiral methyl ketones. These procedures involve the handling of air-sensitive lithium reagents, crystallizations, and the assessment of diasteromeric purity by NMR spectroscopy or gas chromatography.

This experiment will involve the oxidation of 2-iodobenzoic acid to IBX. IBX will then be acetylated to form the Dess–Martin periodinane (DMP). These procedures involve the handling of potentially explosive compounds, as well as crystallizations and filtrations under inert atmosphere. The DMP will be used to oxidize a sensitive alcohol to the corresponding aldehyde. The epimerizable aldehyde will be engaged in an E-selective Horner-Wadsworth-Emmons reaction using conditions developed by Professor Myers.