Homogeneous catalysis

- Reagents and catalyst are all in the same phase (typically solution)
- Selective, efficient reactions at mild conditions
- Usually well understood

- Transition metal catalysis → Metal Organic Chemistry (MOL096)
- Catalysis by main-group element compounds
- Organocatalysis

- Cooperative catalysis
- Tandem catalysis

- Photocatalysis
- Electrocatalysis

➡ Separate videos

Definitions and Terminology

- Turnover number (TON) {(mol substrate)(mol catalyst)$^{-1}$}
- Turnover frequency (TOF) {(mol substrate)(mol catalyst)$^{-1}$h^{-1}}
- Chemoselectivity
- Enantioselectivity
- Enantiomeric excess
- Stereospecificity
- Stereoselectivity
- Diastereoselectivity
- Regioselectivity
- Atom economy
- Intermediate, transition state
- Rate-determining step (RDS)

(textbook, page 74)

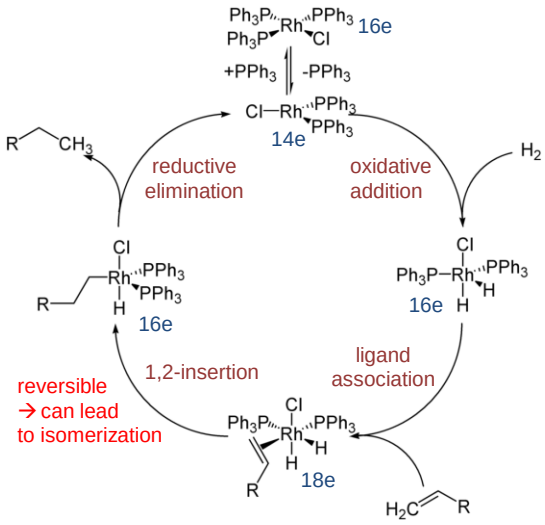
Transition metal catalysis

- most widely used
- catalysts – organometallic compounds
- **typical reaction steps** (follow MOL096 to learn details)
  - oxidative addition and reductive elimination
  - migratory insertion and elimination
  - reactions at ligands (nucleophilic and electrophilic attacks)
  - metathesis reactions

- **typical reactions**: hydrogenation, hydroformylation, polymerization, C-C bond forming reactions, alkene metathesis

Homogeneous hydrogenation

Wilkinson's catalyst



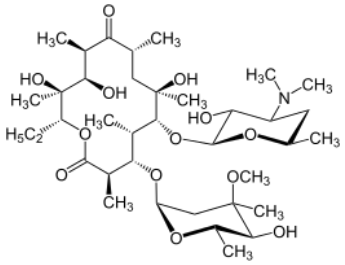
Rate limiting step

H_2 oxidative addition

More electron-donating ligands → higher rates

Small, electron donating ligands (such as PEt_3) do not dissociate from the metal → catalyst inactive

Stereochemistry



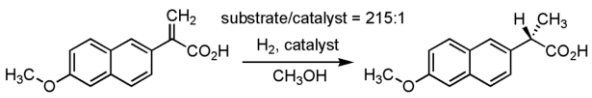
Erythromycin a

18 stereocenters
262 144 stereoisomers

→ an urgent need
of asymmetric reactions

Asymmetric homogeneous hydrogenation

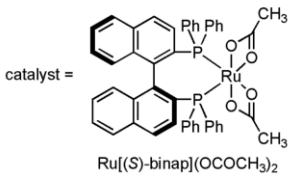
an anti-inflammatory agent



2-(6-methoxy-2-naphthyl)propenoic acid (**1**)

(*S*)-naproxen (**2**), 97% ee

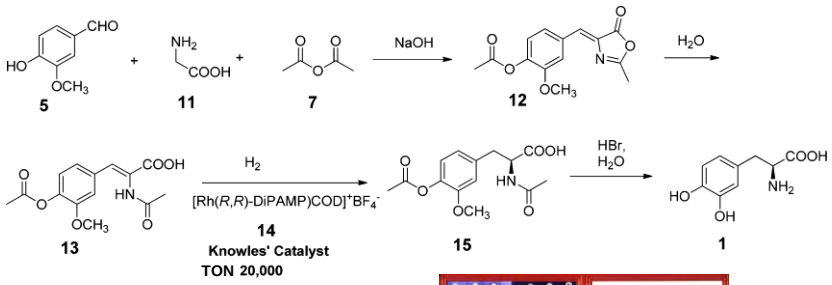
92% yield

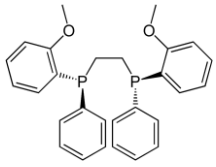


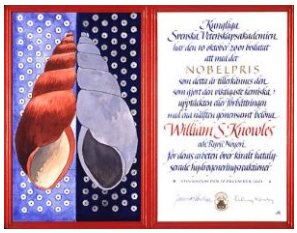
Ru[(*S*)-binap](OCOCH$_3$)$_2$

T. Ohta, H. Takaya, R. Noyori, *Inorg. Chem.* **1988**, *27*, 566.

Monsanto L-dopa process





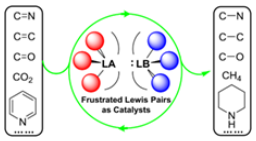


W. S. Knowles, Acc. Chem. Res. 1983, 16, 106-112; J. Chem. Edu. 1986, 63, 222-225.
T. Li, X. Li, *Green Chem.* **2014**, 16, 4241-4256.

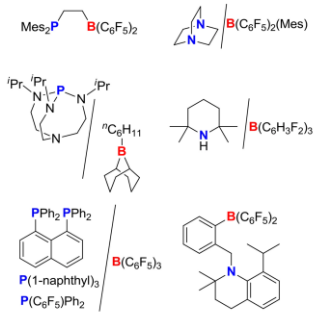
Main group catalysis

- catalysis dominated by transition metal catalysis, but they are expensive and toxic
- need for alternatives → earth abundant metals and main group elements (Ca, Mg, B, Al)
- asymmetric 1,4-additions, hydrosilylations, hydrogenations, phosphonylations

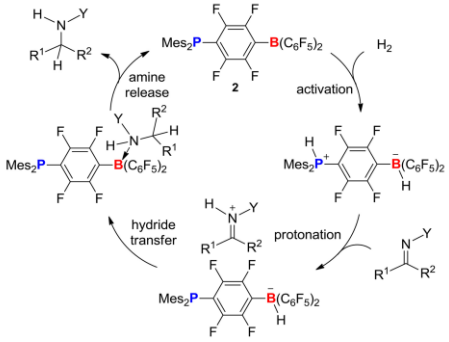
Frustrated Lewis-pair catalysis



Frustrated Lewis pairs

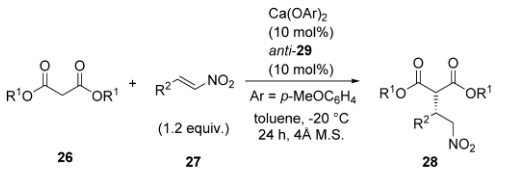


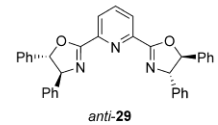
Catalytic cycle for the reduction of imines by phosphine-boranes

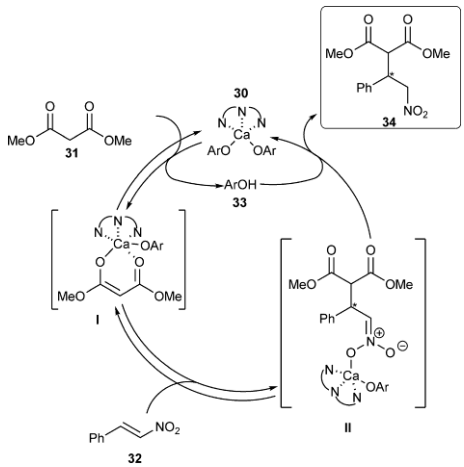


Chase, P. A., Welch, G. C., Junea, T., Erker, G. & Stephan, D. W. *Angew. Chem. Int. Ed.* 2007, *46*, 8050–8053.
N. Li, W. X. Zhang, *Chin. J. Chem.* **2020**, *38*, 1360-1370.

Asymmetric addition reactions







L. C. Wilkins, R. L. Melen, *Coord. Chem. Rev.* **2016**, *324*, 123 – 139.

Main group catalysis

- catalysis dominated by transition metal catalysis, but they are expensive and toxic
- need for alternatives → earth abundant metals and main group elements (Ca, Mg, B, Al)
- asymmetric 1,4-additions, hydrosilylations, hydrogenations, phosphonylations

→ Intense research for cheaper and safer alternatives to the transition metal catalyzed processes

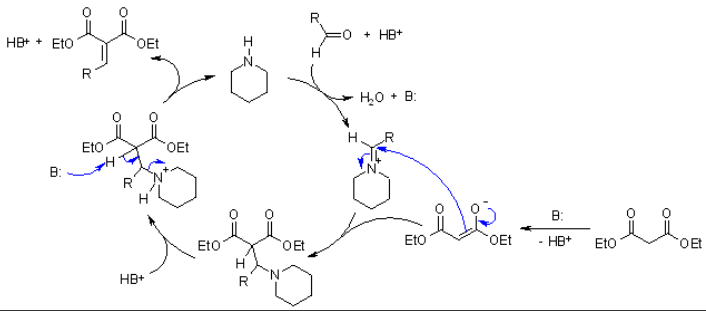
Organocatalysis

catalyst → (small) organic molecule

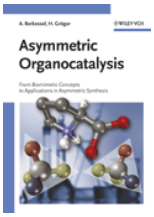
- tolerant to air, moisture
- low cost
- low toxicity

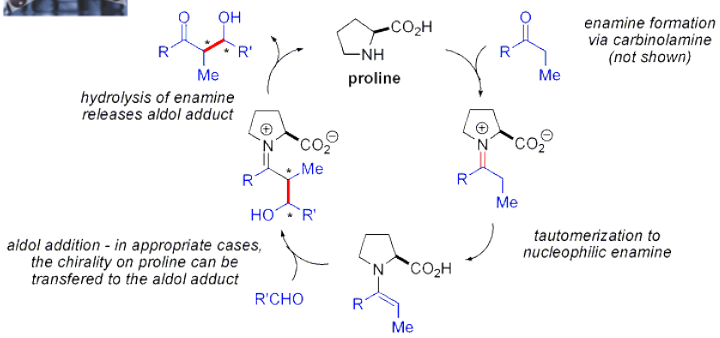
→ safer for pharmaceutical industry

Knoevenagel condensation

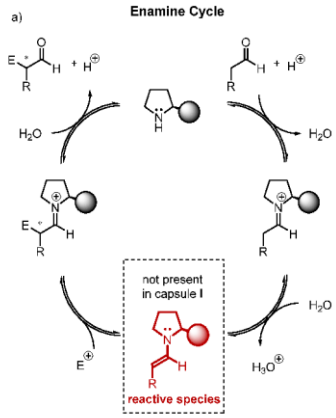


Organocatalysis





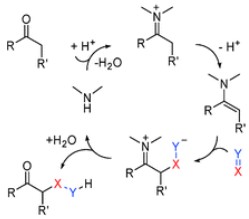
Organocatalysis

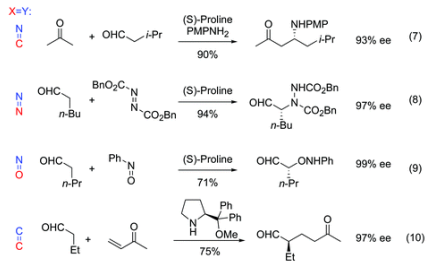


T. M. Brauer, Q. Zhang, K. Tiefenbacher, *J. Am. Chem. Soc.* **2017**, *139*, 48, 17500–17507

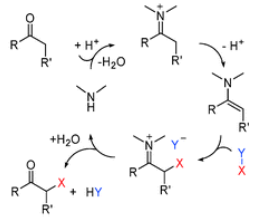
Organocatalysis - Enamine catalysis

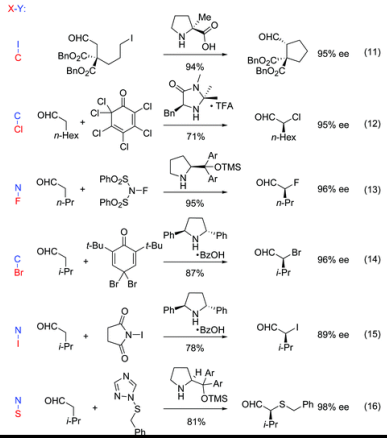
Nucleophilic addition reactions





Substitution reactions

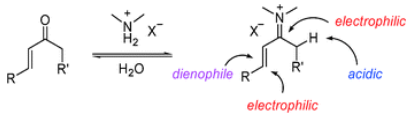


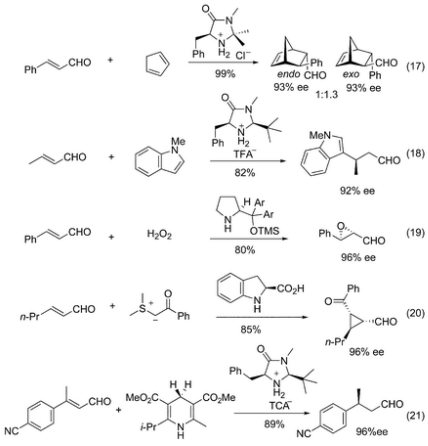


B. List, *Chem. Commun.* **2006**, 819 – 824.

Organocatalysis

Iminium catalysis





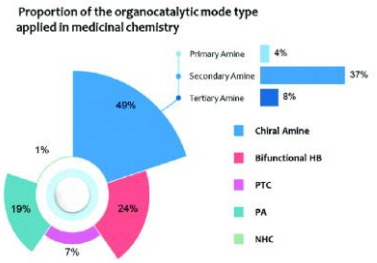
- Diels-Alder reactions
- Conjugate addition
- Epoxidations
- Cyclopropanations
- Conjugate reductions

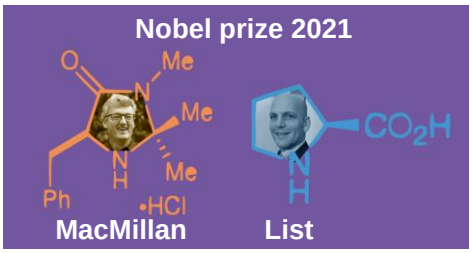
B. List, *Chem. Commun.* **2006**, 819 – 824.

Organocatalysis

Safe method to prepare chiral compounds → pharmaceutical industry

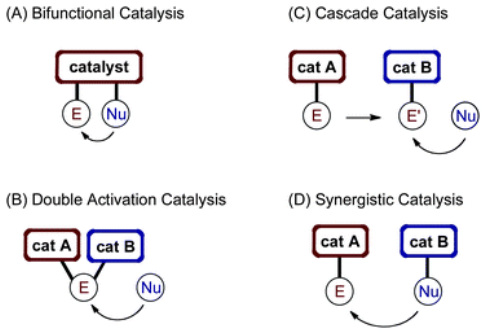
- Chiral amine catalysis (enamine-, iminium catalysis)
- Chiral phosphoric acid catalysis
- N-heterocyclic carbene catalysis
- Phase-transfer catalysis
- Bifunctional hydrogen bond catalysis





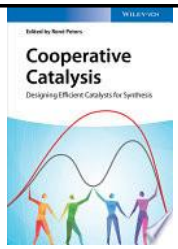
B. Han, X.-H. He, Y.-Q. Liu, G. He, C. Peng, J.-L. Li, *Chem. Soc. Rev.* **2021**, *50*, 1522 – 1586.

Catalysis involving two catalysts

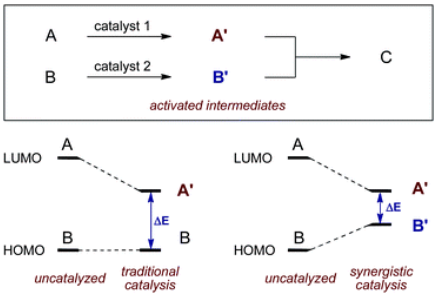


A. E. Allen, D. W. C. MacMillan, Chem. Sci. 2012, 3, 633-658.

Cooperative (synergistic, dual) catalysis

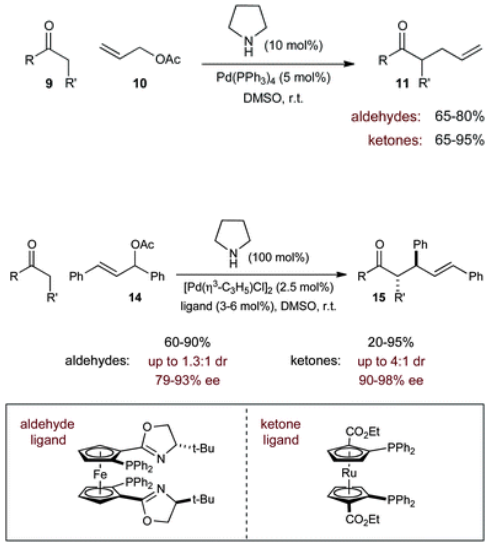


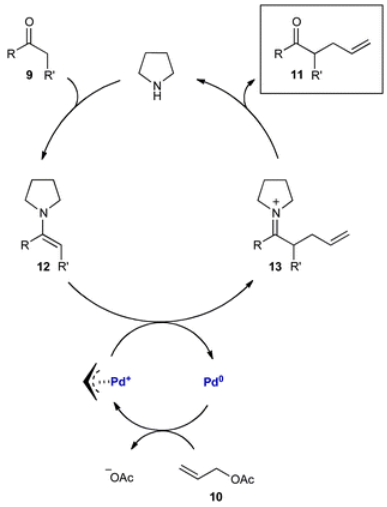
Two catalysts and two catalytic cycles work in concert to create a single new bond
→ both reactants are activated by two different catalysts



A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633-658.

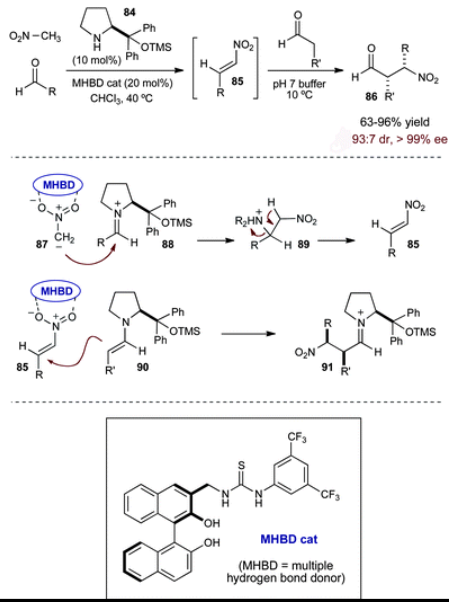
Combining organo- and transition-metal catalysis





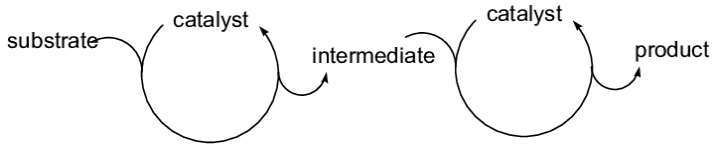
A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633-658.

Combining two types of organocatalysis



A. E. Allen, D. W. C. MacMillan, *Chem. Sci.* **2012**, *3*, 633-658.

Tandem catalysis



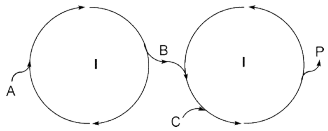
- Multiple (usually two) catalysts produce a product in a sequence of reactions in one pot

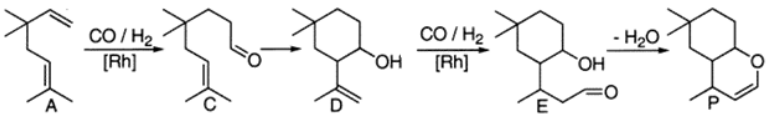
→ avoids need of isolating and purifying the intermediates
→ reduction of waste and cost
→ unstable reaction products can be directly transformed in a consecutive reaction

→ risk of unwanted side reactions
→ requires matching of catalysts (rates)

W. Kroutil, M. Rueping, ACS Catal. 2014, 4, 2086.

Tandem catalysis using one catalyst

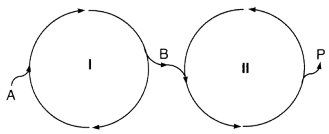




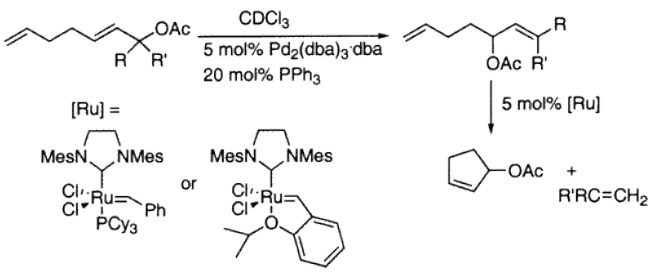
[Rh] = $[RhCl(COD)]_2$

J.-C. Wasilke, S. J. Obrey, T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001.

Tandem catalysis using different catalysts

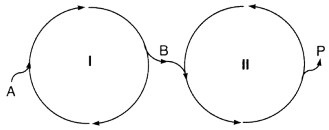


1. Pd-catalyzed allylic acetate isomerization
2. Ring closing metathesis

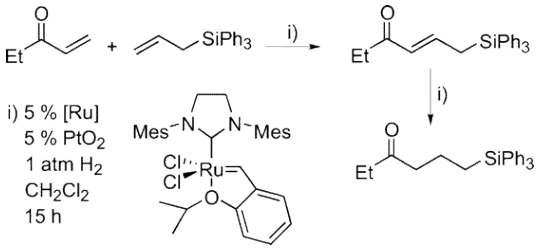


J.-C. Wasilke, S. J. Obrey, T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001.

Tandem catalysis using different catalysts



1. Metathesis
2. Reduction



J.-C. Wasilke, S. J. Obrey, T. Baker, G. C. Bazan, *Chem. Rev.* **2005**, *105*, 1001.

Homogeneous catalysis

- development of tandem catalytic processes
  - compatible catalysts, compatible kinetics, compartmentalization, combination with biocatalysts
  - novel transformations, catalytic generation of reactive species and employing them in tandem reactions

→ "Although there have been great strides in homogeneous catalysis, great opportunities and expectations abound. Meeting these objectives will require advances in our fundamental understanding of reactions and mechanisms along with fundamentally new approaches to homogeneous catalysis."

E. M. Carreira: Homogeneous catalysis in the future (Catalysis in Chemistry and Biology, 2018)

Learning objectives

- You should be able to explain and understand:
  - Homogeneous catalysis
  - Basic terms used for characterization of homogeneous catalytic reactions
  - Transition metal catalysis - describe at least three examples (hydrogenation, hydroformylation, Suzuki reaction - see also the additional short videos)
  - Main group catalysis - describe at least two examples (hydrogenation, addition reactions)
  - Organocatalysis - describe enamine and iminium catalysis
  - Principles of cooperative and tandem catalysis

Do the quiz and
see you in the class!