Dipartimento di Chimica

Sapienza Università di Roma

Seminari di Natale 2021

WellChem: CHIèaMICA del Futuro

lunedì 20 dicembre 2021

PLS

Quando la natura ispira la scienza: rompere le molecole oltre lo specchio

di Fabrizio Vetica

Seminari di Natale 2021 del Dipartimento di Chimica
https://www.chem.uniroma1.it/Seminari%20di%20Natale
canale YouTube **Wellchem Chimica**

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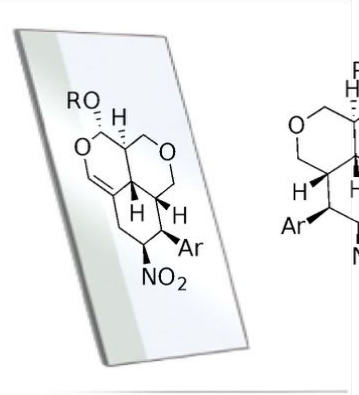
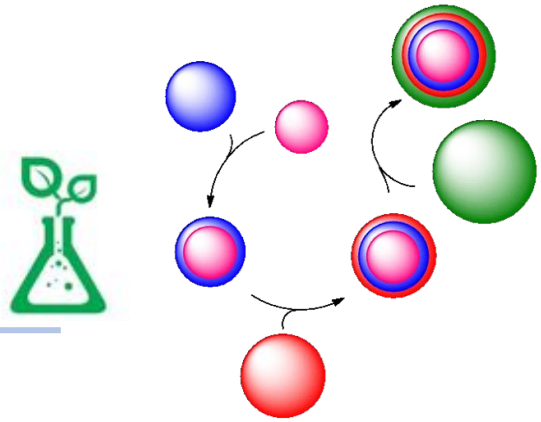
Viaggio alla scoperta della chiralità dagli oggetti alle molecole. L'esistenza di molecole come strutture isomeriche, immagini speculari tra loro, influisce sulla vita di tutti i giorni, dai profumi, ai sapori, ai principi attivi di farmaci. La necessità di studiare gli ambienti chirali e capire come queste molecole *"specchiate"* interagiscano diversamente con essi ha portato i chimici a cercare nuove soluzioni per *rompere lo specchio*, e sintetizzare uno solo dei due isomeri: la sintesi asimmetrica. Il contributo di Benjamin List and David W. C. MacMillan allo sviluppo dell'organocatalisi asimmetrica è valso ai due chimici il Premio Nobel per la Chimica 2021. Questa tecnica "green" prevede l'uso di piccole molecole organiche omochirali per rompere lo specchio in maniera efficiente, alla continua ricerca di una chimica più economica e sostenibile.

SAPIENZA
UNIVERSITÀ DI ROMA



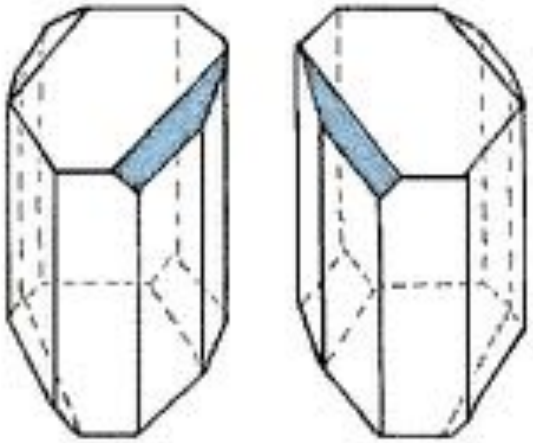
Quando la natura ispira la scienza: rompere le molecole oltre lo specchio

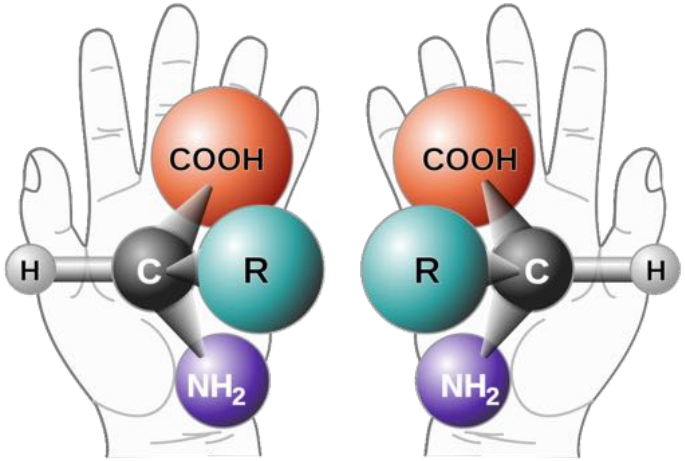
Dr. Fabrizio Vetica, PhD
Dipartimento di Chimica



Rome, 20-12-2021

La **chiralità** (dal greco χειρ (cheír) = mano) è una proprietà di un oggetto rigido di non essere sovrapponibile alla sua immagine speculare nelle tre dimensioni.

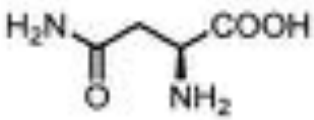




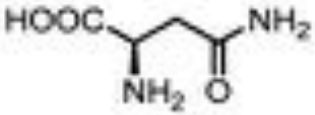
Enantiomeri diversi – comportamento differente

(–)-Limonene
Odore di acquaragia
tremetina

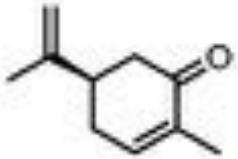
(+)-Limonene
Odore di agrumi



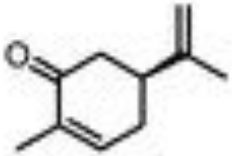
(+)-Asparagina
sapore amaro



(–)-Asparagina
sapore dolce

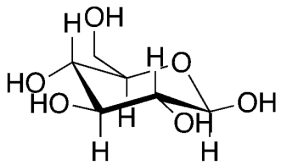


(–)-Carvone
odore di menta

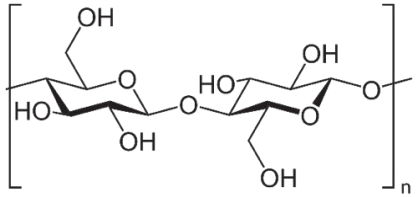


(+)-Carvone
odore di cumino

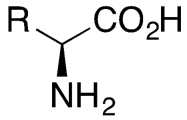
Omochiralità in natura



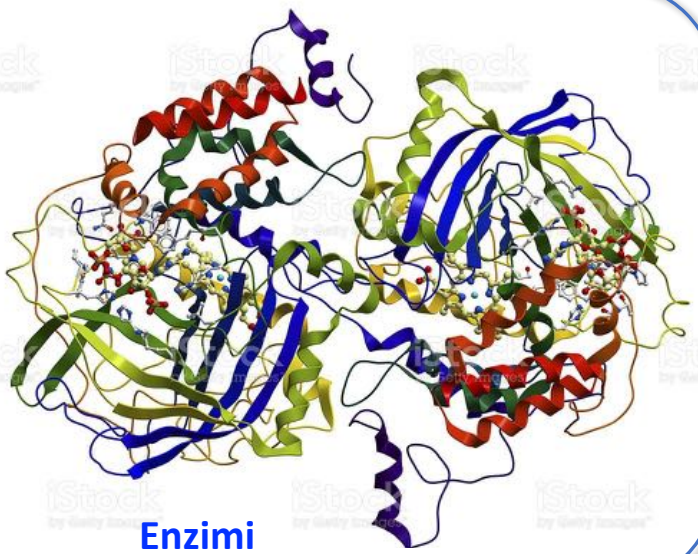
D-glucosio



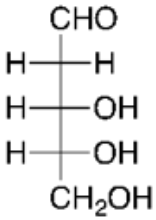
Cellulosa



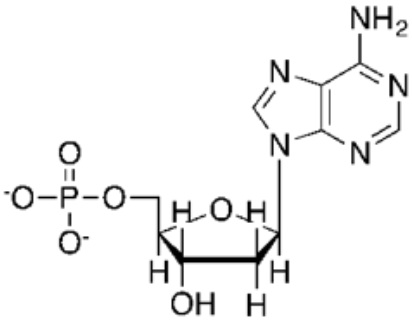
amminoacidi



Enzimi

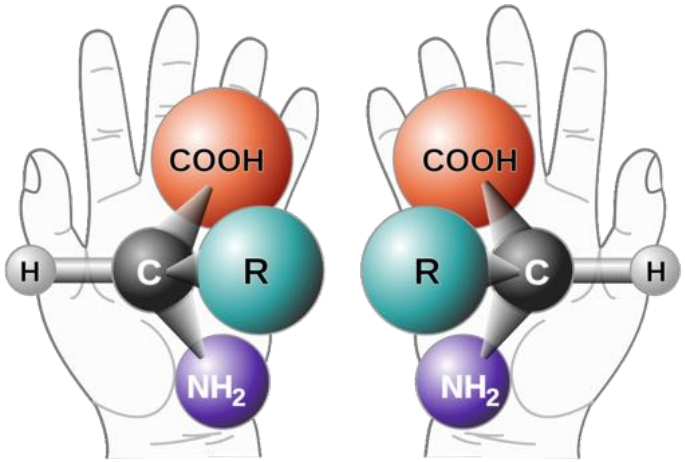


D-Deossiribosio

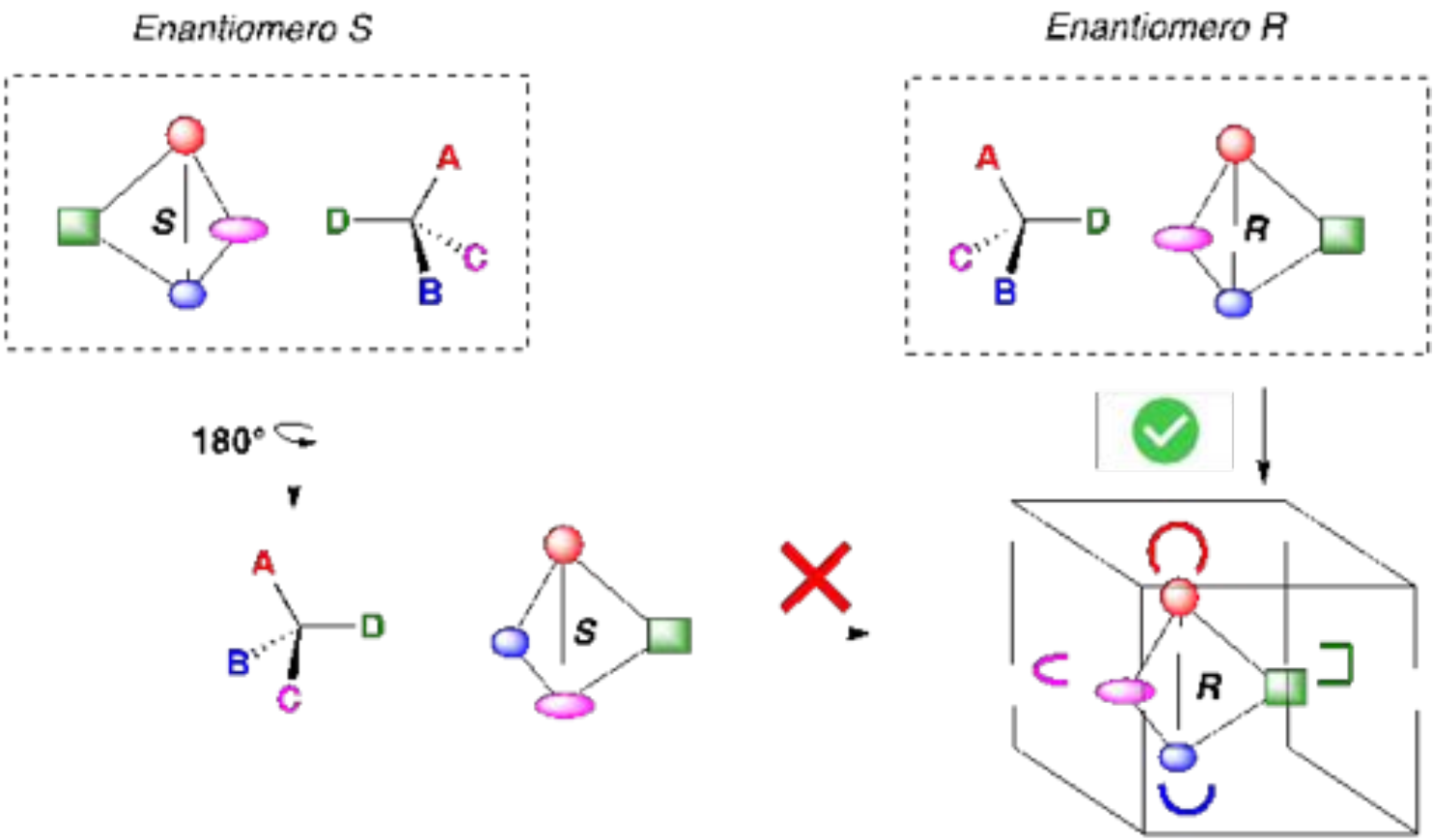


Deossinucleosidi

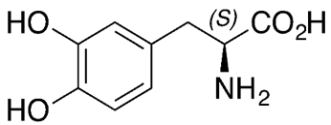
DNA


COOH
H
C
R
NH2
COOH
R
C
H
NH2

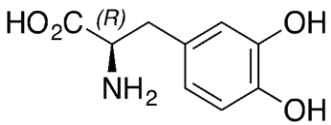
Ambiente chirale – concetto di chiave/serratura



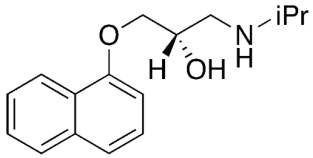
Importanza della chiralità in ambito biologico/farmaceutico



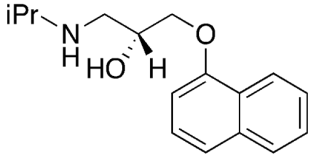
L-Dopa
Pro-drug – attivato dall'enzima
Dopamina decarbossilasi
Trattamento del morbo
Di Parkinson



D-Dopa
Non attivato dall'enzima
Accumulato - granulocitopenia

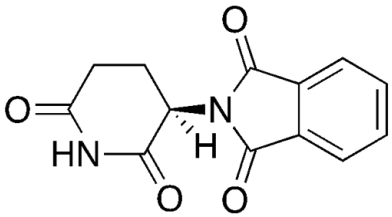


(–)-Propanolol
Beta-bloccante - antiipertensivo
Nobel per la Medicina 1988

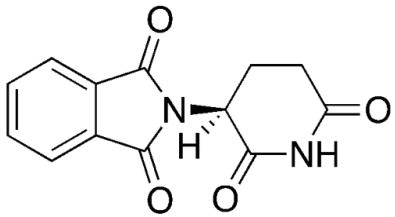


(+)-Propanolol
inattivo

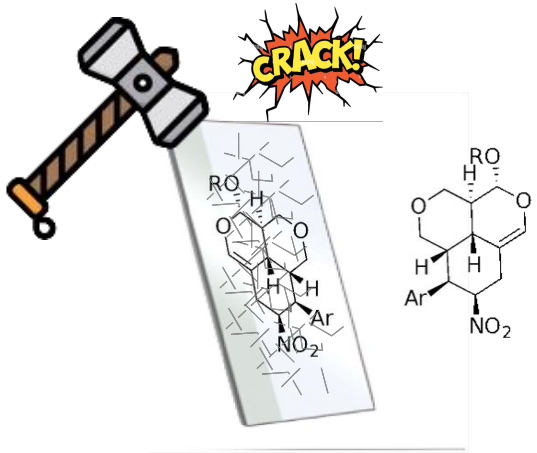
Grünenthal Chemie (1957)



(+)-Thalidomide
Sedativo - antiemetico

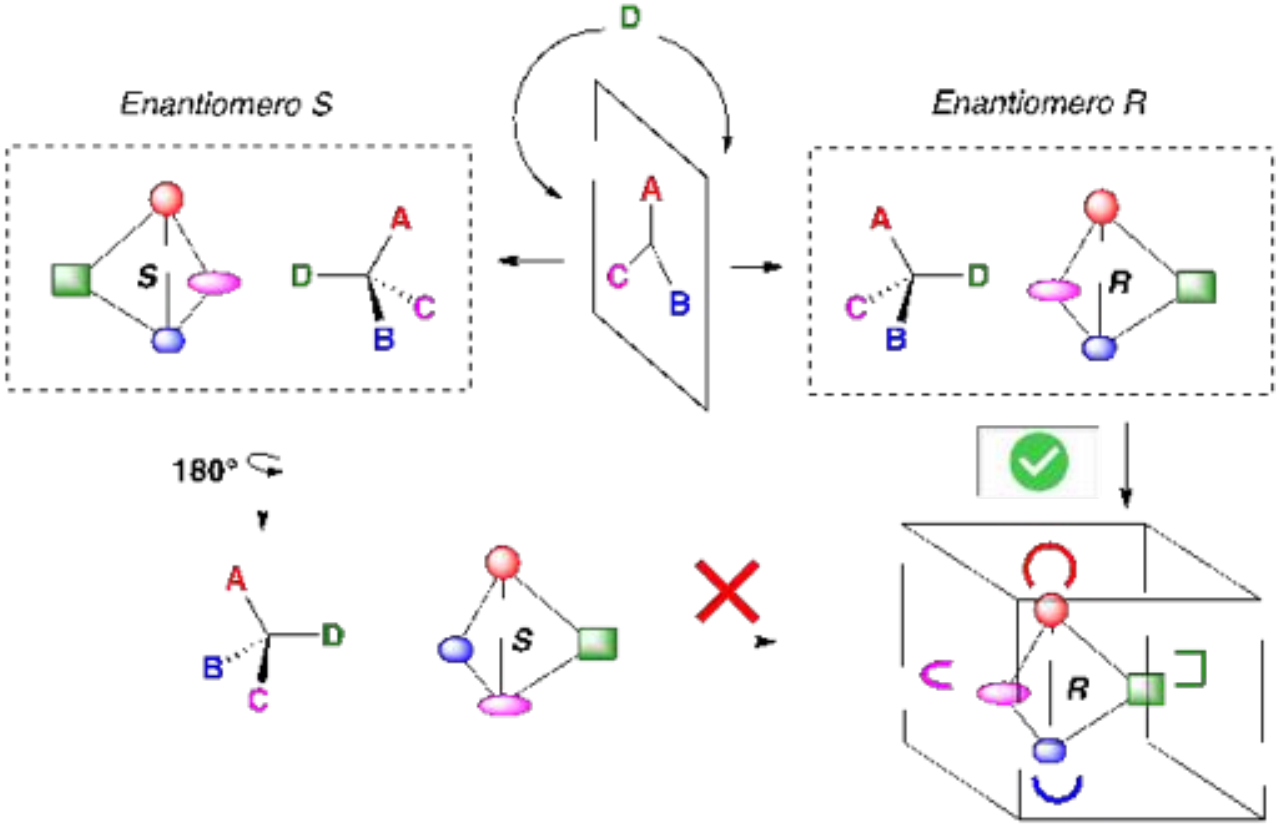


(–)-Thalidomide
teratogeno



Possibili stereoisoeri = 2^n

n = numero di centri chirali

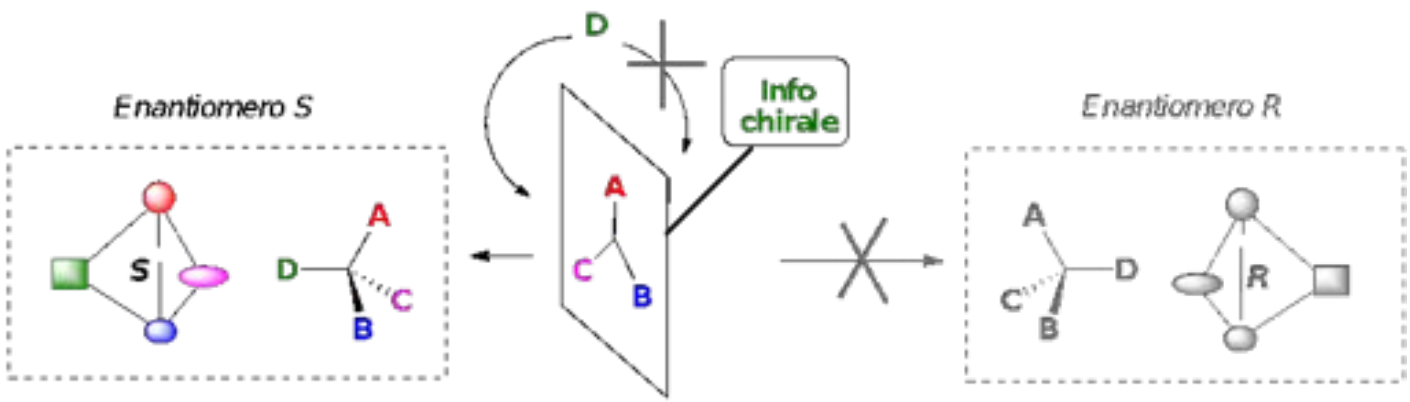


Induzione asimmetrica

Info chirale

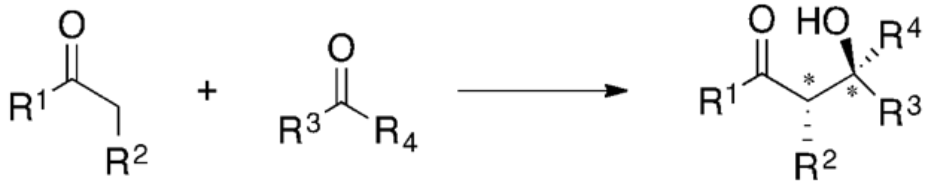
Molecola chirale

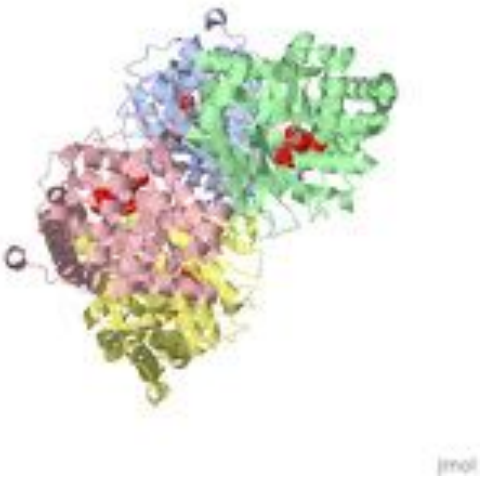
Introduzione di ”asimmetria” in un reagente simmetrico

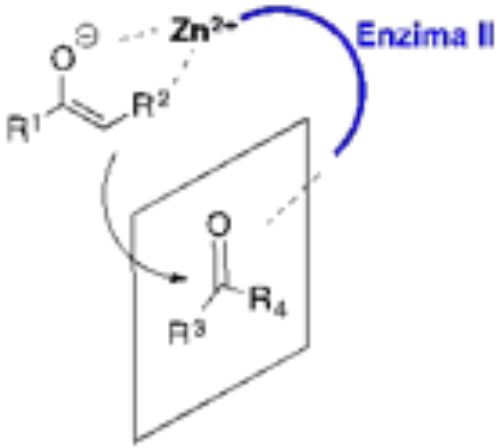


Generazione di un ambiente chirale su un substrato simmetrico

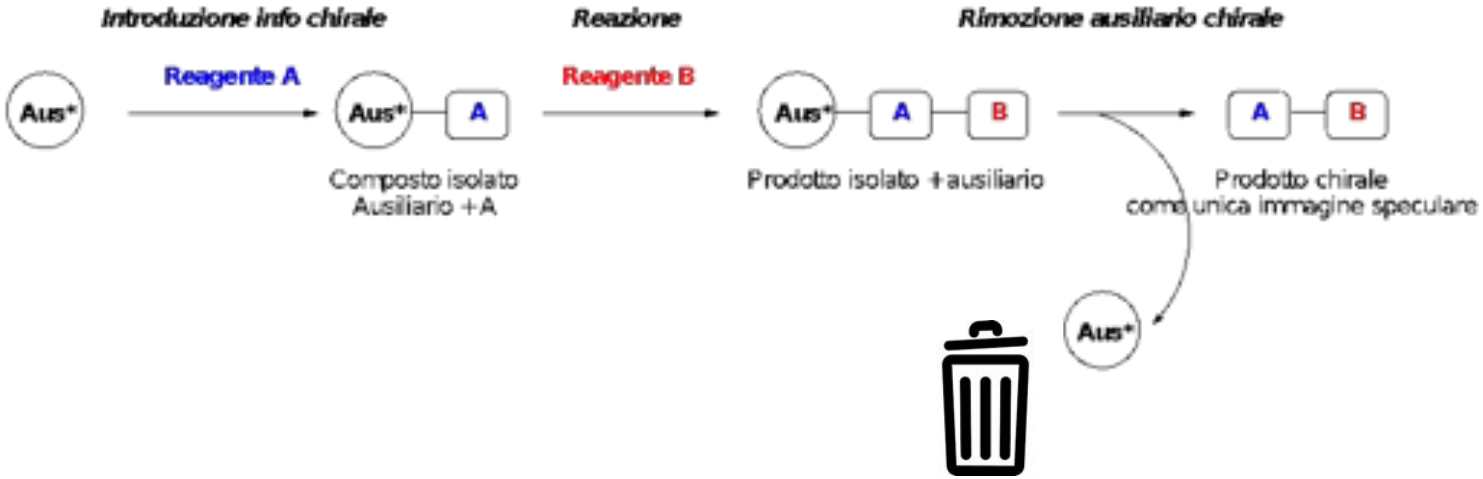
Reazione aldolica ed enzima aldolasi



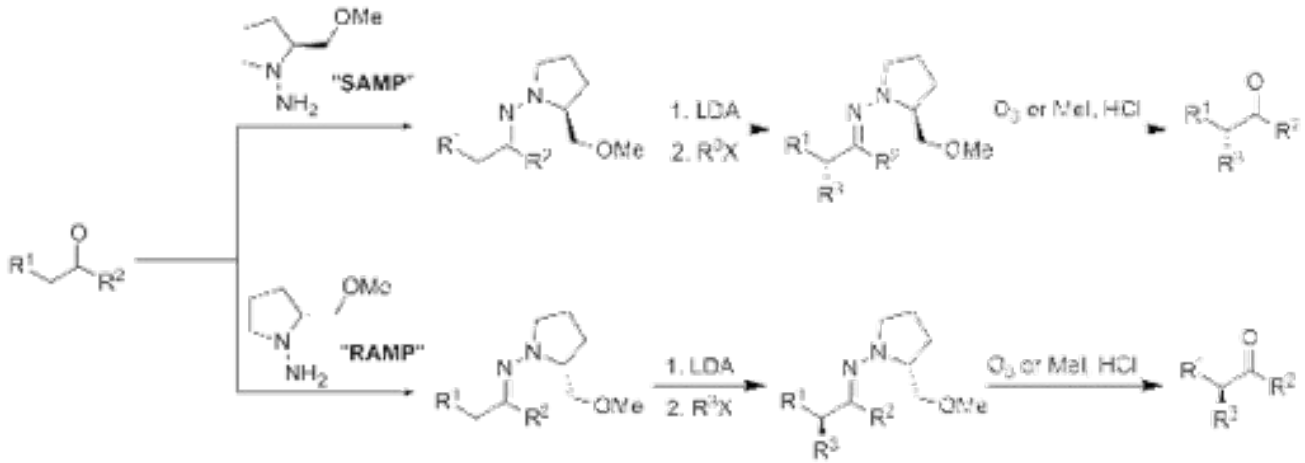




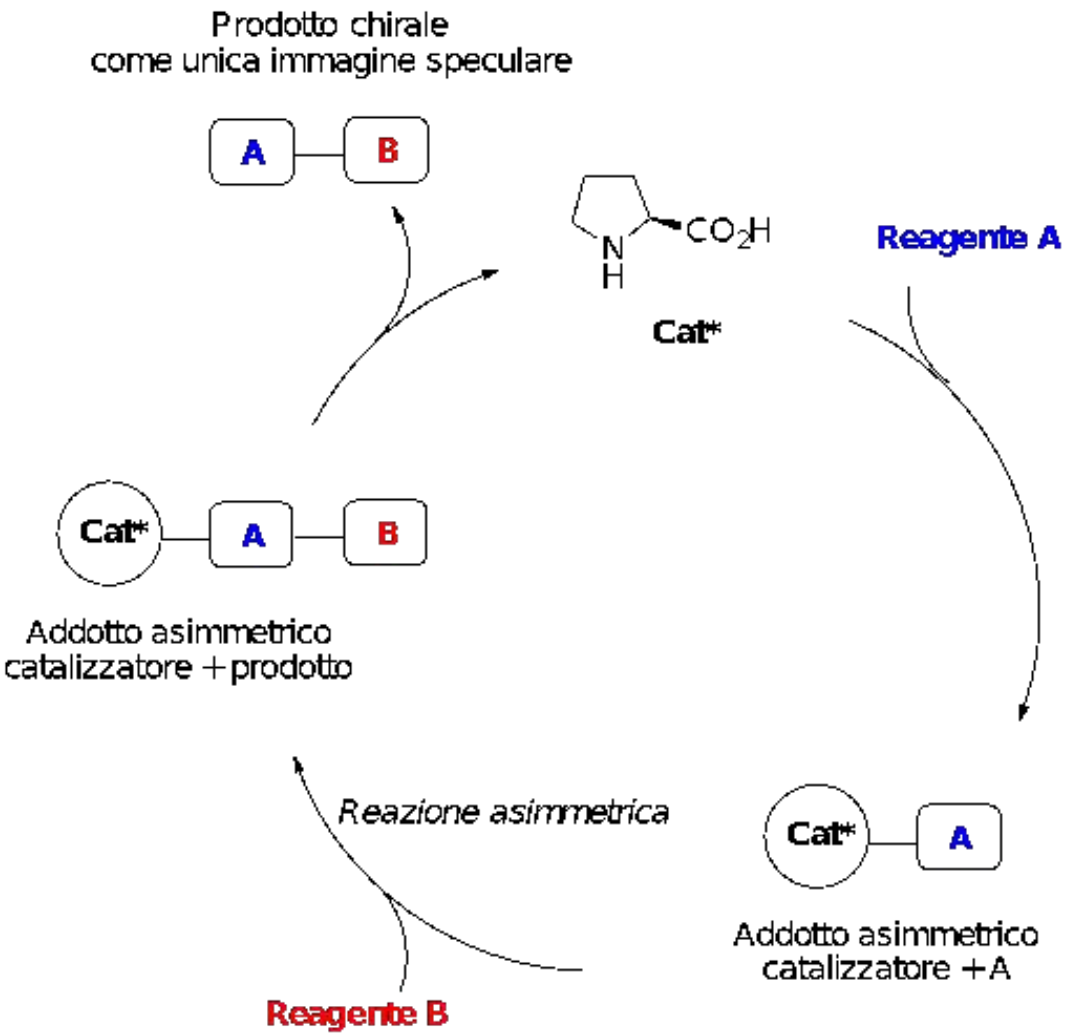
Ausiliario chirale – specie chimica che viene introdotta in un reagente con una reazione, dando informazione chirale, e poi viene rimosso con una successiva reazione dal prodotto



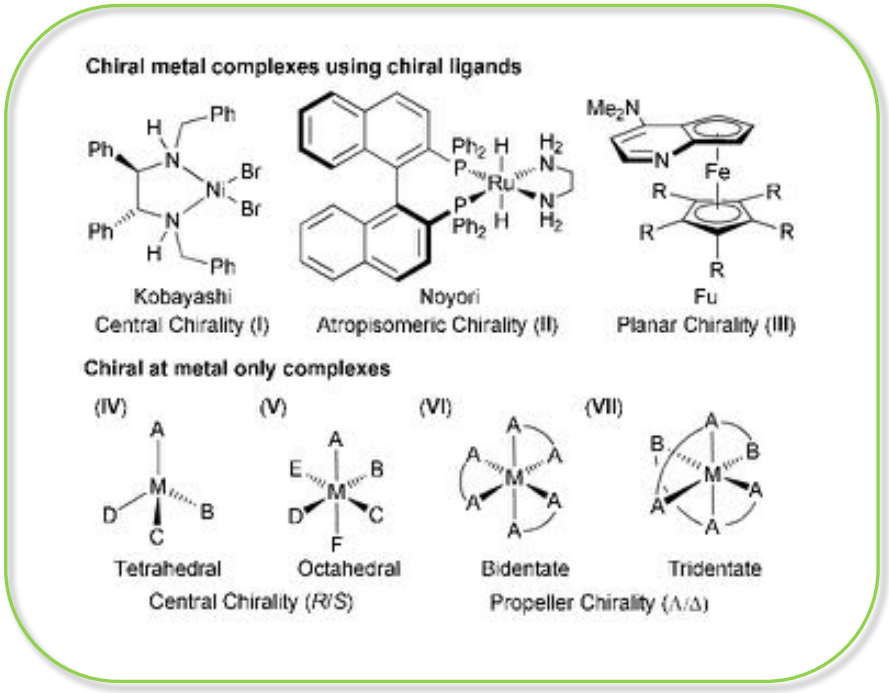
Prof. Dieter Enders – ausiliario chirale SAMP



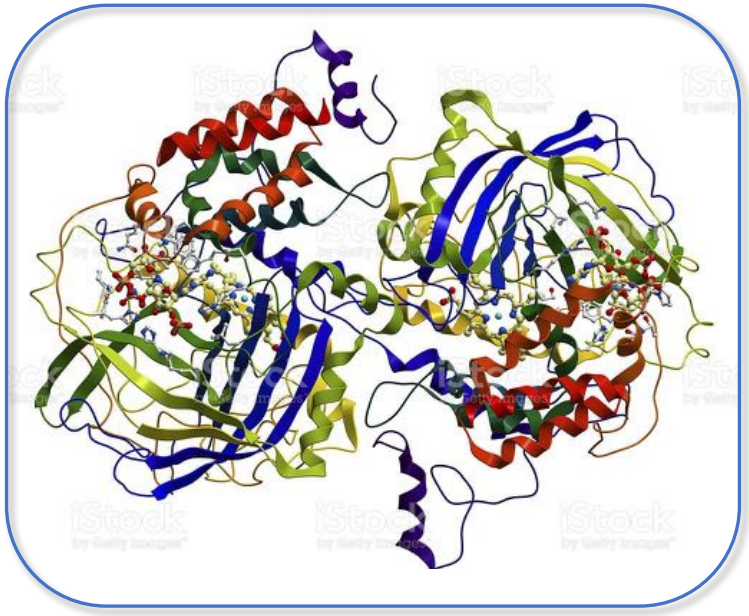
Catalizzatore – specie chimica che attiva una reazione, senza consumarsi e rimanendo inalterato al termine della reazione stessa



Catalizzatori utilizzati fino al 2000



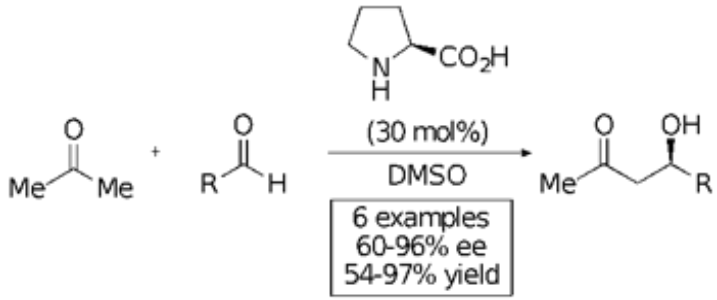
Complessi chirali di metalli di transizione

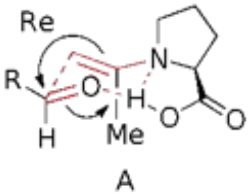


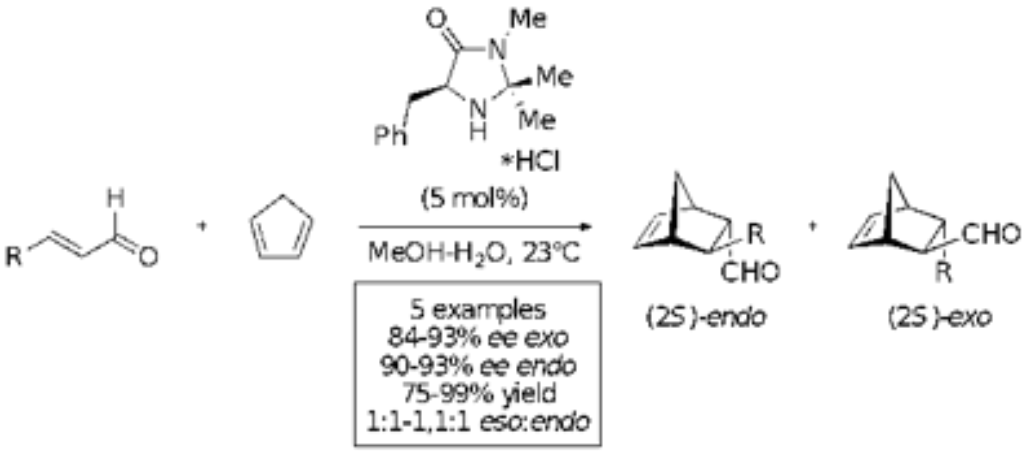
Enzimi

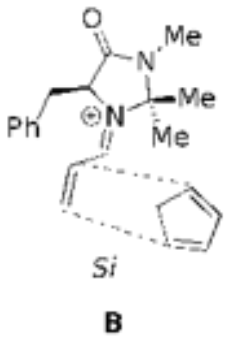
Svantaggi – costi elevati, instabilità all'aria e all'umidità, difficile sintesi, specificità su singoli substrati

Organocatalisi asimmetrica – utilizzo di piccole molecole organiche omochirali per promuovere reazioni chimiche in modo asimmetrico







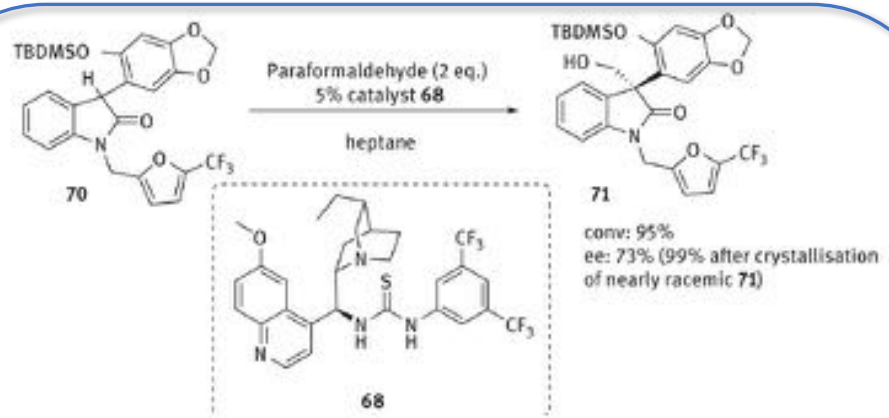


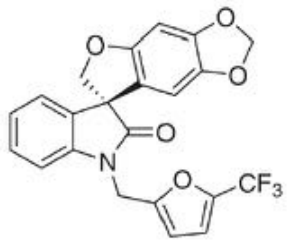
Premio Nobel per la Chimica 2021

J. Am. Chem. Soc. **2000**, 2395; *J. Am. Chem. Soc.* **2000**, 4243

"Democratizzare la sintesi asimmetrica – chiunque può condurre questa tipologia di reazioni, senza un particolare *know-how*"

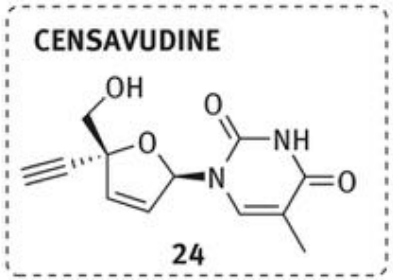
- Facile reperimento dei catalizzatori, spesso da composti naturali quali amminoacidi
- Basso costo e più semplice ottenimento sintetico
- Elevata stabilità all'aria e umidità
- Diversa possibilità di attivazione in termini di substrati
- Minore selettività alle variazioni della struttura



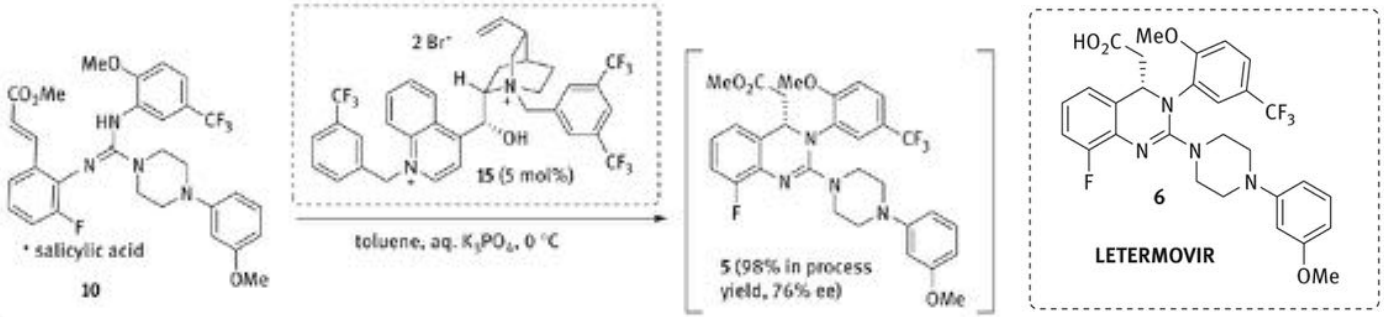


53: FUNAPIDE

Antagonista del canale del sodio
Teva Pharmaceuticals



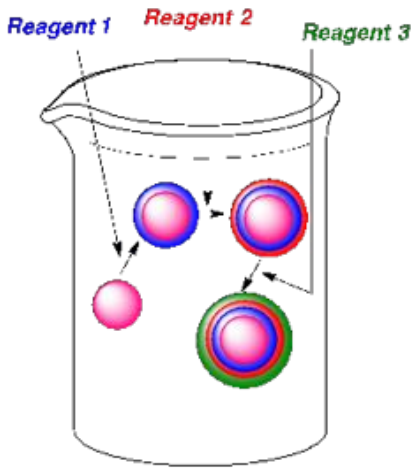
Attività antiretrovirale
Nucleoside reverse transcriptase (NRTI)
Bristol Myers-Squibb

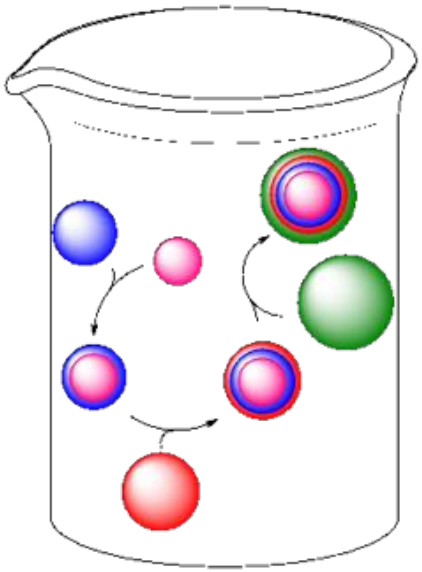


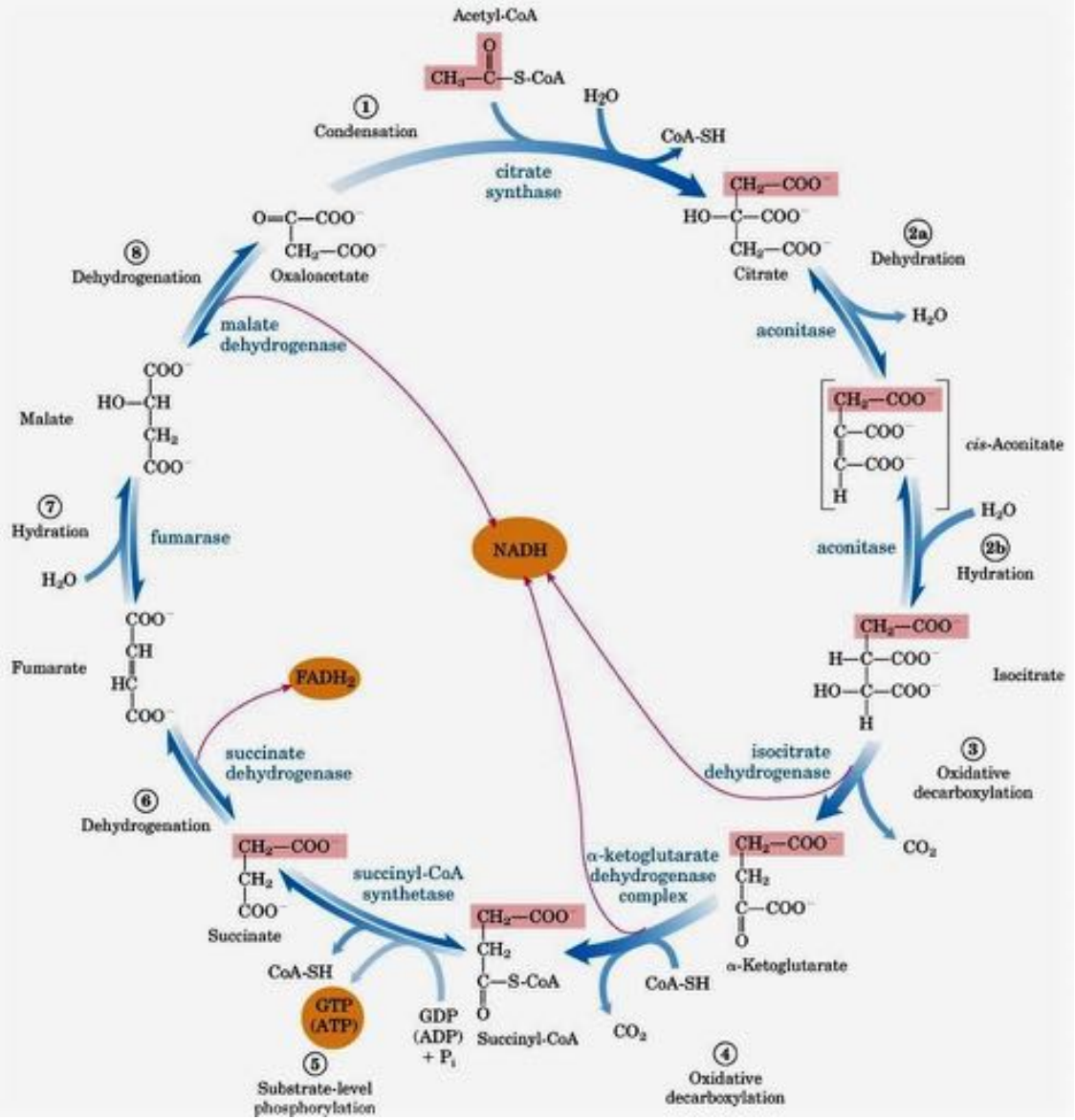
Antivirale
Cytomegalovirus
(*Prevymis*)
Merck & Co

A. Carlone, L. Bernardi, *Physical Syiences Review* **2019**, 4, 20180097

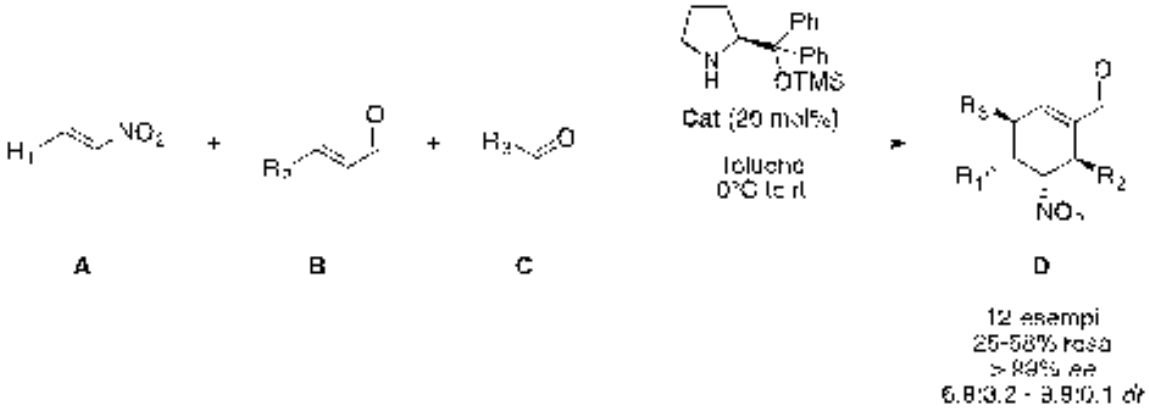
Green asymmetric organocatalysis






Acetyl-CoA
CH3—C—S-CoA
H2O
CoA-SH
1
Condensation
citrate synthase
CH2—COO⁻
HO—C—COO⁻
CH2—COO⁻
Citrate
2a
Dehydration
H2O
aconitase
cis-Aconitate
H2O
aconitase
2b
Hydration
Isocitrate
isocitrate dehydrogenase
3
Oxidative decarboxylation
CO2
α-ketoglutarate dehydrogenase complex
α-Ketoglutarate
CoA-SH
CO2
4
Oxidative decarboxylation
Succinyl-CoA
succinyl-CoA synthetase
GDP (ADP) + Pi
GTP (ATP)
CoA-SH
5
Substrate-level phosphorylation
Succinate
succinate dehydrogenase
FADH2
6
Dehydrogenation
Fumarate
fumarase
H2O
7
Hydration
Malate
malate dehydrogenase
8
Dehydrogenation
Oxaloacetate
NADH

Organocatalisi asimmetrica e reazioni domino



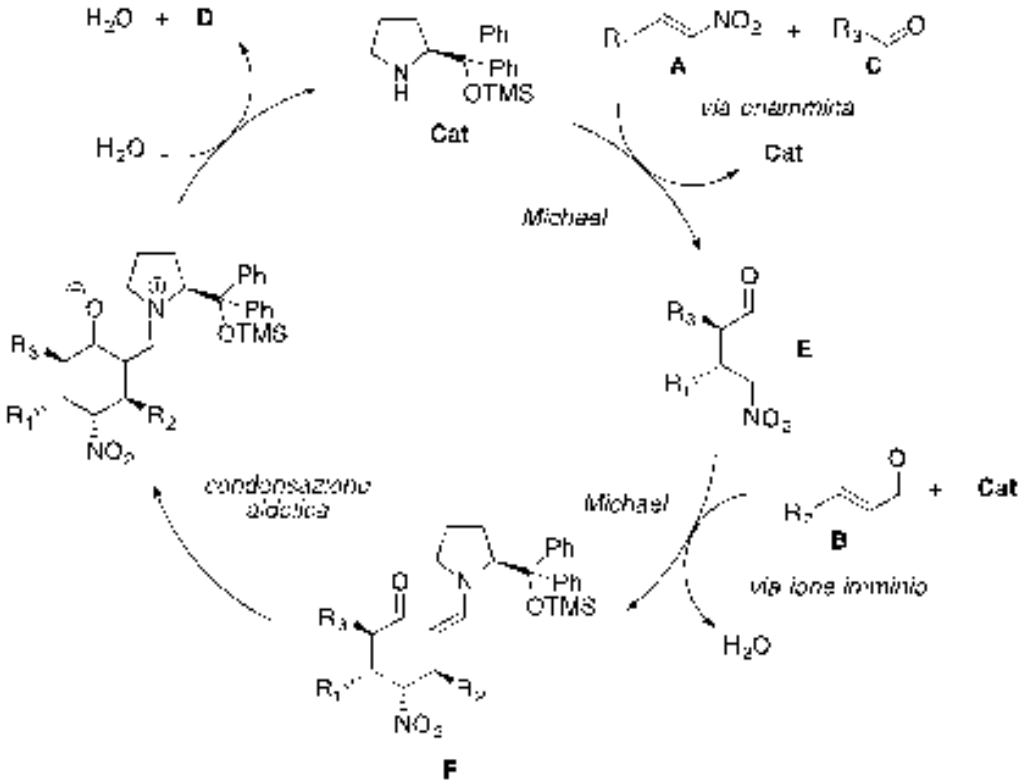


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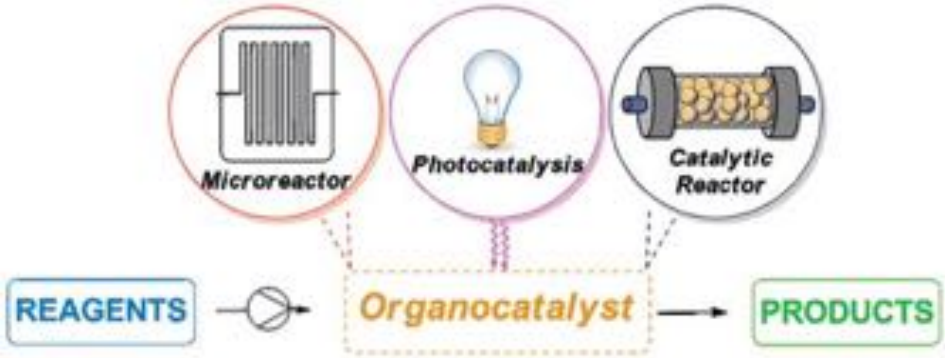
Foto-organocatalisi

Utilizzo della radiazione luminosa per attivare intermedi reagente-catalizzatore per promuovere nuove strade reattive, prima inesplorate

Organocatalizzatori ancorati per catalisi in flow



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What's next? We'll see……

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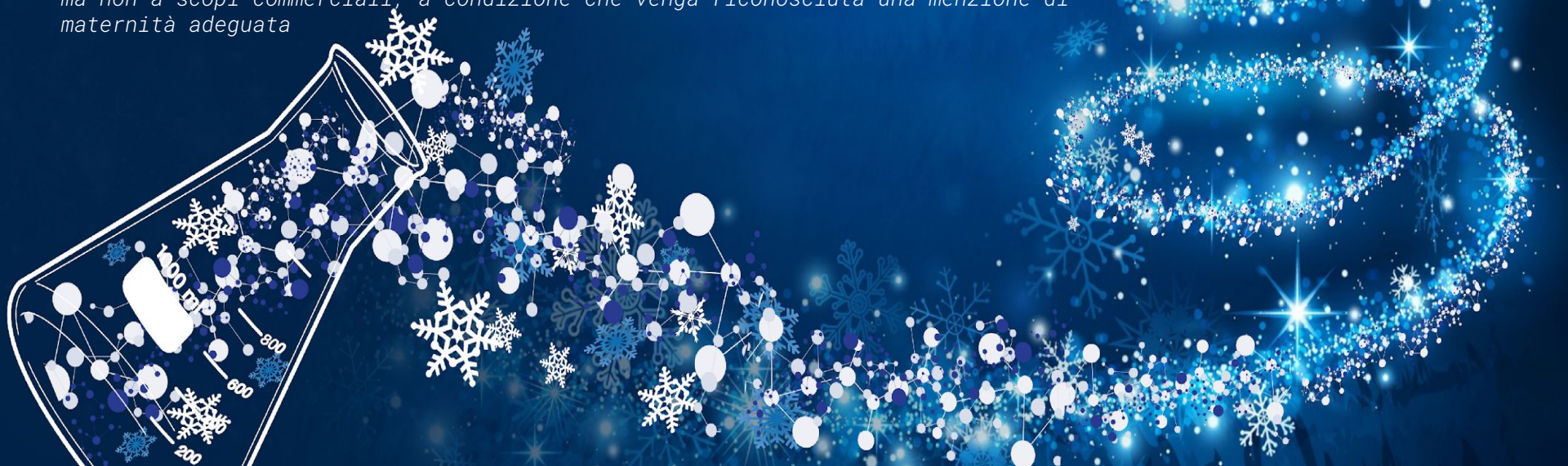
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