CHEM 6352 Organic Reactions & Synthesis
Fall 2019

Jeremy A. May
Office: 5011 SERC
Office hours: W 11 am–12 pm, Th 4:30-5:30 pm, or by appointment (email me)
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Lectures: 162 Fleming
Tuesdays and Thursdays 5:30–7:00pm. August 20–November 26, 2019.
Homework Session Saturdays 2:30 pm to 5:30 pm in Fleming 154/160/162.
No class November 28–30, 2019 (Thanksgiving recess); Oct. 31st is last day to withdraw

Handouts are available as PDFs on the class Blackboard site

Optional Texts (on reserve at MD Anderson Library)
Zweifel, G.; Nantz, M. "Modern Organic Synthesis: An Introduction"
Smith, M; March, J. "Advanced Organic Chemistry"
Corey, E. J.; Cheng, X.-M. "The Logic of Chemical Synthesis"
Warren, S. "Designing Organic Syntheses: A Programmed Introduction to the Synthon Approach"
Kürti, L.; Czakó, B. "Strategic Applications of Named Reactions in Organic Synthesis"
Grossman, R. "The Art of Writing Reasonable Organic Reaction Mechanisms" (Ch. 1–2)

Model Sets:
Students are *strongly* encouraged to obtain *at least* one model set. Recommended HGS biochemistry molecular model sets are available at Research Stores in the Fleming basement.

Other relevant texts and references:
Greene, T. W.; Wuts, P.G.M. "Protective Groups in Organic Synthesis"
Nicolaou, K.C.; Sorensen, E. "Classics in Total Synthesis"
Nicolaou, K.C.; Snyder, S. "Classics in Total Synthesis II"
Larock, R. C. "Comprehensive Organic Transformations"
Hartwig, J. "Organotransition Metal Chemistry: From Bonding to Catalysis"
Tsuji, J. "Palladium Reagents and Catalysts"
Hegedus, L. "Transition Metals in the Synthesis of Complex Organic Molecules"

Problem Sets:
Problem Sets will be distributed on Tuesdays (or before) and are due by the next Saturday at the Homework Session. Answers will be discussed at this weekly problem session starting at 2:30 p.m. in 154/160/162 Fleming. Though working in groups is permitted, each student should personally work out and understand the solution to each problem, as students will be expected to write out and discuss their answers to the problems at the board–***EVERYONE*** will present problems. This homework session will be the only opportunity to see the solutions to the problem sets. After writing down answers, the work will be turned in and a grade will be given based on completing the assigned work and on giving presentation at the board (i.e., a participation grade). A score of 0 = no work done, 1 = partial work done, and 2 = all work done. Homework is worth 15% of the grade along with Literature synopses. A problem set takes a significant amount of time. If you leave it until Friday you will not finish in time.

Current Literature:
The field of chemical synthesis is highly dynamic and changes on a daily basis. In order to keep pace with new developments, part of the requirement of this course will be to stay abreast of new and particularly relevant publications in the primary synthetic literature. Students will be required to read this literature, distill out pertinent developments, and report them back to the class. This important exercise will take place during the Saturday problem session. Members of the class will draw a playing card, and during the session the winning two (or more) students will present a synopsis of a relevant communication of an organic reaction or synthesis from the latest issue of *J. Am. Chem. Soc.*, *Angew. Chem. Int. Ed., Org. Lett.*, *Nature Chem.*, *Chem Sci., Cell Chem, Chem. Commun., Synlett*, *J. Org. Chem.*, or *Tetrahedron Lett.* Be sure to include the corresponding author, institution affiliation, and proper reference in your description. This serves not only the purpose of keeping the class current, but will help students to launch their own database of relevant chemical literature. (See "Reading the Chemical Literature")

Name Reactions:
There are a number of key reactions in organic synthetic chemistry that have become identified by a name (either a person or a specific transformation) for convenient discussion. Knowledge of these reactions is fundamental to your success in this class and future career in organic chemistry. You should learn each of the reactions listed by the date indicated on the name reactions handout at the end of this syllabus. They will appear on exams and problem sets in a timely fashion.

Synthesis Proposal (Graduate Students Only)
Around the time of the first midterm a short list of molecules will be distributed. Each student is expected to choose a target and then evaluate its challenges, produce a retrosynthetic analysis, and propose a synthesis for that target. The proposal will be evaluated on feasibility, efficiency, and innovation. While the final proposal will be due ***5 pm*** on ***Thursday, Dec. 12th***, work toward the proposal must be demonstrated earlier (see Class Schedule; TM = target molecule).

Exams:
There will be two midterm exams and a comprehensive final, each worth 25% of your grade.

Exam Dates:
Midterm #1: Friday, Oct. 4^{h}, 6:00 pm to 9:00 pm.
Midterm #2: Friday, Nov 1st, 6:00 pm to 9:00 pm
Final Exam: Tuesday, December 10, 5-9 pm

Course Grade:
The course grade will be based on midterm exams (50%), problem sets, literature presentation, and discussion (15%), proposed synthesis (10%), and the final exam (25%).

Natural Product Synthesis and other Target Oriented Synthesis:
Synthesis problems will appear on the homeworks and in the tests. For an interactive guide to learn how to approach and plan a synthesis, see the Warren book on reserve. Several lectures will have a portion devoted to an iconic synthesis of a natural product. The material from this part of lecture will also be required learning and will bear on homework and test problems.

Counseling and Psychological Services (CAPS) can help students who are having difficulties managing stress, adjusting to the demands of a professional program, or feeling sad and hopeless. You can reach CAPS (www.uh.edu/caps) by calling 713-743-5454 during and after business hours for routine appointments or if you or someone you know is in crisis. No appointment is necessary for the "Let's Talk" program, a drop-in consultation service at convenient locations and hours around campus. http://www.uh.edu/caps/outreach/lets_talk.html

Class Schedule Fall 2019

Class Day	Day of Week	Topic	Assignment Due
20-Aug	T	Retrosynthetic Analysis/Prot. Grps.	
22-Aug	TH	Protecting Groups	
24-Aug	Sa	Homework Session	HW #1
27-Aug	T	Oxidation	
29-Aug	TH	Oxidation	
31-Aug	Sa	Homework Session	HW #2
3-Sep	T	Oxidation	
5-Sep	TH	Oxidation	
7-Sep	*Sa*	*Homework Session***	*HW #3***
9-Sep	T	Diastereoselective Oxidation	
11-Sep	TH	Diastereoselective Oxidation	
14-Sep	Sa	Homework Session	HW #4
17-Sep	T	Enantioselective Oxidation	
19-Sep	TH	Enantioselective Oxidation	
21-Sep	Sa	Homework Session	HW #5
24 Sep	T	Reduction	
26-Sep	TH	Reduction	
28-Sep	Sa	Homework Session	HW #6
1-Oct	T	Diastereoselective Reduction	
3-Oct	TH	Diastereoselective Reduction	
4-Oct	**F**	**Midterm #1**	TM list given
8-Oct	T	Enantioselective Reduction	
10-Oct	TH	C-C bond forming reactions	
12-Oct	*Sa*	*Homework Session***	*HW #7***
15-Oct	T	C-C bond forming reactions	
17-Oct	TH	Diastereoselective C-C bonds	
19-Oct	Sa	Homework Session	HW #8
22-Oct	T	Diastereoselective C-C bonds	Welch Symposium
24-Oct	*TH*	*Enantioselective C-C bonds***	
26-Oct	Sa	Homework Session	HW #9
29-Oct	T	C=C bond forming reactions	
31-Oct	TH	C=C bond forming reactions	
1-Nov	**F**	**Midterm #2**	
5-Nov	T	C=C bond forming reactions	TM Retro Due
7-Nov	TH	C≡C bond forming reactions	
9-Nov	Sa	Homework Session	HW #10
12-Nov	T	C≡C bond forming reactions	
14-Nov	TH	3-4 Member Rings	
16-Nov	*S*	*Homework Session***	*HW #11***
19-Nov	T	5-6 Member Rings	TM Retro Mk II Due
21-Nov	TH	5-6 Member Rings	
23-Nov	Sa	Homework Session	HW #12
26-Nov	T	6 Member Rings	TM Forward Check
12-Dec	TH	***Synthesis Proposal Due 5pm***	

***Home Football Game Scheduled*

FINAL EXAM Tuesday, December 10, 5-9 pm

Name Reactions

Below are some name reactions that are of importance in synthetic organic chemistry. You are expected to know the overall transformation and a reasonable mechanism for each reaction by the date indicated.

Good references:

Kürti, L.; Czakó, B. "Strategic Applications of Named Reactions in Organic Synthesis"
J. March, "Advanced Organic Chemistry"
A. Hassner and C. Stumer, "Organic Syntheses Based on Name Reactions and Unnamed Reactions,"
B. P. Mundy and M. G. Ellerd, "Name Reactions and Reagents in Organic Synthesis."
http://stoltz.caltech.edu/chemlinks.html has many useful links to name reactions pages.

8/26/2019
Aldol reaction
Michael Addition
Robinson Annulation
Henry reaction
Baeyer-Villiger Oxidation
Diels-Alder reaction
Ene reaction

9/2/2019
Swern Oxidation (see Kornblum and Moffatt variations)
Jacobsen epoxidation
Rubottom oxidation
Sharpless Asymmetric epoxidation
Sharpless Asymmetric dihydroxylation (SAD)
Tamao-Fleming oxidation
Saegusa-Ito oxidation

9/9/2019
Claisen rearrangement
Ireland-Claisen rearrangement
Cope rearrangement
Oxy-Cope rearrangement
Johnson-Claisen Rearrangement
Wharton fragmentation
Eschenmoser-Tanabe fragmentation

9/16/2019
Overman rearrangement
Prins-Pinacol rearrangement
Aza-Cope Mannich rearrangement
Brook rearrangement
Wittig rearrangement
Mislow-Evans rearrangement
Stevens rearrangement

9/23/2019
Chugaev Reaction
Arbuzov Reaction
Wittig reaction
Horner-Wadsworth-Emmons reaction
Grignard chemistry
Corey-House-Posner-Whitesides reaction
CBS reduction

9/30/2019
Meerwein-Ponndorf-Verley reduction
Oppenauer Oxidation
Tischenko reduction
Cannizzaro reaction
Arndt-Eistert rearrangement
Wolff rearrangement
Curtius rearrangement
Payne Rearrangement

10/7/2019
Beckmann rearrangement
Hofmann rearrangement
Hofmann-Löffler-Freytag Reaction
Knoevenagel reaction
Mannich reaction
Mukaiyama Aldol reaction
Dieckmann Condensation (and Claisen condensation)

10/14/2019
Darzens reaction
Sakurai reaction
Reformatsky reaction
Finkelstein reaction
Hunsdiecker reaction
Mitsunobu reaction
Gabriel synthesis
Tsuji-Trost Allylation

10/21/2019
Grubbs olefin metathesis
Stille reaction
Suzuki reaction
Heck reaction
Nozaki-Kishi coupling
Pauson-Khand reaction
Wacker oxidation
Buchwald Hartwig coupling

10/28/2019
Takai reaction
Julia-Lythgoe coupling
McMurry Coupling
Tebbe Olefination
Peterson Olefination
Cope Elimination
Corey-Fuchs Alkyne Synthesis
Corey-Winter Olefination

11/4/2019
Favorskii Reaction
Petasis-Ferrier Rearrangement
Krapcho Reaction
Benzoin Condensation
Acyloin Condensation
Corey-Chaykovsky Epoxidation and Cyclopropanation
Fleming-Tamao oxidation
Pummerer Rearrangement

11/11/2019
Bamford-Stevens Reaction
Shapiro Reaction
Wolff-Kischner Reduction
Friedel-Crafts Acylation
Fries Rearrangement
Glaser Coupling
Nicholas Reaction
Polonovski Reaction

11/18/2019
Fischer indole synthesis
Nef Reaction
Barton-McCombie Deoxygenation reaction
Barton Deacarboxylation reaction
Bayless Hillman Reaction
Stetter Reaction
Strecker reaction
Nazarov Cyclization

11/25/2019
Yamaguchi Macrolactonization
Sonagoshira coupling
Keck Allylation
Kulinkovich Reaction
Meyer-Shuster/Rupe rearrangement
Simmons-Smith Cyclopropanation
Pictet-Spengler Reaction
Staudinger Reaction

The task of the chemist is to effect chemical transformations and to discover chemical reactions…

…Now chemical synthesis always has some element of planning in it. But, the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are these that he finds out in the course of attempting to react that objective.

And so it is this role of synthetic chemistry in providing a kind of matric within which discovery can be made which I think is perhaps its most important role for the chemist as such. And, of course, discovery leads also, ultimately, to understanding.

R. B. Woodward
Welch Chemistry Conference
1968

If a definitive history of twentieth century science is ever written, one of the highlights may well be a chapter on the chemical synthesis of complex molecules, especially the total synthesis of naturally occurring substances. I state this, while trying to be as objective as possible, because it is not easy to find an area of scientific work that encompasses so many interesting elements. I shall name just a few: great complexity and variety; challenge verging on impossibility; demand for both mental and manipulative rigor, and for dedication, persistence, and hard work; never-ending frontiers for discovery and never-ending advances in sophistication; unlimited opportunities for intellectual excitement and satisfaction; strong coupling not only with all areas of chemistry, but also with biology and medicine; relevance, at a very fundamental level to human well-being, health, and education.

E. J. Corey
Harvard University
30 October 1995

In our judgment, the huge advances in the power of total synthesis have been fueled primarily by advances in synthetic methodology. While it is often more aesthetically pleasing to focus on strategy-level issues, in reality, new strategic insights and increasingly powerful retrosynthetic analyses are inextricably interwoven with the development of enhancing reaction methodology. Most exciting from our perspective is the creative synergism of methodology and target pursuits. Thus, opportunities in natural product total synthesis open up major prospects and incentives for accomplishments in methodology. Correspondingly, the emergence of new reactions, which provide new enablements, prompt more daring "strategies."

Samuel Danishefsky
J. Org. Chem. **2006**, *71*, 8329

Natural product synthesis is like walking on eggshells…

Samuel Danishefsky
Columbia University
Group Meeting 2006

Synthesis will be dead when limited by imagination, not tools…

Ryan Shenvi
Organic Reactions and Processes Gordon Research Conference
July 2016

Reading the Chemical Literature

1. You don't have time to read everything. Focus on articles that (A) you find interesting; (B) are pertinent to your and your group's research; (C) challenge an assumption that you have.

2. Use abstracts, figures, and schemes to your advantage. A well-written paper will have 90% of the information there, and you can use the text to fill in important details. Conversely, when reporting your research you should use those means to convey your results as quickly as possible (and always put reagents *in* the schemes *over arrows*). Otherwise, no one will know your work.

3. When looking at new chemistry, consider its relevance in both the forward and retro synthetic directions. In target directed synthesis, retron and synthon recognition is vital. Also, always attempt to understand/formulate reaction mechanisms. This knowledge will provide insight into functional group compatibility.

4. Discuss with colleagues. This will (A) help you remember and (B) help you better understand by repetition and by explaining the information to someone else.

5. If the reaction is *selective*, add it to your notes!!! These are indispensible to synthetic chemistry and having the information together and organized will save hours of library time.

7 Make note of the author and affiliation to help remember the information and whose work interests you. Knowing a lab's research can help you find the information you need later.

8. "Don't believe the hype!" Avoid a knowledge based only on the latest trend in C&E news (and other secondary/tertiary sources).

9. Read critically! Many manuscripts contain incomplete, unlikely, flawed, or just plain false information. Make the paper and its data prove the idea to you, and if you are still skeptical, do your own background check. *Very* few advances in science are not built upon precedents, and you can use these precedents to judge new reports.

10. To help keep tabs on impactful synthetic methods and strategies, there are many sites that compile references (e.g., http://www.organic-chemistry.org/, which also is a great resource for Name Reactions).