Chemistry 457 & 557: Organic Synthesis,** Spring 2020

Prof. Rob Hinkle, rjhink@wm.edu, ISC 1039-A, X-1501

Office Hours: by appt. or drop by … *but it's always better to check in advance*.

Course Meetings: TR 11:00–12:20 in ISC-2280

Required Materials:
(a) Carey and Sundberg, *Advanced Organic Chemistry*, 5th Ed., **Part B.**
(b) Model Kit: If you don't have one, they're with Chem. 206 supplies. See me for other kits if you want to buy something better than what we have for Orgo I/II!
(c) PollEverywhere (Pollev.com) application for smartphone and/or tablet/PC; it is envisioned that this will be used to answer in-class questions, to submit project critiques and sometimes to track attendance for extra credit.

Add/drop deadline is Jan. 31st; the deadline to withdraw is March 23rd.

Organic Synthesis involves the selective and strategic "construction" of complex molecules. Synthesis is, in fact, "architecture" in the organic chemistry realm. Much of the class material focuses on the stereoselective adaption of well-established chemical transformations. Therefore, **very early in the semester, you should review Grignard reactions, Gilman reagents, the aldol reaction, reductive amination, oxidations, reductions, hydrogenations, hydroboration and the Sharpless asymmetric epoxidation (SAE) from *Organic* *Chemistry II***. As with my Chem. 209 class, "favorite reactions" show up in so many syntheses that you must commit them to memory!

Most people, including professors, learn the most when they have to compile some sort of document or presentation for others (e.g., grant proposal, journal article, presentation, etc.). Therefore, each of you will create a PowerPoint that outlines the synthesis of a relatively complex *chiral molecule*, compares two literature syntheses of a molecule, or describes an important stereoselective reaction in significant detail. The best examples of syntheses, ***but ones that lack enough detail for your assignment***, are contained on Prof. Jon Njardarson's *Chemistry by Design* website (in Internet Links & PDFs on Bb). You'll need to add transition state models, etc. to explain selectivities. For larger molecules, you can also work in small teams of two or three students, but each person has to clearly indicate what they contribute to the resulting file and each part should address some stereo- or regiochemical issues. All topics/articles must be approved by Prof. Hinkle **before spring break**, so start looking for molecules or reactions soon! **You cannot just repeat a synthesis that's already on Njardarson's website with minor tweaks or additions! Articles should also be from after 2010.**

Each of you must also write a critique of another person's file (not your partner's). *The goal of the critiques is to make you pay attention, learn something new, think, and provide thoughtful and constructive criticism; they are not to be used as a medium to maliciously attack someone or otherwise belittle their efforts.*

Exams: There will be two mid-term exams, each with in-class as well as take-home portions; the final exam will just be a take-home due at 4:00 On Friday May 8th (can't be changed). Take home exam portions are comprehensive and open-book, but ***must be completed independently***. You may not consult your peers for these exams. Using SciFinder or Reaxsys and submitting a literature synthesis as an answer for your exam would be an Honor Code violation and you must start from *small, readily available starting materials* like those on the "available chemicals" sheet on Bb (within "Exams"). Most, if not all reactions you will need have been presented in *Orgo I/II* or in *Synthesis* at William & Mary. You can, of course find some new reactions and the text is a great source! However, if you "use" reactions not presented in class, you MUST provide a reference for that reaction (for journal articles, list authors, journal title, year and pages; for a book, list author, title, publisher, year and page(s)). **Please give me a copy of each article for "new reactions" you propose to use**.

Grading (Pts in parenthesis):

1) In Class Midterm I (100) on Thursday 27 February; Take-Home Midterm (100) due on Friday, 06 March **by 4:00**.

**Syllabus as of 1/14/2020 and is subject to change according to weather and other circumstances.

2) In-Class exam II (100) on Thursday 26 March; Take-Home midterm (100) due on Friday 03 April **by 4:00**.
3) Take-Home Final Exam (200) due by 5:00 p.m. on Friday 08 May.
4) Homework assignments (100 = 25 pts each X 4). These problem sets will be posted to Blackboard and are *tentatively scheduled* to be due on: 1/31, 2/7, 2/14, 3/20) **by 4:00 p.m.**
5) MSWord/PPT projects (100); Send electronically **to your reviewer and me** on 4/16.
6) MSWord/PPT file critiques (30 points). Return to me and author by 4/21; Final due date for project after revisions = 4/30
7) 25 Points extra credit for "perfect attendance." Grad-school visits or a *real illness* won't count against you, but you should let me know ahead of time if you'll be absent! You'll get 15 extra points if you have only one unexplained absence and the remaining 10 points with perfect attendance.

Total course points w/out extra = 830

CHEM. 557; Anyone registered as an M.S. student will be required to write a paper on a particular reaction or synthesis of molecule (mini-review) (100 pts).

Blackboard Site: Handouts, lecture notes and other information will be posted on this course's Blackboard site.

Coverage:

This course will focus on the reactions necessary to "build" moderately complex molecules. The beginning of the course will be devoted to synthesizing and modifying particular functional groups including stereochemical control of the reactions. The second part of the course will incorporate these "tools" into larger and more complex molecules with an emphasis on stereocontrol and strategy.

The text will be heavily supplemented and will include many of the following topics with some additions/deletions during the evolution of the course.

Tentative Course Topics

I. Review of Chemistry 209/207.
- A. Basic Nomenclature
- B. Hybridization and conventions
- C. Isomers and their relationships
- D. Stereoelectronic relationships
- E. Reactions:
  1. S_N1, S_N2 and Elimination
  2. Reduction and Oxidation
  3. Reactions of Grignards, Lithium reagents and Cuprates
  5. Acyl Substitution
  6. Aldol addition and condensation
  7. Oxonium (oxocarbenium) ion formation.

II. Organometallics (Simple)
- A. Grignards
- B. Lithium Reagents
- C. Transmetallation
- D. Cuprates
- E. Chelation Control

III. Alkene Syntheses/degradation
- A. Dehydration/Elimination
- B. Wittig

C. Horner-Emmons-Wadsworth
D. Peterson Olefination
E. Ozonolysis/Oxidative Cleavage
F. Ring Closing Metathesis

IV. Diastereo- and Enantioselective Reactions
A. Alkylations and Aldols
B. Reduction w/ Organometallics
C. Corey Reduction
D. Sharpless & Jacobsen Epoxidations
E. Sharpless Dihydroxylation

V. Organometallic transformations
A. Heck Reaction
B. Suzuki Coupling
C. Negishi Coupling
D. Stille Coupling
E. C-H Activation

VI. Cyclic Ether Synthesis
A. Lewis Acid Catalysis
B. Kishi & Woerpel models for stereoselection

VII. Organocatalysis
A. Early Organocatalysis (e.g., Corey's synth. of W-M Ketone)
B. MacMillan's Catalyst.

I hope to get to the following:

C. Cinchona Alkaloids.

VIII. Photocatalysis
A. MacMillan
B. Yoon

IX. Total Syntheses (Molecular Architecture).

Class Attendance: The more times you see the reactions, the better, so in accordance with College policy, class attendance is expected. See the undergraduate catalog for more information. Please notify me of any expected absences by email. Attendance will be recorded daily via PollEverywhere (see below) or via hard-copy lists.

Student Accessibility Services: Students with disabilities must contact the Student Accessibility Services in the Dean of Students office to arrange for special accommodations or extra-time during exams.

We will use **Poll Everywhere** ("PollEv") this semester (mostly informally). With PollEv, you use your computer, tablet, or phone to answer questions, take a poll, discuss, and more. You should always bring an operable device to class each session in order to participate in the polls. I will do my best to remind you to use a laptop on a few occasions. You will need to connect your device to the W&M wireless network. If you use an Apple or Android device, please download the free Poll Everywhere app. The app isn't required, but it will make participation easier.

Instructions for logging into your PollEv account can be found on the IT website here. There is no fee associated with your student PollEv account, however you must login with your W&M email and password by selecting the "Single Sign-On" option at login. For **help** setting up your device to work on the W&M wireless network, please click here. You can participate in polls using only your account. Additionally, use of Poll Everywhere should adhere to the College of William & Mary honor code expectations"

Honor Code: All students are bound to the Honor Code. There will be zero tolerance for cheating and all incidences will be reported to the Dean of Students and the Honor Council. See the student handbook for more information on the honor code.

Valuable Resources:

(a) SciFinder Scholar software—available via on-campus IT links.
(b) Reaxys software—available via on-campus IT links (https://www.reaxys.com/reaxys/secured/search.do;jsessionid=1B50E992847AAAF47B098DD5F6BD05F4)
(c) Wuts, P. G. M. Greene's *Protective Groups in Organic Synthesis*, 5th ed. Wiley: New York, 2014. (http://onlinelibrary.wiley.com/book/10.1002/9781118905074) .
(d) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*, Wiley: New York, 1995 (***aka, EROS***) –Chem. Reading Rm.
(e) Dalko, Peter I., Enantioselective Organocatalysis: Reactions and Experimental Procedures (Swem Electronic: http://onlinelibrary.wiley.com/book/10.1002/9783527610945)
(f) Prof. David A. Evans' Website at Harvard University: http://evans.rc.fas.harvard.edu/
(g) Prof. Andrew G. Meyer's Handouts at Harvard: https://faculty.chemistry.harvard.edu/myers/pages/chem-115-handouts
(h David W. C. MacMillan's group members' presentations from Princeton: http://chemlabs.princeton.edu/macmillan/presentations/
(i) Jon Njardarson's site on synthetic sequences: http://chemistrybydesign.oia.arizona.edu/
(j) Mahrwald, R., Ed., *Modern Aldol Reactions*, Volumes I and II, Wiley-VCH: New York, 2004.
(k) Otera, J., *Modern Carbonyl Chemistry*, Wiley-VCH: New York, 2000.
(l) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH Publishers: New York, 1996.
(m) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis, II*, VCH Publishers: New York, 2003.

I've requested that books (j-m) be put on reserve on the shelf across from the elevator in the chem. reading room (open 8-5 on weekdays).