LECTURE SCHEDULE

Training Course

ORGANOMETALLIC CATALYSIS

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On November 27th, 28th, 29th, 30th, 2017

ESPCI
10 Rue Vauquelin
75005 Paris
France

Day 1

9h00-10h30 **Lecture 1: Basic chemistry of transition metals complexes**

- Introduction
- Historical reactions on homogeneous catalysis: few main reactions
- Formation of transition metal complexes
- Electronic configurations. The 16 and 18 electrons rule
- Definition and interest of organometallic catalyst: MtLn
- General presentation of organic ligands and nomenclature
- Electrons counting and degree of oxidation
- Examples and applications
- Exercises on organometallic chemistry: Problems set

10h30-10h45 Coffee break

10h45-12h15 **Lecture 2: Elementary steps in organometallic chemistry**

- Introduction
- Non-reductive elimination
- Oxidative addition
- Insertion reaction
- Reductive elimination
- Transmetallation
- Ligands substitution
- Coordination
- Insertion
- Nucleophilic addition on ligand coordinated to transition metal
- β and α elimination of hydrogen atoms (dehydrometallation)
- Applications: mechanisms of Stille, Suzuki, Heck, Sonogashira coupling reactions.

12h15-14h00 Lunch

14h00-15h30 **Lecture 3: Notions de ligands**

Main types of ligands

- Alkyls, allyls
. Phosphines, water-soluble phosphines
. Phosphites
- Phosphoramidites
- Phospholes
- Amines
- Bisoxazolines and imidazolines
- P-N ligands: phosphinooxazoline
- Carbenes
- Carbon monoxide

15h30-15h45 Coffee break

15h45-17h15 **Lecture 4: Reactivity of metal complexes**

- Metal ligand interactions (σ et π effects)
- Factors influencing the reactivity and the selectivity
- Role of ligands
- Steric parameters (Tolman cone angle)
- Electronic effects
- Example: optimization of L-DOPA synthesis

Day 2

9h00-10h30 **Lecture 5: Double bond hydrogenation reactions**

-Introduction
-Preparation of complexes (Rh,Ir)

Hydrogenations of non-substituted olefins (Rh,Ir)
-Osborn-Wilkinson catalyst
-Mechanism
-Crabtree catalyst: synthesis and applications
-Selectivity/ hydrogenations assisted by functional groups

Asymmetric hydrogenation of prochiral olefins
- Chiral ligand
- Dehydroaminoacids synthesis
- Application to the synthesis of L-DOPA
- Origin of enantioselectivity

Asymmetric hydrogenation of alkenes (Ru)
- Preparations of ruthenium chiral complexes
- Allylic alcohols
- Applications in perfumery (lilial, florydral)
- α,β–Unsaturated acids and dehydroaminoacids
- Mechanism
- Application to the antiflamatory drug: Naproxen
- Enantioselectivitity orientation : comparison between Ru (II) and Rh (I) catalysts
- Asymmetric hydrogenation of non-functionalized olefins, lactones and unsaturated ketones
- Application in perfumery: an industrial example the Paradisone
- Applications to the synthesis of active pharmaceutical ingredients (API): thrombin inhibitor CRC 220, synthesis of a renin inhibitor , anti-HIV drug indinavir, endopeptidase C inhibitor candoxatril, endothelin antagonists such as SB 209670, chiral succinate moiety of metallo- protease inhibitor UK-370,106, pregabalin a marketed anticonvulsant, building blocks for a new prototype of HCV protease inhibitor BILN 2061, vitronectin receptor antagonist SB-273005 ….

- Examples of catalysts recovery

10h30-10h45 Coffee break

10h45-12h15 **Lecture 6: Hydrogenation of carbonyls and imines**

- Preparation of catalysts

- Hydrogenation of ketoesters
- Mechanism
- Enantioselectivity-orientation
- Selectivity: influence of the dihedral angle of the metal-diphosphine catalyst
- Applications in organic synthesis and comparison with biochemical reduction
- Hydrogenation of fluorinated β−diketones (optimization of enantioselectivity with electron deficient diphosphine)
- Application to the synthesis of rivastatin
- Dynamic kinetic resolution (DKR
- Application:synthesis of a key chiral intermediate of the therapeutically important class of carbapenem antibiotics.
- Synthetic applications

Reductions by hydrogen transfer (Rh, Ru, Fe)

- History
- The different developments
- Noyori reaction: mechanism and applications
- Applications for the synthesis of pharmaceutical intermediates: NMDA 2B Receptor Antagonist Ro 67-8867, synthesis of neurokinin receptor antagonist, vasopressin receptor antagonist OPC-4106, enantioselective approach to PDE-IV inhibitor

Asymmetric hydrogenation of imines

- Catalysts
- Use in organic synthesis: chiral synthesis of the antibiotic (*S*)-levofloxacin, synthesis of the neuromuscular blocker GW 0430, AMPA receptor modulator S-1898
- Industrial synthesis of Metolaclor
- Conclusions

12h15-14h00 Lunch

14h00-15h30 **Lecture 7: Isomerizations**

Isomerizations of double bonds

- Mechanism: 1,2 and 1,3 hydrogen shifts
- Isomerization of allylic and propargylic alcohols
- Isomerization of ethers
- Applications in perfumery
- Kinetic resolution
- Isomerization of allylic acetates
- Mechanisms: comparison between Pd (II) and Pd (0) catalysts.
- Chirality transfer

Enones isomerization

Catalysts
Mechanisms
Examples

15h30-15h45 Coffee break

15h45-17h15 **Lecture 8: Asymmetric isomerization**

Isomerization of allyl amines.

- Catalysts (Mo, Rh, Ir)
- Chemoselectivity : Comparison between isomerization catalyzed by bases/acids and isomerization catalyzed by transition metals
- Enantioselectivity
- Mechanism
- Developments in organic synthesis
- Industrial applications: synthesis of menthol, ambrox…
- Enantioselective isomerization of allylic alcohols
- Applications in perfumery
- Synthesis of florydral

Other substrates

- Isomerization of allylic and propargylic alcohols
- Applications for prenal, geraniol and citral synthesis
- Epoxides isomerization (Pd)
- Secondary alcohols racemization (Ru)
- Dynamic kinetic resolution (DKR): Chemoenzymatic reactions
- Applications

Day 3

9h00-10h30 **Lecture 9 : Oxidations I**

Wacker oxidation (Pd)

- Mechanism
- Industrial applications

Olefins epoxidation

- Different classes of oxidizing agents
- Oxidations catalyzed by transition metals
- Chemoselectivity
- Stereocontrol by the substrate/comparison with organic peracids
- Asymmetric epoxidation of allylic alcohols
- Sharpless epoxidation
- Origin of enantioselectivity
- Kinetic resolution
- Synthetic applications

Other methods

- Chiral dioxiranes
- Katsuki-Jacobsen reaction
- Origin of enantioselectivity
- Mechanism
- Synthetic application: taxotere side chain

10h30-10h45 Coffee break

10h45-12h15 **Lecture 10: Oxidations reactions II**

Dihydroxylation of olefins (AD)

- History
- Chiral ligands
- Mechanism
- Synthetic applications

Oxidation of sulfur compounds

- Catalytic systems
- Chiral sulfoxides
- Applications to large scales production of sulfoxides of industrial interest : Esomeprazole used in the treatment of gastroesophageal reflux disease, , ACAT inhibitor

12h15-14h00 Lunch

14h00-15h30 **Lecture 11: Carbonylations**

Hydroformylation of olefins

- Introduction
- Catalysts and mechanisms
- Regioselectivity
- Catalysts and stereo-oriented hydroformylation
- Hydroformylation of propene use of water-soluble catalysts (Rh-TPPTS)
- Hydroformylation of alkynes
- Asymmetric hydroformylation
- Applications in perfumery
- Carbonylation of compounds with benzyl and allyl chlorides
- Double carbonylation of benzyl chlorides
- Carbonylation of methanol
- Acetic acid synthesis

15h30-15h45 Pause café

15h45-17h15 **Lecture 12: Metathesis**

Carbenes

Introduction
Structure of carbenes
Generation of carbenes : Fisher and Schrock types
Synthesis and functionalization of carbenes
Reactivity of carbenes
Tebbe reagent
Olefination of esters and amides
Catalytic reactions and applications in organic synthesis

Olefins metathesis

- Different types: RCM, ADMET, ROMP
- Mechanism: Y. Chauvin
- Industrial processeses

- Catalysts Mo, Ru
-Ring formation (RCM), Mechanism
-Industrial synthetic applications (medium ring, macrolactonisations) Stagonolide A,Decalactone
- Application to the synthesis of HCV protease inhibitor BILN 2061,
- Asymmetric synthesis
- Enynes metathesis

Cross Metathesis (CM)

- Alkenes, Synthesis of Aplysamine
- Alkynes metathesis: molybdenum and tungsten catalysts
- Formation of ring from alkynes (RCAM)

Conclusions

Day 4

9h00-10h30 **Lecture 13: Creation of bonds C-C (I)**

Cyclopropanations

- Carbenoïdes
- Mechanism
- C-H and N-H insertion: inter and intramolecular reactions
- Applications

Palladium/ Nickel catalyzed reactions ; C-C and C-N bonds formation

- Sonogashira reaction (synthesis of galbanolene)
- Negishi coupling and Heck reactions
- Application to the syntheses of prosulfuron (herbicide) and pharmaceutical compounds : carbacyclin,discodermolide, xerulinic acid , singulair …
- Suzuki coupling (Pd, Ni) and applications to the synthesis of pharmaceutical drugs: prostaglandins, palytoxin, myxalamide, Valsartan (Novartis) , Valsartan (Novartis), ABT-963(Abbot), RO0094889 (Roche)
- Buchwald-Hartwig reaction
- Allylic substitution (Tsuji-Trost reaction)
- Application to the synthesis of the neuromuscular blocker GW 0430, AMPA receptor modulator S-18986, synthesis of MGS0028, an mGluR 2 receptor agonist
- α arylation of enolates
- Intramolecular arylation

10h30-10h45 Coffee break

10h45-12h15 **Lecture 14: Formation of C-C bonds (II)**

Dienes / Applications in fine chemistry

- Telomerizations /applications synthesis of jasmonate
- Additions
- Cycloadditions

- Few examples of applications in organic synthesis

Cycloisomerizations

- Enynes, Diynes
- Mechanism
- Applications

12h15-14h00 Lunch

14h00-15h30 **Lecture 15: C-H Activation: towards a green catalysis**

- Introduction
- Olefination of C(sp^2) H Bonds
- Arylation of C(sp^2) H and C(sp^3) H bonds-
- Ortho Alkylation Sequential olefination of aryl iodides
- Arylation and Alkylation of C(sp^2) H and C(sp^3) H bonds
- Conclusions and perspectives

15h30-15h15 Coffee break

15h15-16h45 **Lecture 16: Other types of reactions**

Asymmetric Michael reactions

- Additions of organoboron compounds
- Boronic acids and organopotassium trifluoroborates to Michael acceptors
- Stereochemical outcome of the asymmetric 1,4-addition Reactions
- Application to the synthesis of tolterodine
- Synthesis of chiral α and β -amino acids (Mechanism and DFT calculations)
- Epoxides opening

- Dienes isomerizations : Claisen, Cope reactions
- Protecting groups in fine chemistry
- Conclusion and perspectives

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