

**Chemistry 457 & 557: Organic Synthesis,\*\* Spring 2022**Prof. Rob Hinkle, [rjhink@wm.edu](mailto:rjhink@wm.edu), ISC 2043 & Ewell 136, X-7536

Office Hours: by appt. At the end of add/drop, I will set up hours so most can attend.

**Course Meetings:** TR 11:00–12:20 in ISC-2280 (small lecture room in ISC-3).

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, or to submit project critiques.

- **Friday, Feb. 4<sup>th</sup>: add/drop deadline.**
- **Monday, March 28<sup>th</sup>: withdrawal deadline.**

**Spring 2022 with COVID:** This semester, the world will enter its third year with COVID. As we experience a fifth surge of pandemic with the highly transmissible omicron variant, it is reasonable to expect significant levels of infection at W&M, especially right after we convene again ... in more particularly if members of the community disregard prudent practices. As an academic community based on faculty and students *convening*, this is scheduled to be taught in-person. However, all of us will follow W&M requirements - vaccinations and boosters, indoor masking, as well as quarantine and isolation when ill. That last part is really important: for those who have tested positive, W&M's requirements must be fulfilled before you can attend class, and, out of an abundance of caution, anyone with symptoms consistent with COVID- even if they don't have a positive test- should not come to class.

That said, we are still dealing with a pandemic, even as it evolves toward an endemic. In this setting, we need to have a way to communicate when students or the instructor cannot be in person. As soon as any of you knows that you will not be able to attend class in person (either because of having tested positive, having symptoms consistent with COVID, or other health matters), please email the instructor ([rjhink@wm.edu](mailto:rjhink@wm.edu)). In that case, the instructor will activate our mode of accommodating absences for your situation. Since this is a very challenging time with the potential for quite complicated comings and goings, we need to operate on the basis of trust; please try your very best not to miss classes for non-health related reasons; you will learn more as we work together in class.

Most fully-vaccinated people supposedly experience mild symptoms, but can still be contagious. I have structured the course so that there will be a "dropped assignment" policy in which a missed grade will be replaced with the average of the other grades for assignments with the same point values.

I will post all notes from lectures. If you do become ill and cannot come to class, I also expect to make videos available to you through Panopto. However, we will be doing some in-class work designing syntheses for target molecules. In those cases, I plan to post lectures a few days ahead of time so that you come to class prepared to work on these problems.

If I become ill and have to quarantine, I expect to work from home and post lectures during normal class times via Zoom. I will still post PDFs of notes. If I expect to only miss one class, I will likely just cancel it, but if I become ill enough that I cannot teach for more than one class, Prof. Scheerer has agreed to fill in for me as I'll make notes available to him.

However, I'm optimistic that we will be meeting in-person for the vast majority of the semester. The vaccinations have all been very effective, even though there have been some break-through cases.

**\*\*Syllabus as of 1/26/2022 and is subject to change according to weather illnesses, and other circumstances.**

**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 cyclohexane chair forms, Newman projections, 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 (This is *not* a joke)!

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 may 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 stereo- and 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 additions! Send article PDFs (not just a link) to Hinkle for approval.**

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 quizzes, and two take-home assignments (propose syntheses of complex molecules); and a final take-home assignment/exam, but double the length of the mid-semester ones. The final take-home is due at 5:00 on Tuesday May 10<sup>th</sup> (this date can’t be changed w/out notifying the DOSO with appropriate reason). Take home exam portions are comprehensive and open-book, but ***must be completed independently.*** **You may not consult your peers for these exams.** *The mere process of asking a peer lets them know your strategy and can give them ideas, so ask me!* **Using SciFinder or Reaxsys and submitting a literature synthesis (or even a big part of your synthesis) as an answer for your exam would be an Honor Code violation.**

**The object of these exercises isn’t to see how good of a literature search you can do for a related compound.** Instead, 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 might need have been shown in *Orgo I/II* or in *Synthesis* at William & Mary. You can, of course find some new reactions (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 include a PDF copy of each article for “new reactions” you propose using.**

**Assignments and dates; Grading** (Pts in parenthesis) will largely be done using Bb or Gradescope:

- 1) In Class Quiz (50) Tuesday 22 February;
- 2) Take-Home assignment I (50) due on Thurs, 10 March **by 5:00.**
- 3) Homework assignments (100 = 25 pts each X 4). These problem sets will be posted to Blackboard and are *tentatively scheduled* to be due on: 2/1, 2/8, 2/15, 3/1) by 5:00 p.m. I also plan to upload them to Gradescope.
- 4) In Class Quiz (50) Thursday 31 March;
- 5) Take-home assignment II (50) on Thursday 07 April;
- 6) MSWord/PPT projects (100); Send e-copy **to your reviewer and me** Tuesday, 4/19.
- 7) MSWord/PPT file critiques (25 points). Return to me and author(s) by 4/21;
- 8) Final due date for project after revisions = 4/28.
- 9) Take-Home Final Assignment (100) due by 5:00 p.m. on Tuesday 10 May.

**Total course points = 525**

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***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<sub>N</sub>1, S<sub>N</sub>2 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. Retrosynthetic Analysis

### IV. Alkene Syntheses/degradation

- A. Dehydration/Elimination
- B. Wittig
- C. Horner-Emmons-Wadsworth
- D. Peterson Olefination
- E. Ozonolysis/Oxidative Cleavage
- F. Ring Closing Metathesis

### V. Diastereo- and Enantioselective Reactions

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

### VI. Organometallic transformations

- A. Heck Reaction
- B. Suzuki Coupling

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- C. Negishi Coupling
- D. Stille Coupling
- E. C-H Activation
- VII. Cyclic Ether Synthesis
  - A. Lewis Acid Catalysis
  - B. Kishi & Woerpel models for stereoselection
- VIII. Organocatalysis
  - A. Early Organocatalysis (e.g., Corey's synth. of W-M Ketone)
  - B. MacMillan's Catalyst.
  - C. List's asymmetric aldols.

**I hope to get to the following:**

- VIII. Photocatalysis
  - A. MacMillan
  - B. Yoon
  - C. Others

**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.

**Student Accessibility Services:** William & Mary accommodates students with disabilities in accordance with federal laws and university policy. Any student who feels they may need an accommodation based on the impact of a learning, psychiatric, physical, or chronic health diagnosis should contact Student Accessibility Services staff at 757-221-2512 or at [sas@wm.edu](mailto:sas@wm.edu) to determine if accommodations are warranted and to obtain an official letter of accommodation. For more information, please see [www.wm.edu/sas](http://www.wm.edu/sas). *Students will be responsible for adhering to the guidelines for their particular accommodation (i.e., if the accommodation states 50% more time on exams, the student is responsible for completing their exam within the SAS approved timeframe, even if not specifically listed on the assessment).*

We will occasionally 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. I will do my best to remind you to bring an operable device to class when necessary 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 <https://www.wm.edu/offices/it/services/responsecollection/studentresponsesystem/index.php>. 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.

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**Valuable Resources:**

- (a) SciFinder Scholar software—available via on-campus IT links (<https://libraries.wm.edu/databases/scifinder-n>).
- (b) Reaxys software—available via on-campus IT links (<https://www.reaxys.com/#/institution>)
- (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. Andrew G. Meyer's Handouts at Harvard: <https://faculty.chemistry.harvard.edu/myers/pages/chem-115-handouts>
- (g) David W. C. MacMillan's group members' presentations from Princeton: <http://chemlabs.princeton.edu/macmillan/presentations/>
- (h) Jon Njardarson's site on synthetic sequences: <http://chemistrybydesign.oia.arizona.edu/>
- (i) Mahrwald, R., Ed., *Modern Aldol Reactions*, Volumes I and II, Wiley-VCH: New York, 2004.
- (j) Otera, J., *Modern Carbonyl Chemistry*, Wiley-VCH: New York, 2000.
- (k) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*, VCH Publishers: New York, 1996.
- (l) Nicolaou, K. C.; Snyder, S. A. *Classics in Total Synthesis, II*, VCH Publishers: New York, 2003.

**I will request that books (h-l) be put on reserve on the shelf across from the elevator in the chem. reading room (open 8-5 on weekdays).**

**Mental and Physical Well-Being**

William & Mary recognizes that students juggle different responsibilities and can face challenges that make learning difficult. There are many resources available at W&M to help students navigate emotional/psychological, physical/medical, material/accessibility concerns. Asking for help is a sign of courage and strength. If you or someone you know is experiencing any of these challenges, we encourage you to reach out to the following offices:

- For psychological/emotional stress, please consider reaching out to the W&M Counseling Center <https://www.wm.edu/offices/wellness/counselingcenter/>; or (757) 221-3620, 240 Gooch Dr., 2<sup>nd</sup> floor. Services are free and confidential.
- For physical/medical concerns, please consider reaching out to the W&M Health Center at <https://www.wm.edu/offices/wellness/healthcenter/>; or (757) 221-4386, 240 Gooch Drive.
- For additional support or resources, please contact the Dean of Students by submitting a Care Report at <https://www.wm.edu/offices/deanofstudents/services/caresupportservices/index.php>; or by calling 757-221-2510, or by emailing [deanofstudents@wm.edu](mailto:deanofstudents@wm.edu).
- For a list of many other resources available to students, see [Health and Wellness Resources for Students](#)

As your professor, I also ask you to reach out to me if you are facing challenges inside or outside the classroom; I will guide you to appropriate resources on campus.