

**COURSE DATA****Data Subject**

Code	44707
Name	Advanced organic synthesis
Cycle	Master's degree
ECTS Credits	4.0
Academic year	2021 - 2022

Study (s)

Degree	Center	Acad. Period year
2226 - M.D. in Organic Chemistry	Faculty of Chemistry	1 Annual

Subject-matter

Degree	Subject-matter	Character
2226 - M.D. in Organic Chemistry	3 - Advanced organic synthesis	Obligatory

Coordination

Name	Department
DEL POZO LOSADA, CARLOS	325 - Organic Chemistry

SUMMARY

The subject Organometallic reagents in synthesis, together with asymmetric catalysis, constitute the Advanced Organic Chemistry subject. It intends to cover the most relevant methods in organic synthesis, with a equilibrated balance between classical methodologies, still valid nowadays as efficient methods for the preparation of organic compounds, and the new methods that were incorporated to organic synthesis in the last decades.

In this context, the application of organometallic in organic synthesis will be addressed initially, paying special attention to the transition metal derived organometallics, since in the last decades the reactions with those metals have witnessed a spectacular development. The consolidation of homogeneous catalysis in industrial applications played a crucial role as a mechanism of feedback in basic research in this field. The development of new catalysts that adapt initial academic methodologies to strategic products from an industrial point of view is a tendency observed frequently in scientific publications, showing the synthetic potential of those methodologies that progressively are incorporated to the repertoire of methods in organic synthesis.



The subject Asymmetric synthesis and catalysis deals with the synthesis and enantioselective catalysis, an important and intense area of current research. Its understanding requires the combination of all the relevant disciplines in organic chemistry (reactivity/structure, kinetics, molecular recognition, stereochemistry and of course, organic synthesis).

For the pharmaceutical industries, the preparation of enantiomerically pure compounds (EPC) is a very attractive area from an economical point of view, as S. Ley indicated in *Chem. Med. Chem.* **2007**, 2, 768, and for this reason, generates highly qualified work (every year, in *Chemical and Engineering News*, published by the American Chemical Society, appears articles dedicated to this area of research and business). The interest of the chemical-pharmaceutical industries in the synthesis and asymmetric catalysis is easy to understand, since a lot of useful properties of organic compounds are associated to its chirality, or in other words, therapeutic properties of a lot of drugs are inherent of each enantiomer, since biological systems (enzymes and proteins, etc..) of living organisms are able to identify differentially each of the members of two enantiomers. Therefore, each enantiomer is able to induce different biochemical responses. Is important to point out that American FDA and its equivalent in Europe demand strict biological tests of the activity of each enantiomer and the current regulation only permits to patent enantiomerically pure compounds.

PREVIOUS KNOWLEDGE

Relationship to other subjects of the same degree

There are no specified enrollment restrictions with other subjects of the curriculum.

Other requirements

Essential:

They are essential requirements: basic knowledge in advance organic chemistry and basic organic synthesis.

Recommendable:

They are recommendable requirements: basic knowledge in organometallic chemistry (transition metals), inorganic chemistry (coordination chemistry) and kinetics.

For an ideal situation of the subject synthesis and asymmetric catalysis, is convenient that students have studied previously, the subjects organic synthesis and organometallic reagents in synthesis

OUTCOMES

2226 - M.D. in Organic Chemistry

- Students should apply acquired knowledge to solve problems in unfamiliar contexts within their field of study, including multidisciplinary scenarios.



- Students should be able to integrate knowledge and address the complexity of making informed judgments based on incomplete or limited information, including reflections on the social and ethical responsibilities associated with the application of their knowledge and judgments.
- Students should communicate conclusions and underlying knowledge clearly and unambiguously to both specialized and non-specialized audiences.
- Students should demonstrate self-directed learning skills for continued academic growth.
- Students should possess and understand foundational knowledge that enables original thinking and research in the field.
- Use different presentation formats (oral, written, slide presentations, boards, etc.) to communicate knowledge, proposals and positions.
- Be able to access to information tools in other areas of knowledge and use them properly.
- Saber participar en debates y discusiones, dirigirlos y coordinarlos y ser capaces de resumirlos y extraer de ellos las conclusiones más relevantes y aceptadas por la mayoría.
- Poseer habilidades sociales, un buen nivel de comunicación oral y escrita, así como capacidad para trabajar en equipo y con personas de diferentes procedencias.
- Competencias de gestión tales como la capacidad para la planificación y gestión de tiempo y recursos, así como para dirigir y tomar decisiones.
- Ser capaces de valorar la necesidad de completar su formación científica, en lenguas, en informática, asistiendo a conferencias o cursos y/o realizando actividades complementarias, autoevaluando la aportación que la realización de estas actividades supone para su formación integral.
- Conocer y saber aplicar la reactividad de los compuestos organometálicos en síntesis orgánica.
- Profundizar en los principios de la síntesis y catálisis asimétrica.
- Capacidad para utilizar los conocimientos adquiridos para el diseño y realización de síntesis eficaces de productos con valor añadido.

LEARNING OUTCOMES

The final aims of this subject are summarized in the following points:

- The acquisition from the students of the fundamental principles where organic synthesis is based.
- The acquisition from the students of the available resources for the generation of the different types of bonds.
- The acquisition from the students of a general vision of the new catalysts used in organic synthesis
- The acquisition from the students of a general vision of the methodologies, historic evolution and adaptation to the new demands of the current society. From a more specific point of view: be able to employ the acquired knowledge in the design of efficient synthesis of products of high value.



DESCRIPTION OF CONTENTS

1. Introduction

Electronic configuration of the metal and the complex. Saturated and insaturated complexes. MO diagrams of octaedric complexes, tetraedric and square planar. Nature and bonding type in transition metal complexes. High and low spin complexes.

2. Types of reactions and mechanism with organometallics from transition metals

Ligand exchange. Oxidative addition/reductive elimination. Transmetalation. Insertion/desinsertion. Nucleophilic and electrophilic attack of coordinated ligands to transtion metals.

3. Carbon-carbon and carbon-heteroatom bond formation by means of cross coupling reactions. Pd, Ni and Fe catalysis.

Kumada, Negishi, Stille, Suzuki, Hiyama, Sonogashira, Buchwald-Hartwig reactions and analogues. Heck reaction. Tsuji-Trost reaction and analogues. Interesting synthetic applications.

4. Reactions of transition metal complexes with insaturated ligands.

Reactions with carbon monoxide. Reactions with carbenes. Metathesis reactions. Reactions with alkenes and dienes. Cycloaddition reactions. Interesting synthetic applications.

5. Oxidation and reduction reactions with transition metals

Synthetic applications of transition metal hydrides. Regioselectivity. Aerobic and anaerobic oxidation reactions.

6. Catalysis with Au complexes

Cycloisomerization reaction of enynes and analogues. Nucleophilic addition reactions: alcoholes, amines, amides, aryls. Oxidation reactions.

7. Current challenges in transition metal catalysis

Reagent functionalization with transition metals. C-H activation reactions. Substituion of organometallic reagents

**8. Stereochemistry. Introduction to the synthesis and asymmetric catalysis**

Basic stereochemistry. Chirality. Prochirality. Asymmetric induction. Cuth-Hammett principle.

9. Access to enantiomerically pure compounds (EPC)

Methods to access EPC. Racemic mixture resolution by means of physical methods. Racemic mixture resolution by means of chemical methods. De-racemization Viedma of racemic mixtures.

10. Asymmetric synthesis.

Basic principles of asymmetric synthesis. Diastereoselective synthesis, Chiral auxiliaries.

11. Kinetic resolutions and de-racemizations.

Simple kinetic resolutions (KR). Parallel kinetic resolutions (PKR). Kinetic dynamic de-racemization (DKR). Enantioconvergent de-racemizations (ECP). Cyclic de-racemization (CycD). Asymmetric kinetic dynamic transformations (DYKATT I y II).

12. Asymmetric catalysis

Basic principles of asymmetric catalysis. Multiplication of chirality. Non linear effects (NLE). Amplification of chirality. Mono-, bi- and multifunctional catalysis.

13. Enantioselective catalysis.

Organocatalysis: basic principles. HOMO activation through chiral enamines. LUMO activation through chiral unsaturated iminium salts. SOMO activation. Counter-ion activation.

WORKLOAD

ACTIVITY	Hours	% To be attended
Theory classes	20,00	100
Seminars	20,00	100
TOTAL	40,00	

TEACHING METHODOLOGY

The subject is formulated in a manner that the student is the principal actor of its own learning. From the beginning of the course, students will have the whole didactic material necessary and the teaching will be structured in the following manner:



- **Master classes (in person):** In those classes will be directed to discuss with the students the most complicated aspects or those where the students have more difficulties in the previous study of the teaching material provided. Those classes will be complemented with personal study.
- **Seminars.-** In the seminars the specific application of the acquired knowledge of the students during the master classes will be carried out. The students have to work with the problems previously. Their resolution will be take place alternatively for the professor and for the students, either in group or individually.
- **Written assignment.-** Additionally, when the teacher will consider it, some assignments will be proposed, normally related to the study of a practical case, connected with one of the themes of the program, that will be detailed in a scientific publication.

EVALUATION

The assessment of student learning will be performed in a continuous manner for the teacher throughout the course, and it will contain the following points:

- **Direct assessment of the professor:** 15% of the final grade will come from the direct evaluation of the professor both in theoretical and practical classes. In this evaluation, some different aspects will be considered. Among them, we outlined the following:
 - Attendance and participation in the discussions.
 - Progress in the use of the proper language of the field.
 - Problem resolution and question proposal
 - Critic spirit
 - presentation of the exercices.
- **Assessment of the word performed by the student.** The contents and the form will be considered at this stage. The weighting of this part will be 25% of the total grade.
- **Written exams.** 60% of the final grade will come from the grades obtained in those written exams.
 - in person examination (traditional style) with both theoretical and practical questions of contents related to the subject. The nature of those questions and problems will force the students to connect several aspects that come from different themes of the subject, or if the teacher considers it convenient, from different subjects.
 - Not in person exams. The teacher will give to the students directly or by electronic mail, a series of questions that the students have to complete, either individually or in group, depending on the decision of the teacher. In any case, the answers will be sent to the teacher again in person or by electronic mail, in the period previously stipulated.



REFERENCES

Basic

- Transition Metal for Organic Synthesis Vol 1, (Eds: M. Beller, C. Bolm) Wiley-VCH, Weinheim, 2004.
- Cross-Coupling Reactions. Miyaura, N. Springer -Verlag, Berlin Heidelberg 2002
- Dale L. Boger "Modern Organic Synthesis" TSRI Press, 1999, San Diego, Ca., USA
- E.L. Eliel, S.H. Wilen Stereochemistry of Organic Compounds, Wiley Interscience 1994.
- J.D. Morrison, ed. "Asymmetric Synthesis " Vol 1-5, Academic Press, New York 1985.
- M. Nogradi, "Stereoselective Synthesis" Verlag Chemie, Weinheim, 1987.
- R. Noyori "Asymmetric Catalysis in Organic Synthesis , Wiley Interscience, 1994.
- I. Ojima "Catalytic Asymmetric Synthesis" 2nd Edition, VCH, 2000.
- A. Berkessel and H. Gröger. Asymmetric Organocatalysis Wiley-VCH, 2005.

Additional

- R.S. Atkinson "Stereoselective Synthesis" , John Wiley & Sons 1995.
- H.U. Blaser and E. Schmidt. Asymmetric Catalysis on Industrial Scale, Wiley.
- Collins, A.N., Sheldrake, G.N.; Crosby J. (eds) "Chirality in industry: the commercial manufacture and applications of optically active compounds" Vol. I y II, Wiley, Chichester, 1992 y 1997.
- G. Helchem, R.W. Hoffmann, J. Mulzer, E. Shaumann ed. "Stereoselective Synthesis" Houben-Weyl vol. 1-10 Georg Thieme Verlag, 1996, Stuttgart.
- E.N. Jacobsen, A. Pfaltz, H. Yamamoto, ed. "Comprehensive Asymmetric Catalysis" Vol I-III, Springer, 1999. Supplements 1, 2004, and 2, 2004.
- L. Paquette ed, Chiral reagents for Asymmetric Synthesis, Wiley, 2003.
- H.B. Kagan "Asymmetric Synthesis using Organometallic Catalysis" en Comprehensive Organometallic Chemistry, Vol. 8, Pergamon Press, Oxford, 1982

ADDENDUM COVID-19

This addendum will only be activated if the health situation requires so and with the prior agreement of the Governing Council

- **Second call evaluation**



Due to the alarm state imposed by the sanitary situation, the second call evaluation will be performed in the not in person mode. The face to face theoretical classes and the evaluation of the first call was already finished when the alarm state was ordered.

To this end, the tools stipulated in the platform “Aula Virtual” will be employed. In the same token, the integrity of the exams will be verified with the software provided by the UVEG. The students will identify themselves by means of the password necessary to access the “Aula Virtual” platform.