ORGANOCATALISI

"an organic compound of relatively low molecular weight and **simple structure** capable of promoting a given transformation in substoichiometric quantity."

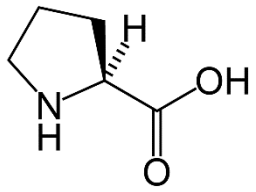
Organocatalizzatori= molecole organiche composte da C, H, N, S e P

Vantaggi:

* robusti
* poco costosi
* facilmente disponibili
* non tossici
* inerti rispetto umidità e ossigeno

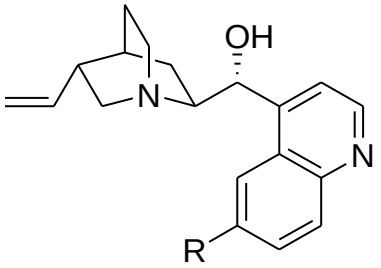
OK per la preparazione di composti che non tollerano contaminazione di metalli

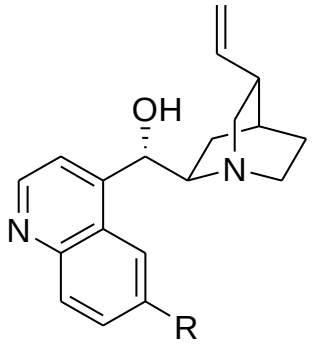
ESEMPI di ORGANOCATALIZZATORI



L-prolina

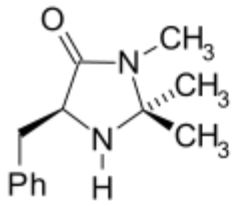
Alcaloidi della cinchona



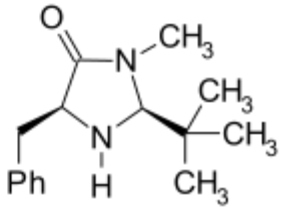


Quinine (QN)	R = OMe	Quinidine (QD)
Cinchonidine (CD)	R = H	Cinchonine (CN)
Cupreine (CPN)	R = OH	Cupreidine (CPD)

Imidazolidinone Catalysts

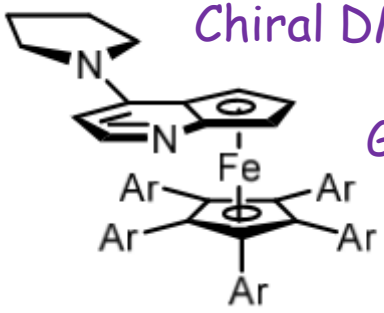


first generation



second generation

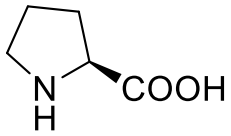
Organocatalizzatori di MacMillan

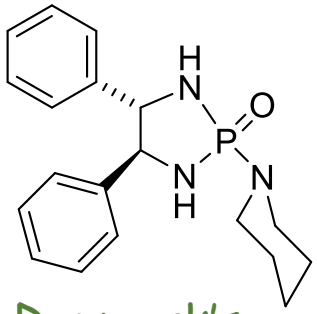


Chiral DMAP

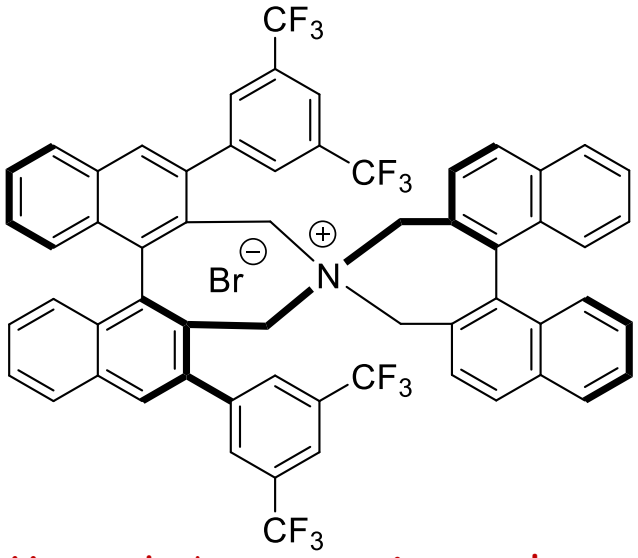
Gregory Fu

"**simple structure**" si riferisce al numero di passaggi ("steps") di sintesi necessary per ottenere l'organocatalizzatore a partire da materiali di partenza economici e largamente disponibili





Denmark's phosphoramidite

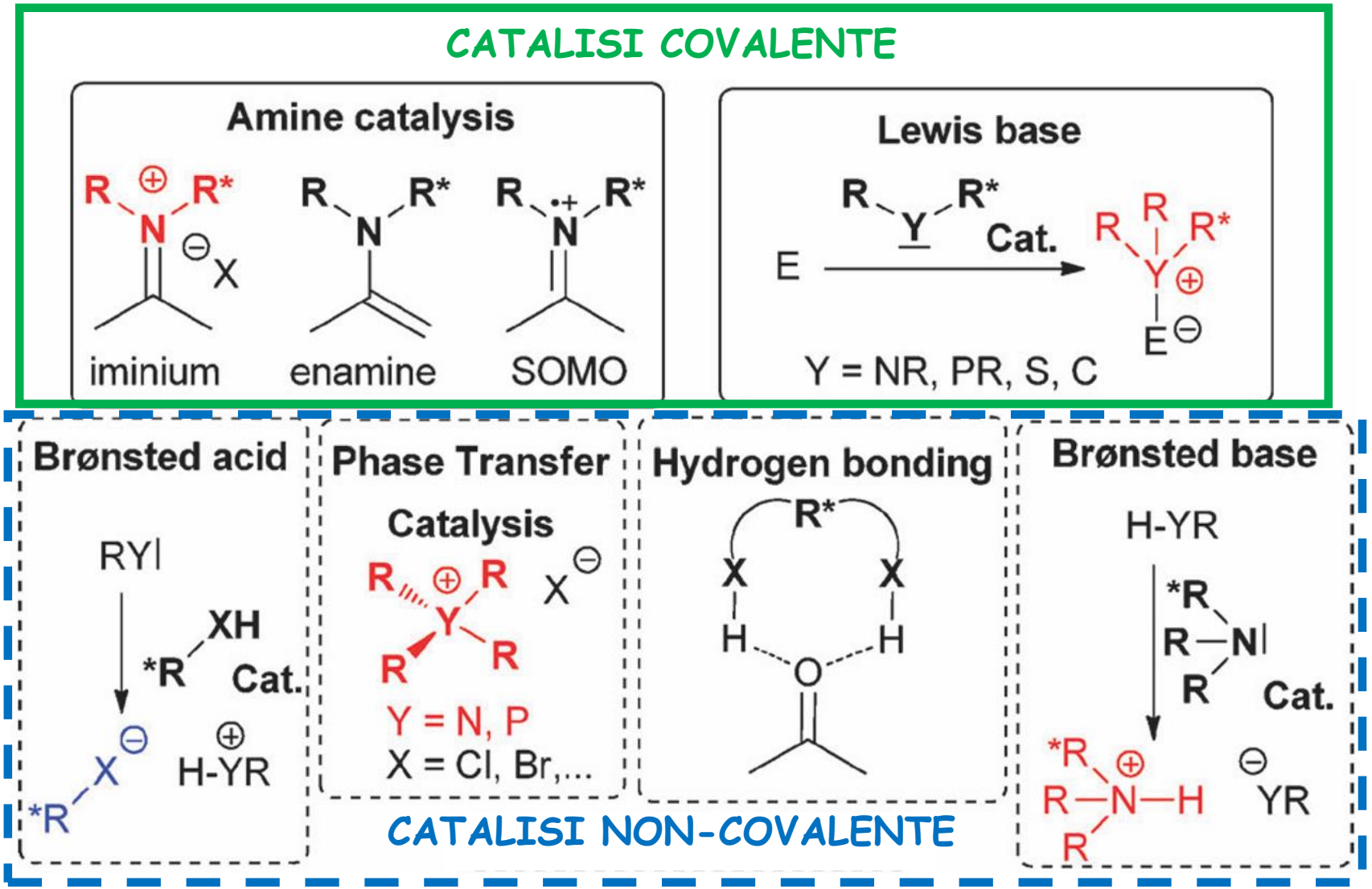


Maruoka's ammonium salt

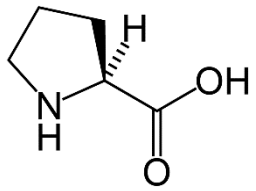
MW	115	369	1078
mol%	30	10	2
n. Steps	0	5	8

Fig. Confrontro tra organocatalizzatori usati nelle reazioni aldoliche

Organocatalizzatori: modi di azione

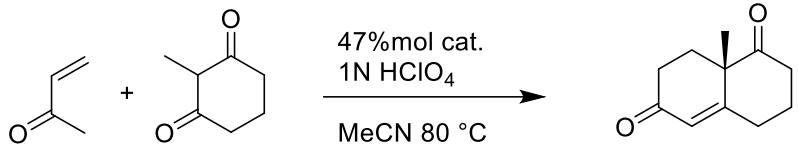


ESEMPI di ORGANOCATALIZZATORI



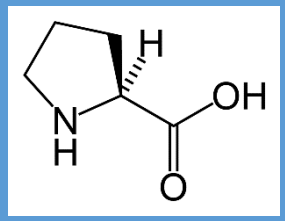
L-prolina

Hajos, Parrish, Eder, Sauer, Wiechert 1971



ciclodisidratazione aldolica intramolecolare

Angew. Chem. Int. Ed. **1971**, *10*, 496-497



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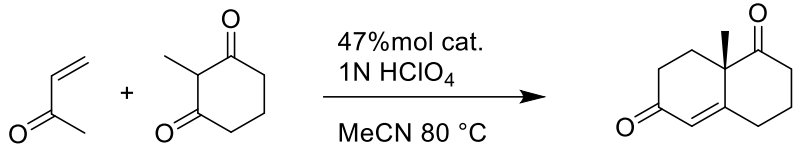
Hajos, Parrish, Eder, Sauer, Wiechert 1971



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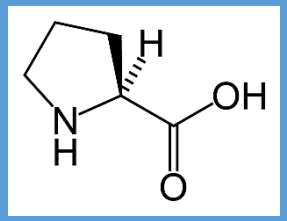
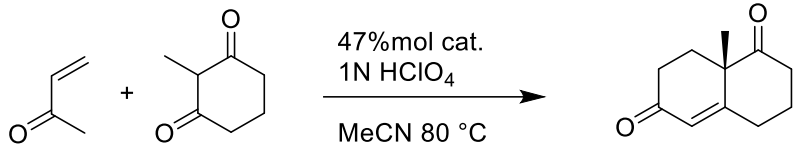


L-prolina

* Amminoacidi o dipeptidi, es. Prolina

* Lunghi peptidi con specifica struttura

Hajos, Parrish, Eder, Sauer, Wiechert 1971



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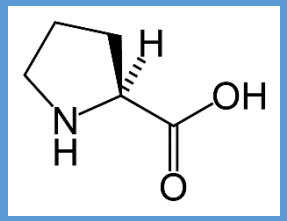
Angew. Chem. Int. Ed. **1971**, *10*, 496-497



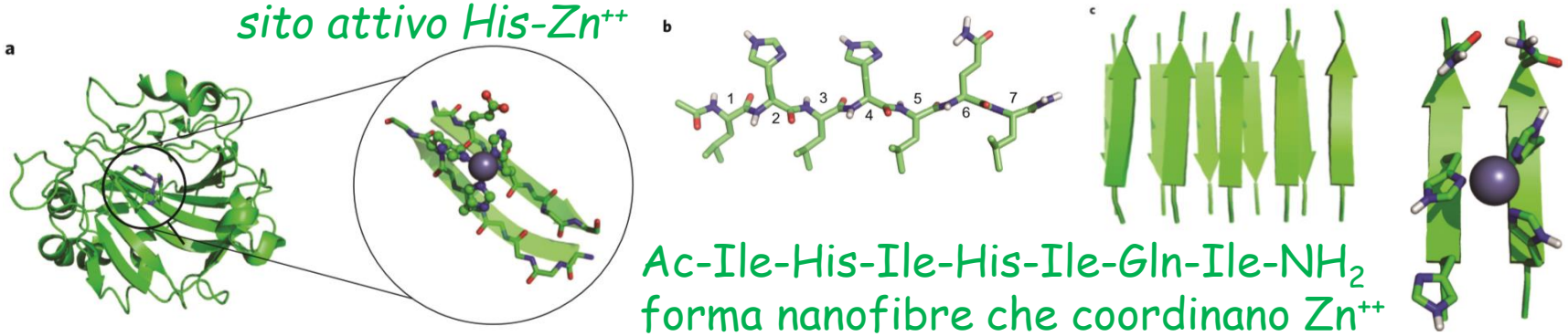
L-prolina

* Amminoacidi o dipeptidi, es. Prolina

* Lunghi peptidi con specifica struttura

* di recente piccoli peptidi che formano fibre supramolecolari che mimano enzimi (es. esterasi)

sito attivo His-Zn^{++}

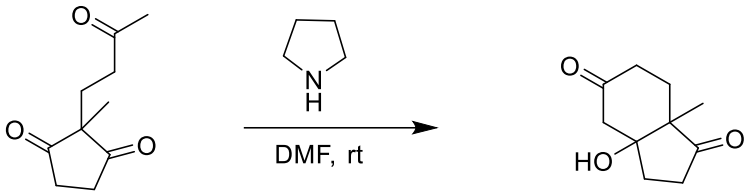


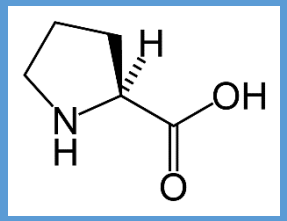
Ac-Ile-His-Ile-His-Ile-Gln-Ile-NH_2
forma nanofibre che coordinano Zn^{++}

Nat. Chem. **2014**, *6*, 303

Perché la prolina?

- Derivato chirale della pirrolidina





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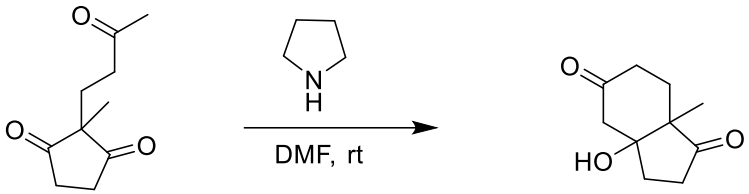
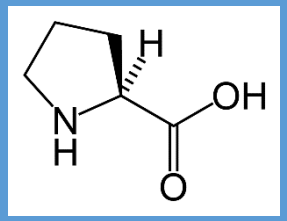


reazione aldolica NON stereoselettiva



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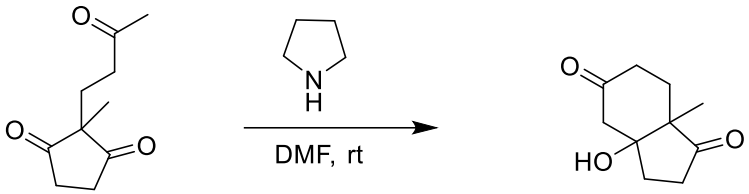
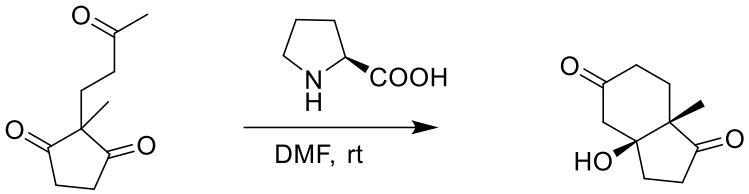
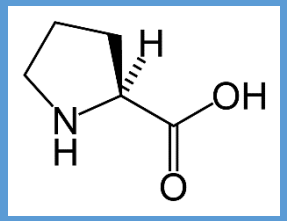


reazione aldolica NON stereoselettiva

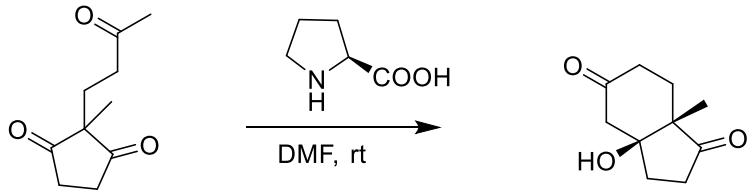


reazione aldolica STEREOSELETTIVA (93 % ee)

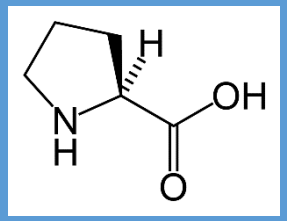


L-prolina

Come funziona?

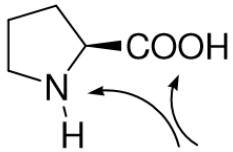


reazione aldolica STEREOSELETTIVA (93 % ee)

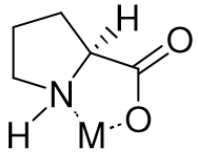


L-prolina

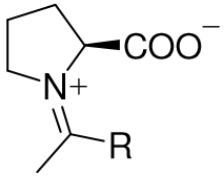
pKa?



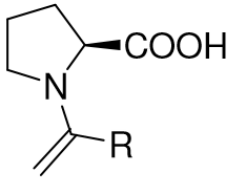
bifunzionale
catalisi acido/base



catalisi metallica

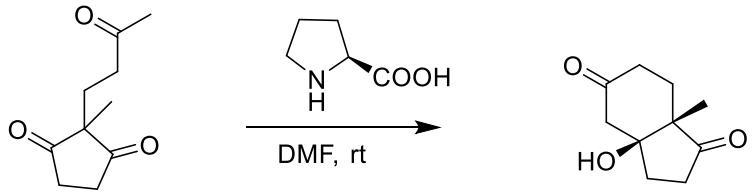


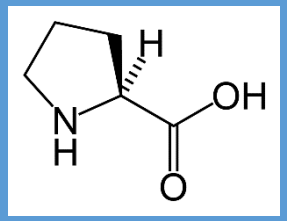
catalizza reazioni via
ione imminio



catalizza reazioni via
enanmmina

Come funziona?

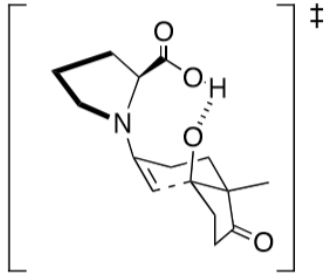




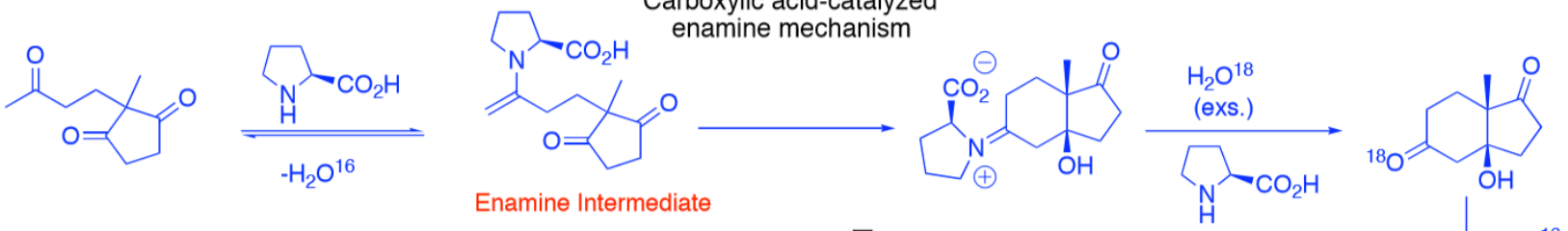
L-prolina

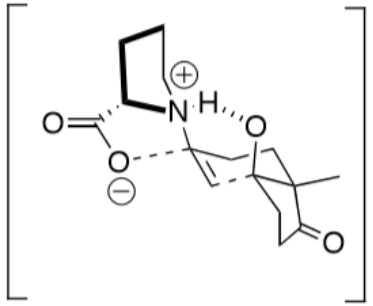
reazione aldolica STEREOSELETTIVA (93 % ee)

stereocontrollo dipende dalla formazione legame a H



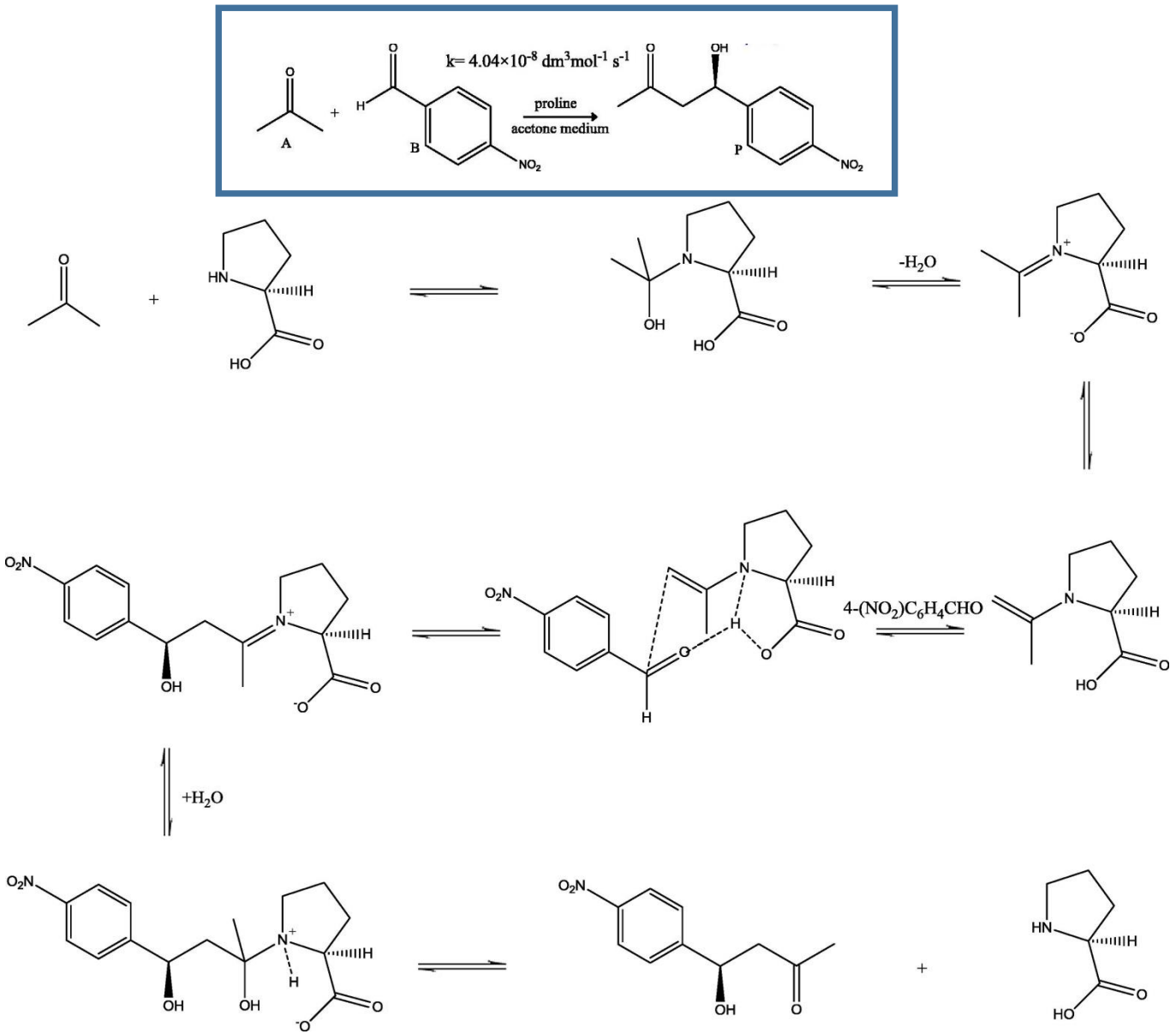
Carboxylic acid-catalyzed enamine mechanism



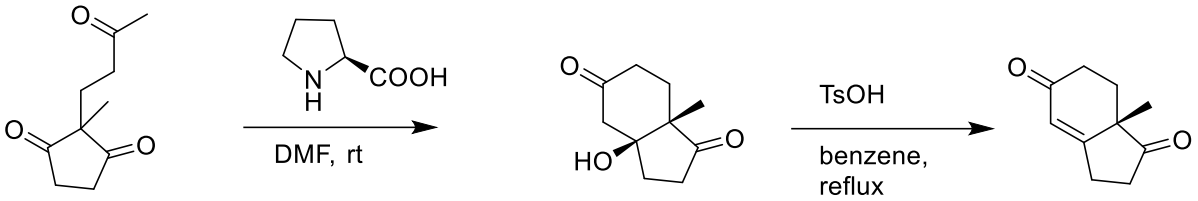


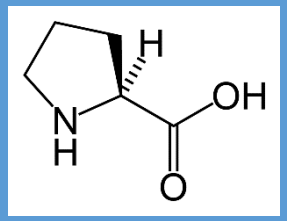
Enaminium-catalyzed mechanism

Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615–1621.



U.I. Tafida *et al., J. Adv. Res.* **2018**, *12*, 11.



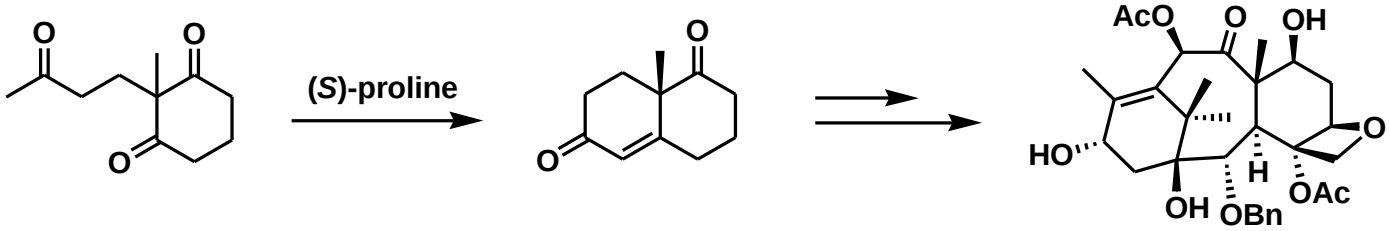


L-prolina

Anellazione Robinson* STEREOSELETTIVA

Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* **1974,** *39,* 1615

Sintesi del Taxol (Danishefsky, 1996)

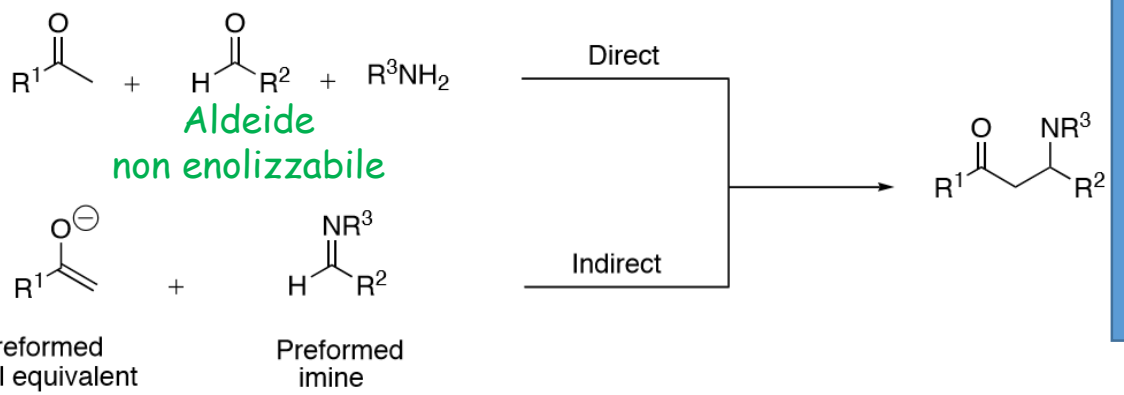


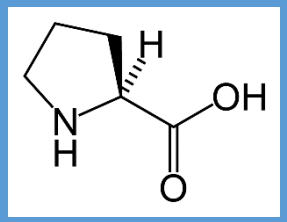
Danishefsky, S. *et al*. *J. Am. Chem. Soc.* **1996,** *118,* 2843

Baccatin III

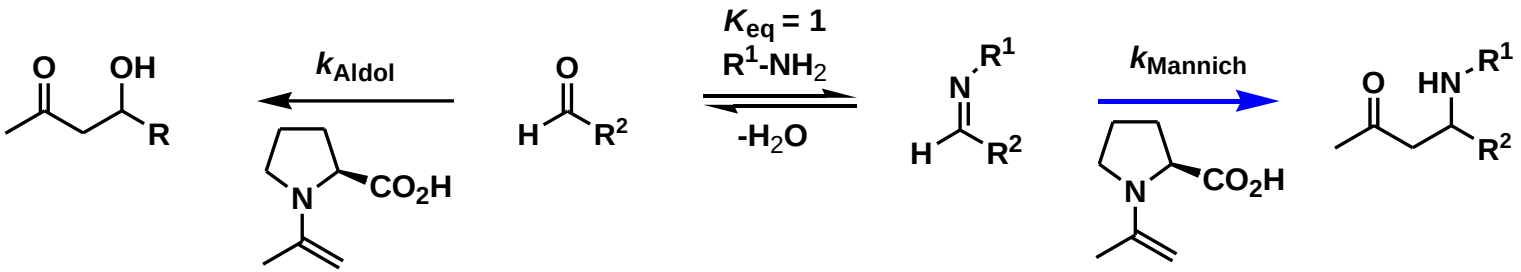
* L'anellazione di Robinson è costituita da un'**addizione di Michael** seguita da una **condensazione aldolica intramolecolare** ed è un metodo per ottenere anelli condensati.

Reazione di Mannich STEREOSELETTIVA





L-prolina

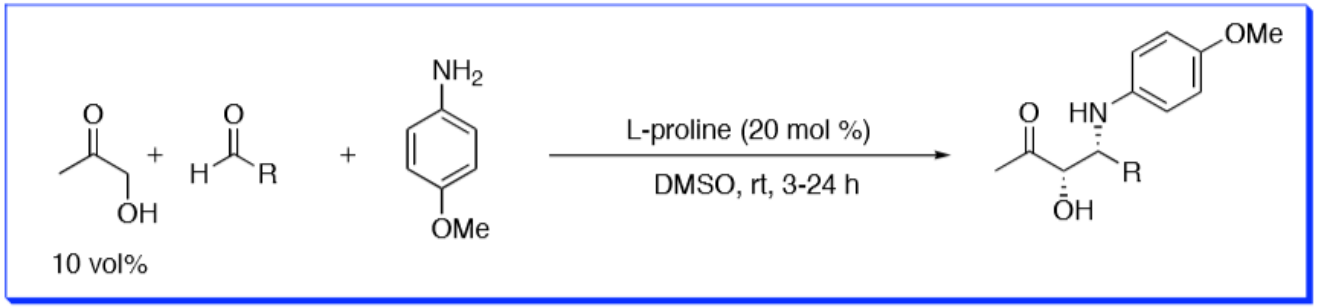


2 requisiti importanti:

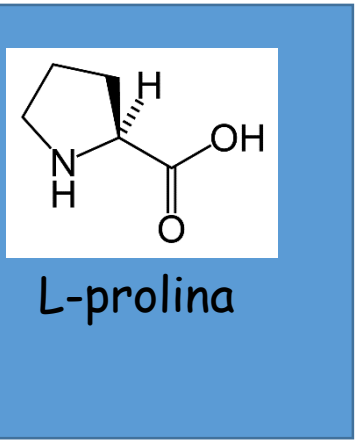
* l'attacco Nu cella prolina enammina verso l'immina (Mannich) deve essere più veloce di quello verso l'aldeide (aldol)

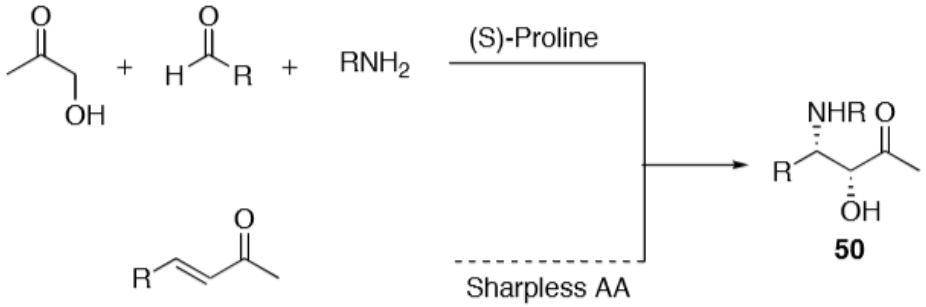
* L'aldeide deve formare preferenzialmente l'immina (Mannich) piuttosto che reagire nella aldol

Reazione di Mannich STEREOSELETTIVA *vs.* Sharpless AA



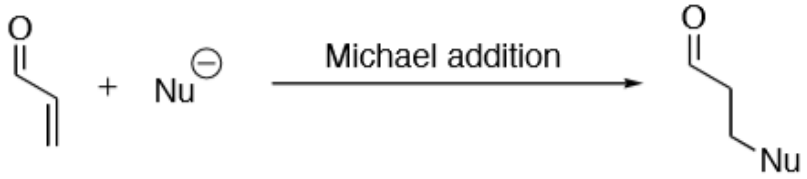
R =	Yield %	dr	%ee
p-$NO_2C_6H_4$	92	20:1	>99
C_6H_5	83	9:1	93
P-$MeOC_6H_4$	88	3:1	61



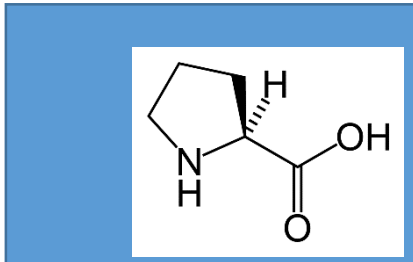


List, B.; Pojarliev, P.; Biller, W. T.; Martin, H. J. *J. Am. Chem. Soc.* **2002**, *124*, 827-833.

Reazione di Michael



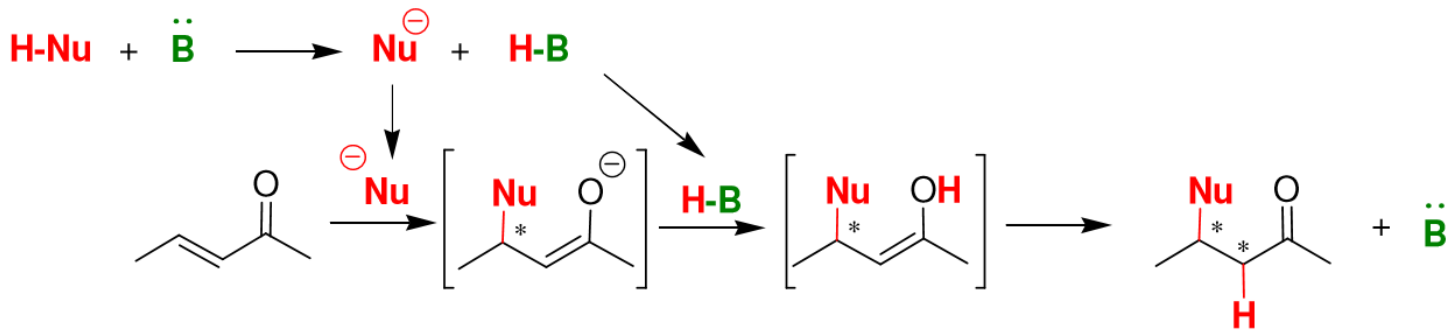
Nu = active methylene center, e.g., malonic acid ester
β-keto esters, nitroalkanes, etc.



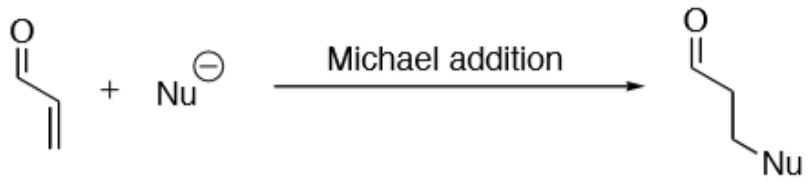
L-prolina

syn / anti

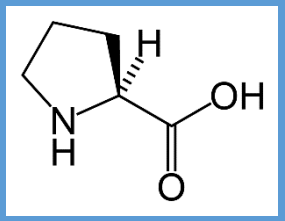
based catalyzed mechanism of Michael addition



Reazione di Michael



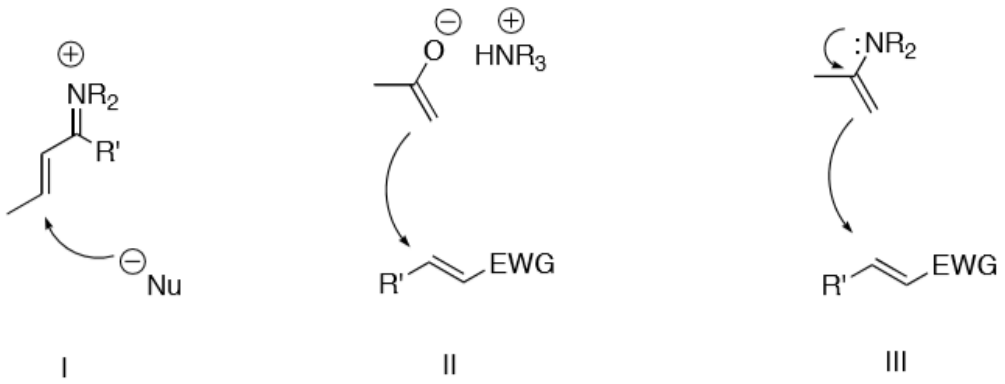
Nu = active methylene center, e.g., malonic acid ester
β-keto esters, nitroalkanes, etc.



L-prolina

Role of chiral amine in previous catalytic asymmetric Michael reaction:

- activate the Michael acceptor via formation of an iminium species (I)
- act as a base forming a complex with enolate to react with the acceptor (II)
- *activation of ketone donors through formation of an enamine intermediate (III)*



I II III

Betancort, J. M.; Sakthivel, R. T.; Barbas, C. F. *Tetrahedron Lett.* **2001**, *42*, 4441–4444.

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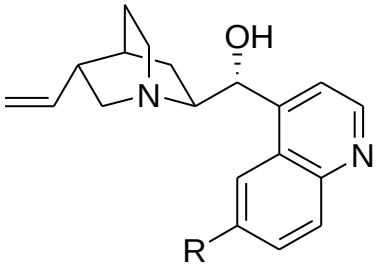
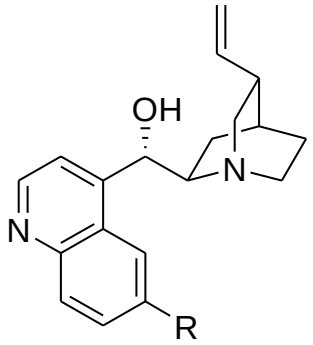
Alcaloidi della cinchona





Quinine (QN)	R = OMe	Quinidine (QD)
Cinchonidine (CD)	R = H	Cinchonine (CN)
Cupreine (CPN)	R = OH	Cupreidine (CPD)

ALCALOIDI DELLA CINCHONA

Quinine isolata da Pelletier in 1820.

Usata da Pasteur per la risoluzione di un racemato (1853)

Chinina e derivati come antimalarici

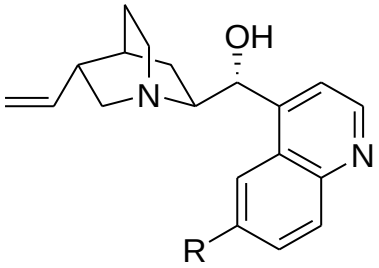
Bifunzionali (β-aminoalcol)

Economici

Facili da funzionalizzare

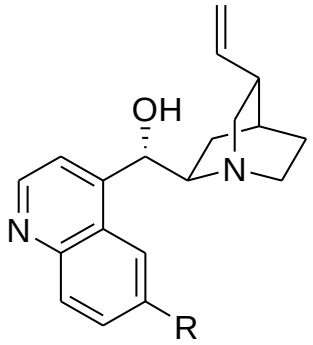
Disponibilità di pseudoenantiomeri

Alcaloidi della cinchona



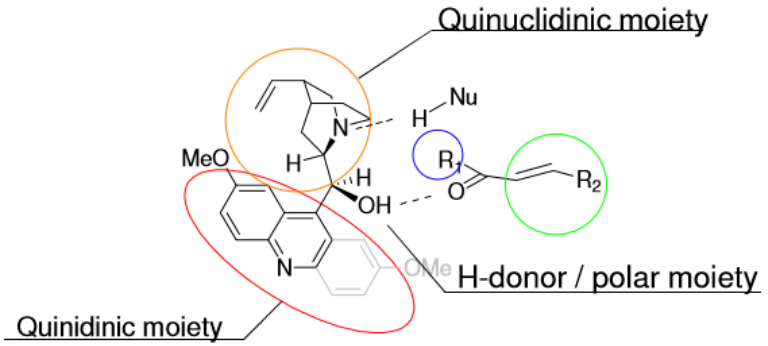
Quinine (QN)
Cinchonidine (CD)
Cupreine (CPN)

R = OMe
R = H
R = OH

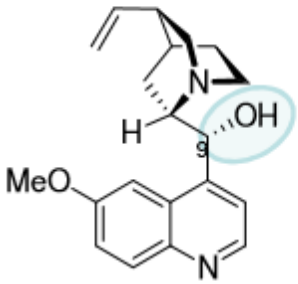


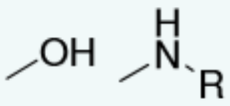
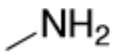
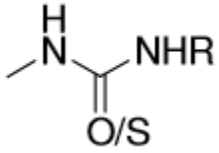
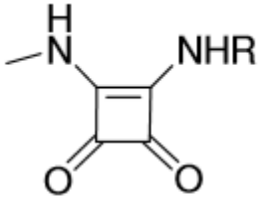
Quinidine (QD)
Cinchonine (CN)
Cupreidine (CPD)

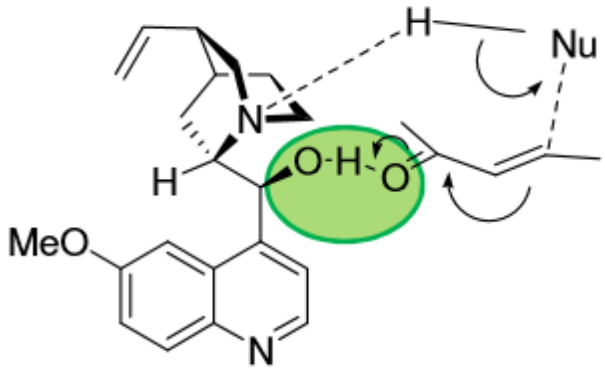
«pseudoenantiomeri» **(diastereoisomeri)**



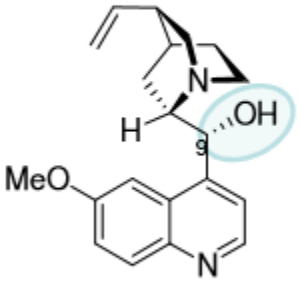
C9-Derivatizations and mechanistic considerations

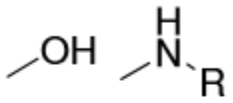


	Alcohols, Secondary amines
	Primary amines
	(thio)ureas
	squaramides

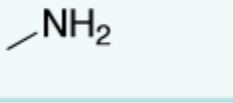


C9-Derivatizations and mechanistic considerations

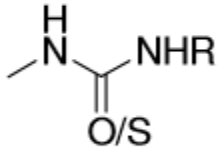




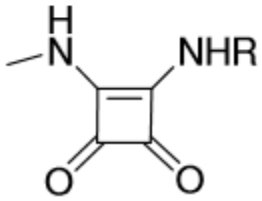
Alcohols, Secondary amines



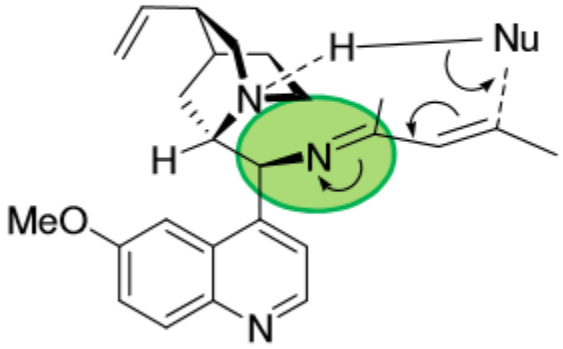
Primary amines



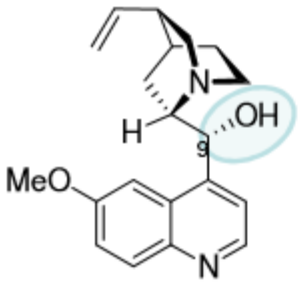
(thio)ureas

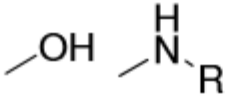


squaramides

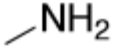


C9-Derivatizations and mechanistic considerations

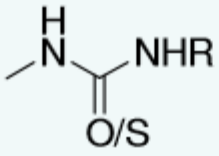




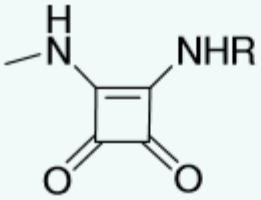
Alcohols, Secondary amines



Primary amines



(thio)ureas



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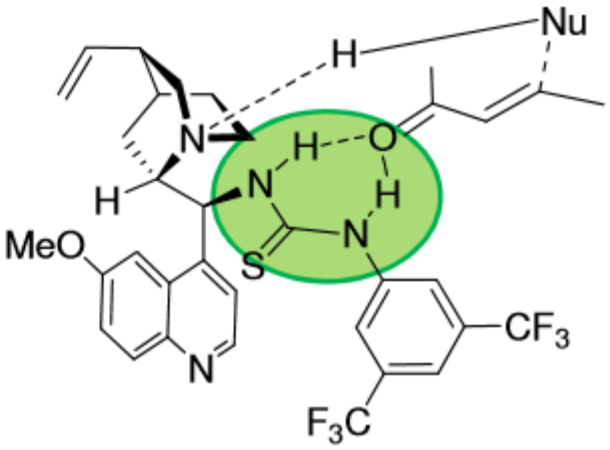
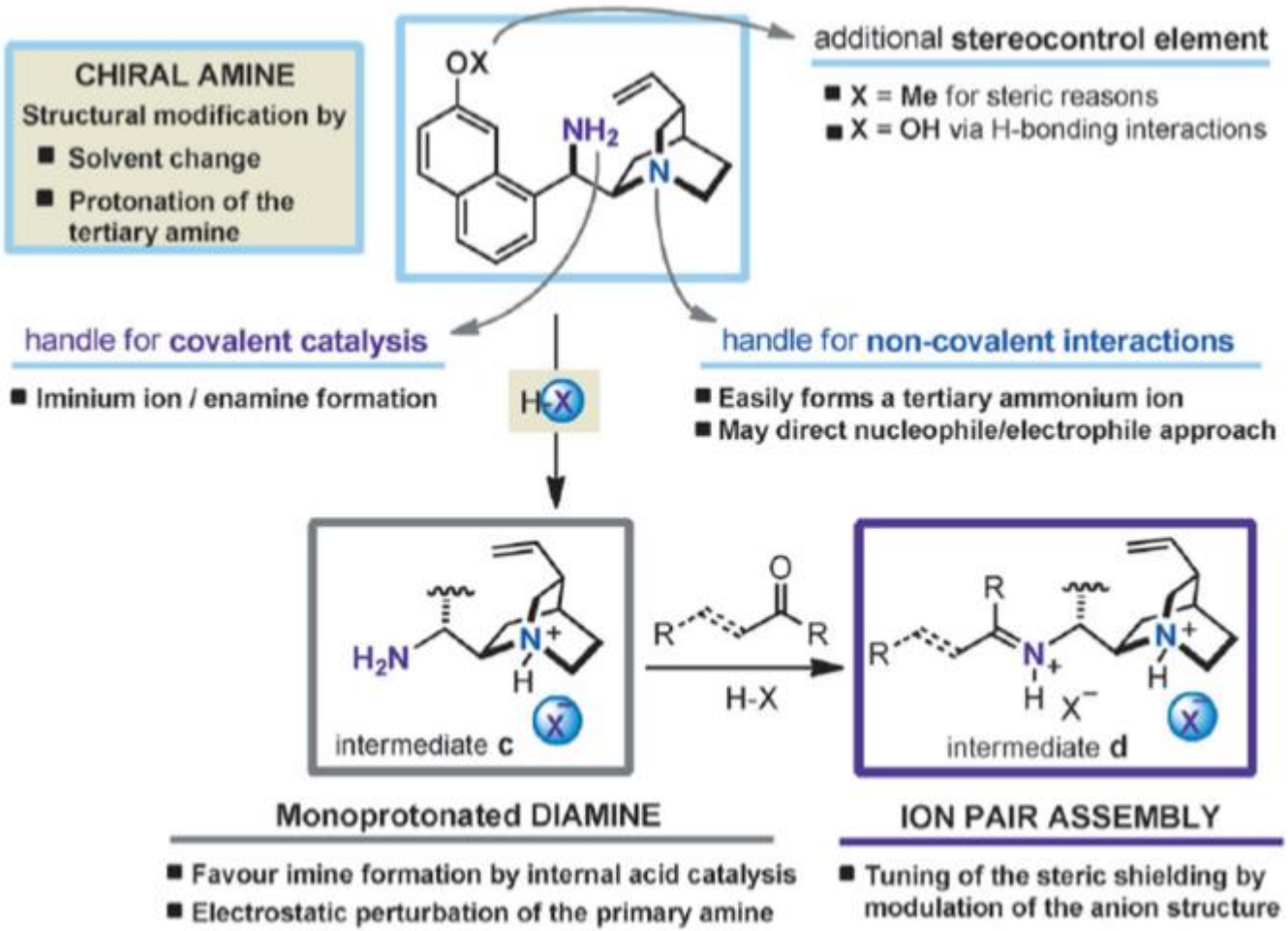



CHIRAL AMINE
Structural modification by
Solvent change
Protonation of the tertiary amine
OX
NH2
N
additional stereocontrol element
X = Me for steric reasons
X = OH via H-bonding interactions
handle for covalent catalysis
Iminium ion / enamine formation
H-X
handle for non-covalent interactions
Easily forms a tertiary ammonium ion
May direct nucleophile/electrophile approach
H2N
N+
H
X−
intermediate c
O
R
H-X
intermediate d
Monoprotonated DIAMINE
Favour imine formation by internal acid catalysis
Electrostatic perturbation of the primary amine
ION PAIR ASSEMBLY
Tuning of the steric shielding by modulation of the anion structure

Cinchona Alkaloids Are Versatile Catalysts

- These are just a few of the reactions that can be performed asymmetrically.

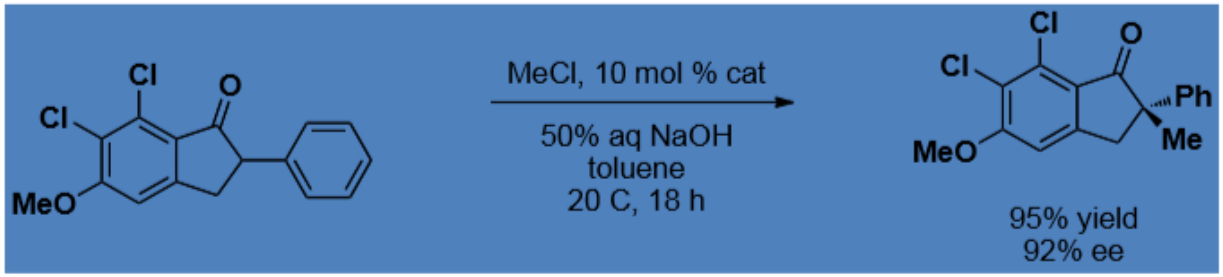
C-C Bond Forming
Alkylation
Aldol
Darzens
Michael Addition
Diels-Alder
Claisen Rearrangement

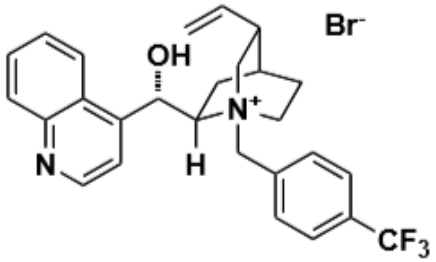
C-O Bond Forming
Epoxidation of Enones
Epoxidation of *cis*-Olefins
Asymmetric Dihydroxylation
Asymmetric Aminohydroxylation
α-Hydroxylation of Ketones

C-X Bond Forming
Aziridination
Azirination
Formation of α-Hydroxyphosphonate Esters
Addition of Thiols to Cyclic Enones

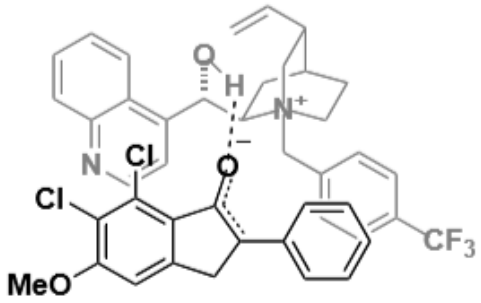
Miscellaneous Reactions
Hydrogenation
Desymmetrization
Decarboxylation

1984: Asymmetric alkylations promoted by modified chincona alkaloids





phase transfer catalyst



H-bonding/pi-stacking

Davis, P.; Grabowski, E. J. *J. Am. Chem. Soc.* **1984**, *106*, 446.

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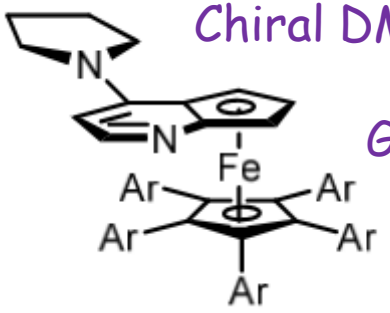
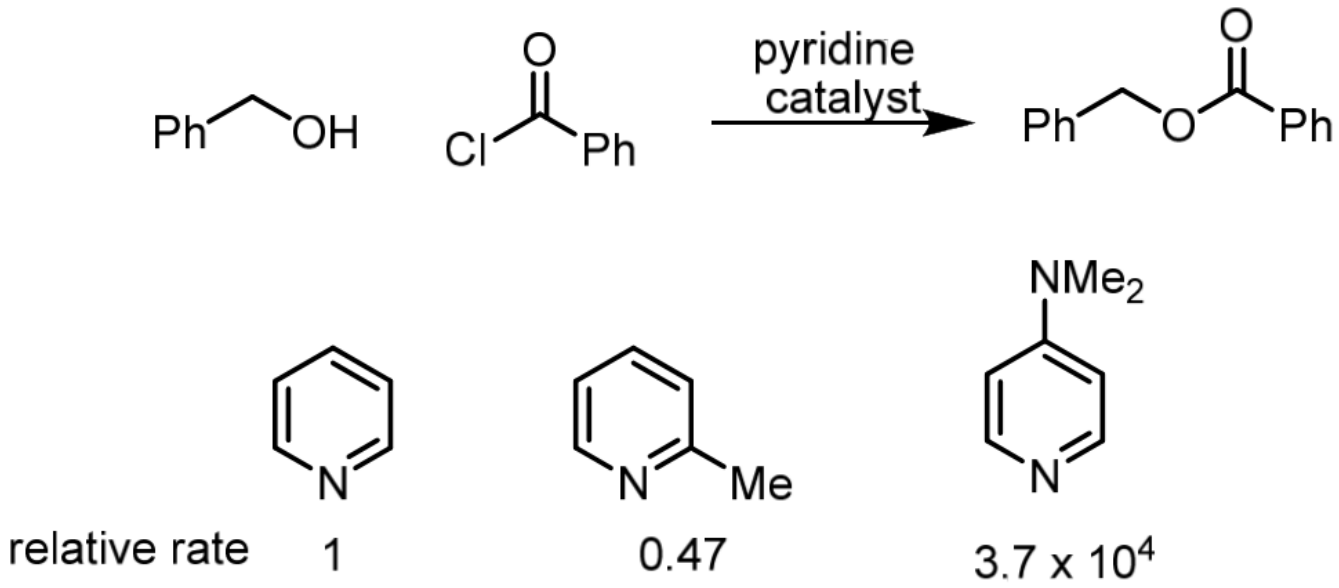


Chiral DMAP

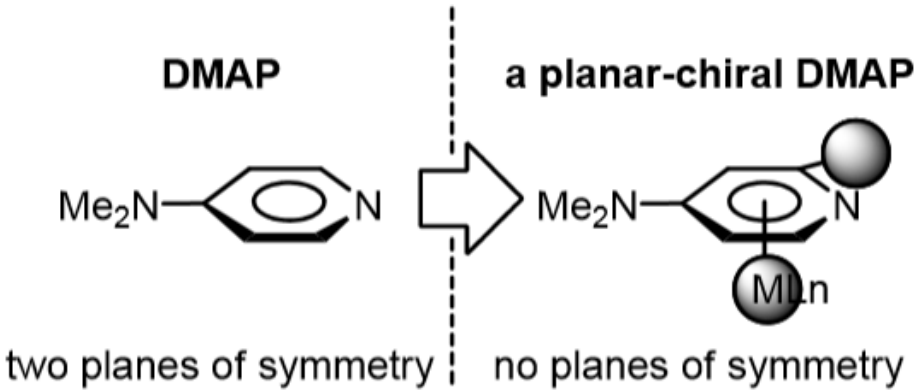
Gregory Fu

Scoperta del DMAP



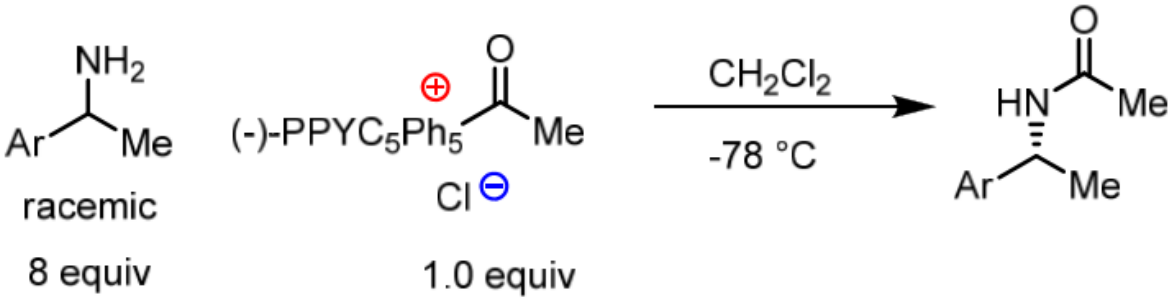
Litvinenko, L. M.; Kirichenko, A. I. *Dokl. Akad. Nauk. SSSR* **1967**, *176*, 97.

Planar-Chiral Catalysts by Fu

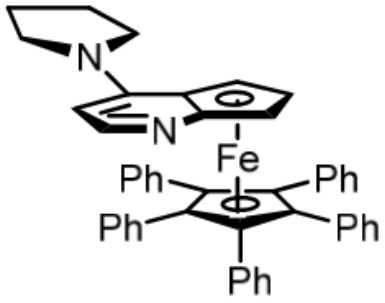


Ruble, J. C.; Fu, G. C. *J. Org. Chem.* **1996**, *61*, 7230.

Enantioselective Acylation of Amines by (-)-$PPYC_5Ph_5$



entry	Ar	% ee of amide
1	Ph	87
2	1-naphtyl	90
3	2-MeC_6H_4	91



$PPYC_5Ph_5$

Ie, Y.; Fu, G. C. *Chem. Commun.* **2000**, 119.