THE ORGANOCATALYTIC APPROACH IN THE ASYMMETRIC SYNTHESIS OF N-CONTAINING ORGANIC COMPOUNDS: SCIENTIFIC NOVELTY OR CULTURAL HERITAGE ?

The rooots of asymmetric organocatalysis

catalysts

alkaloids

Marckwald (1904)
Breding (1912)
Prelog (1954)
Pracejus (1960)
Langstrom and Bergstrom (1973)
Winberg (1986)

enzymes

Pasteur (1850)
Rosenthaler (1908)

aminoacids and small peptides

Dakin (1909)
Langenbeck (1928 and 1932)
Julià, Colonna et al (1980)

proline

Hajos / Parish / Wiechert (1970)

methodologies

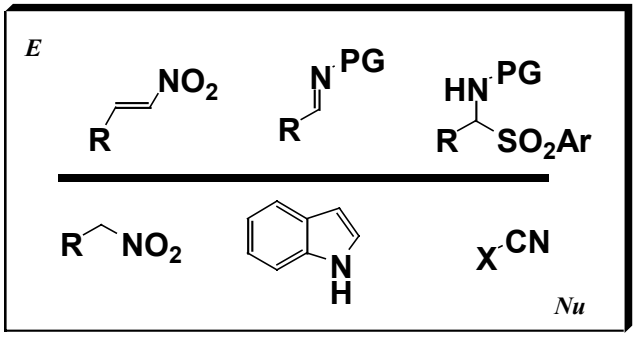
reactions via ion-pairing
phase transfer reactions
} *late 1970s and early 1980s*

reactions

hydrocyanations
1,2-additions
oxidations
Michael additions
intramolecular aldol reactions
kinetic resolutions

this initial phase of organocatalysis was however mainly mechanistic, biomimetic in nature and the field remained 'sub-critical'

Simple nitrogen-containing building blocks to be used in organocatalysed asymmetric synthesis



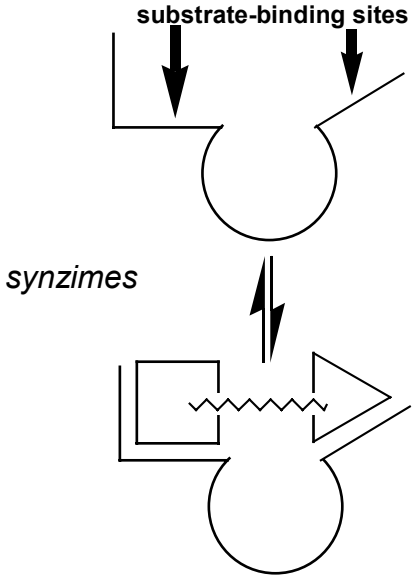
Organocatalysis

new covalent bond formation

weak interactions

Non-Covalent Organocatalysis

Host-Guest Complexation



synzimes

two or more reagents within the same nano space

Acid-Base Association between Catalyst and Substrate

a)- hydrogen bond catalysis

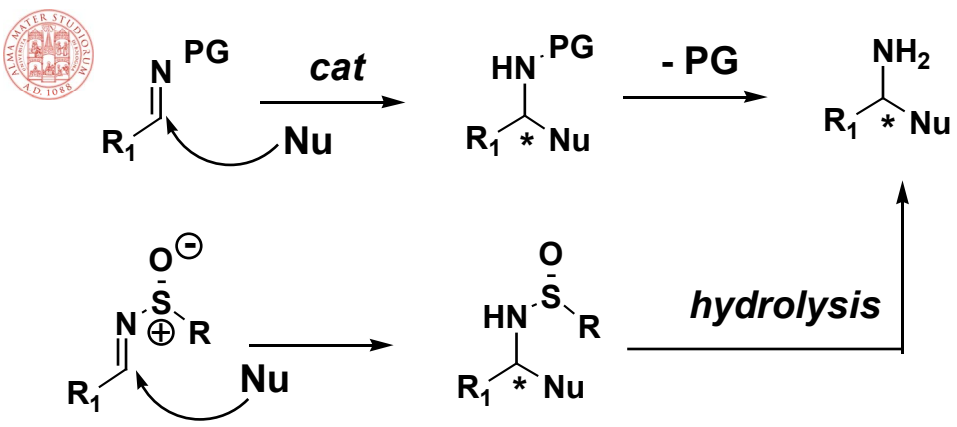
	A-H--------:B	A-H-----:B	A-H---:B	A^- HB^+
	weak	moderate	strong	Broensted-Lowry
kcal mol^{-1}	< 4	4-10	14-40	

b)-ammonium ions as chiral templates

homogenous catalysis

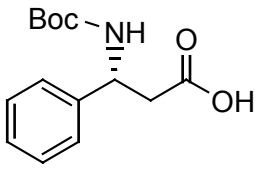
phase transfer catalysis

The nucleophilic addition reaction to azomethine functions

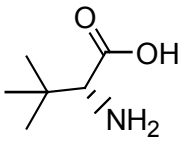


Nu = RM, silylketene acetals, $R_3Sn\text{-}CH_2\text{-}CH{=}CH_2$, $Me\text{-}NO_2$

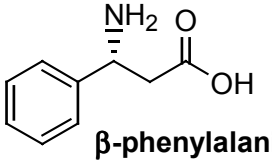
Representative highly prized industrially important chiral amino derivatives



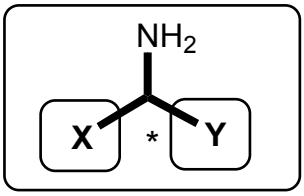
Boc-β-phenylalanine
286 Euro/g, Sigma Aldrich

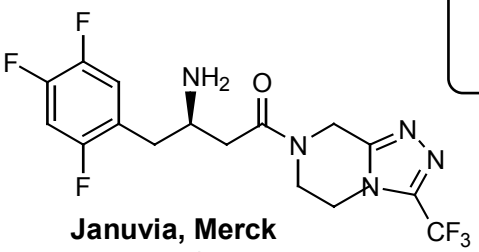


D-*tert*-leucine, Degussa
(multi Kg scale)

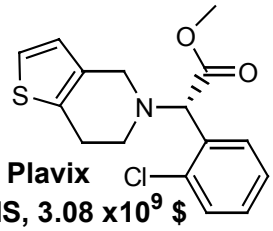


β-phenylalanine
Dowpharma
(metric ton scale)





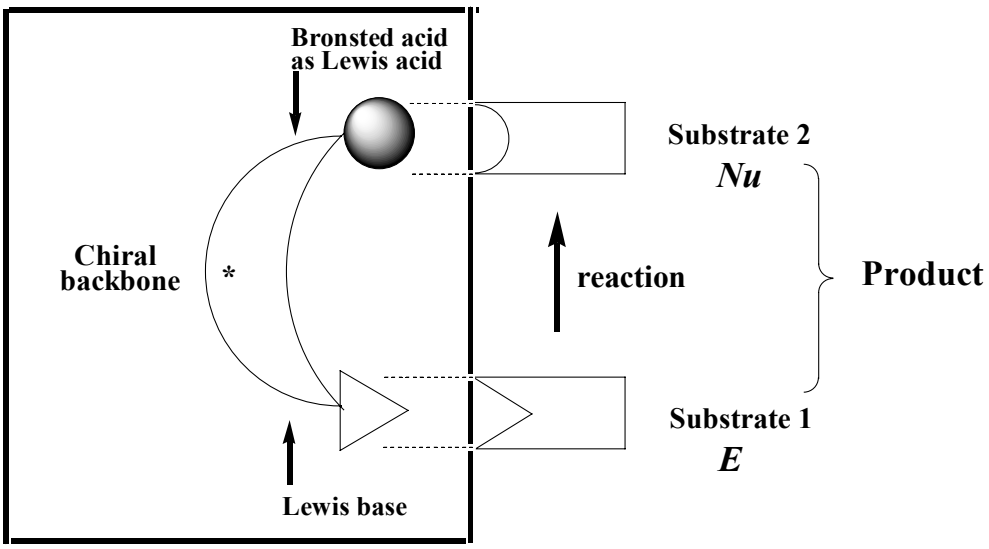
Januvia, Merck
0.5 x 109 $ (2007)



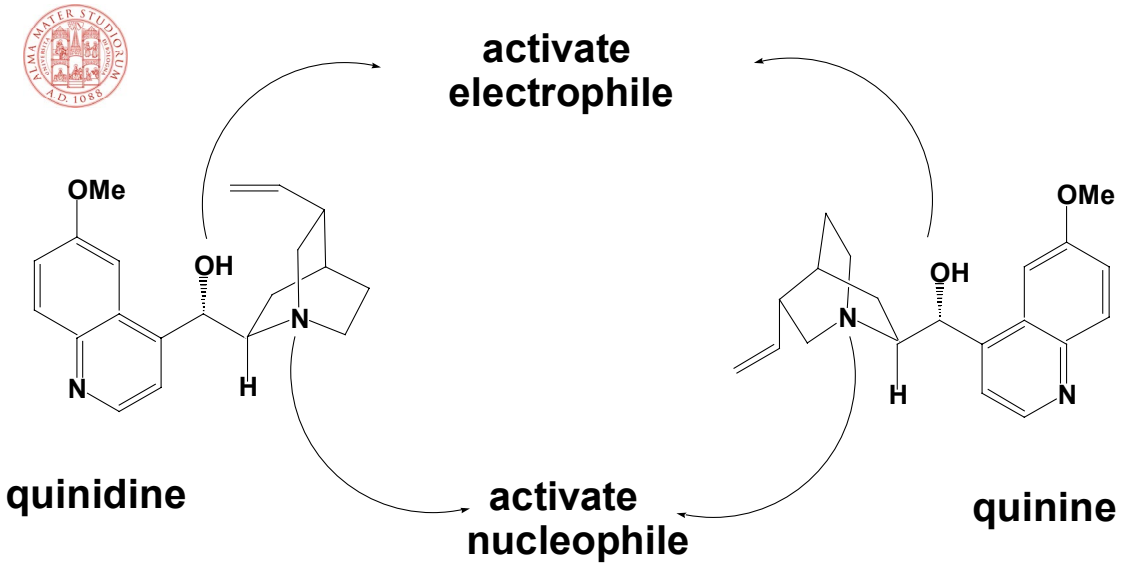
Plavix
BMS, 3.08 x10^9 $

Bifunctionality:
a recurring feature in the major part of the organocatalytic species

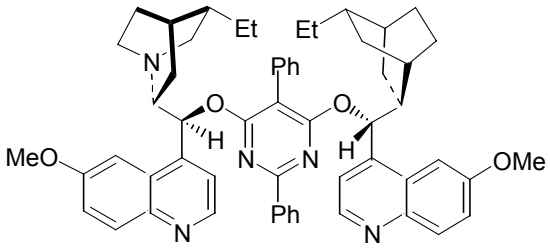
Typical design for a bifunctional organocatalyst



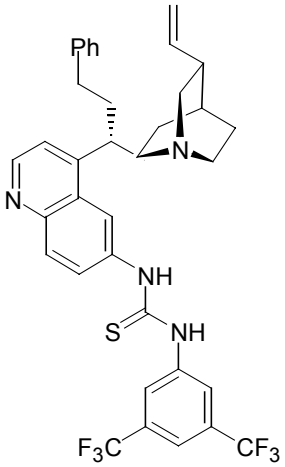
Modes of action of cinchona alkaloids as bifunctional catalysts



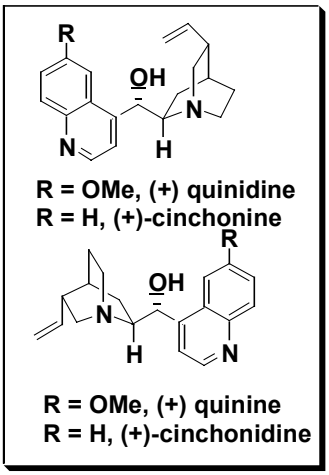
Evolution of the cinchona alkaloids in the field of organocatalysis

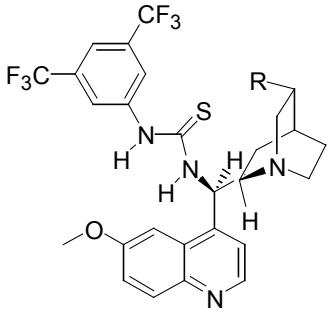


commercially available

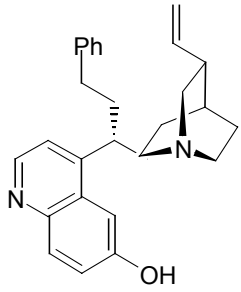


T. Marcelli,R.N.S.van der Haas, J.H. van Maarseveen, H. Hiemstra, *Angew. Chem. Int. Ed.* **2006**, *45,* 929.

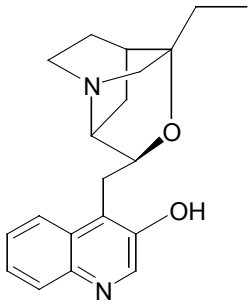




B. Vakyula, S. Varga, A. Csampai, T. Soòs, *Org. Lett.* **2005,** *7*, 1967

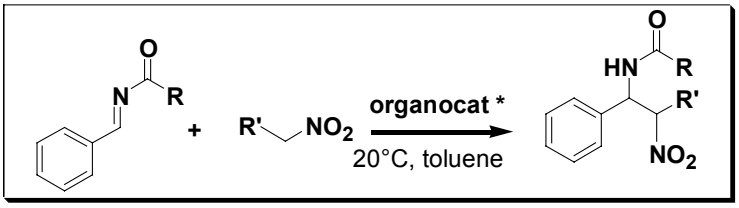


H. Li, Y.-W. Wang, L. Deng, *Org. Lett.* **2006**, *8*, 4063 and ref. therein

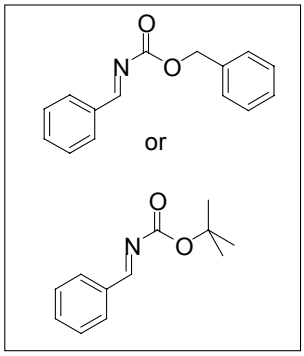


C. von Riesen, H.M.R Hoffmann, *Chem. Eur. J.* **1996**, *2*, 680

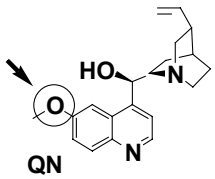
Protocol optimization in the enantioselective aza-Henry reaction using cinchona organocatalysts.



natural
cinchona alkaloids

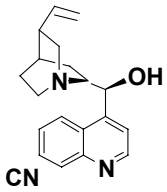


organocat:



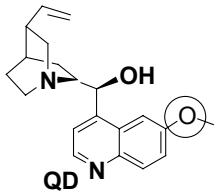
95 % Yield
53 % e.e

organocat:



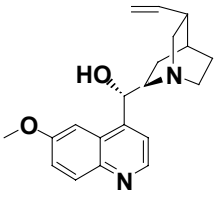
15 % Yield
25 % e.e

organocat: ← **organocatalyst variation**

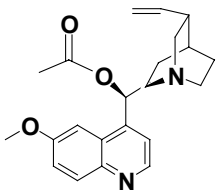


80 % Yield
55 % e.e

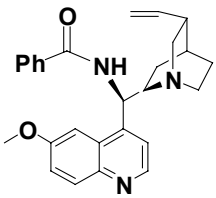
modified
cinchona alkaloids



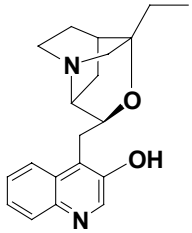
45 % yield
56 % e.e.



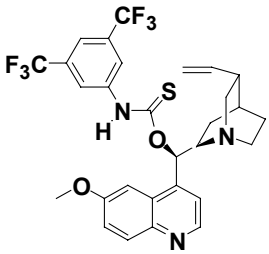
10 % yield
racemic



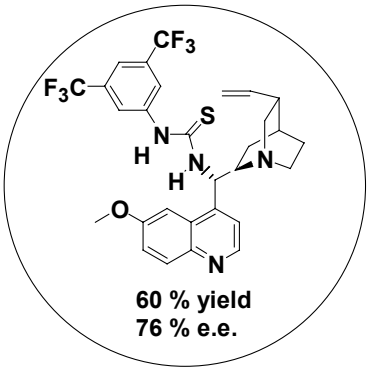
10 % yield
racemic



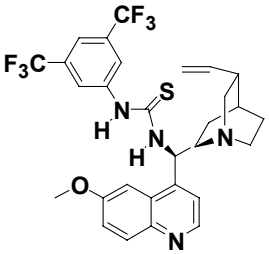
20 % yield
37 % e.e.



15 % yield
racemic



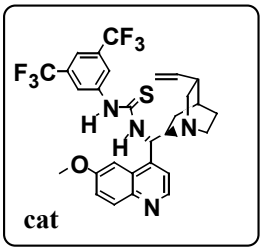
60 % yield
76 % e.e.

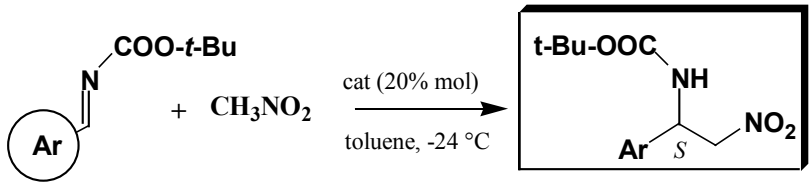


30 % yield
19 % e.e.

Bernardi, L.; Fini, F.; Herrera, R.P.; Ricci, A.; Sgarzani, V. *Tetrahedron*, **2006**, *62*, 375, *Symposium in print on Organocatalysis*

Scope of the aza-Henry reaction using cinchona bases as organocatalysts



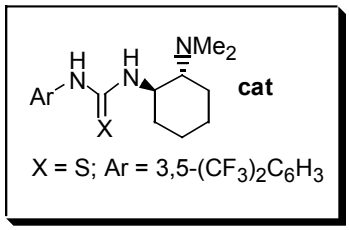


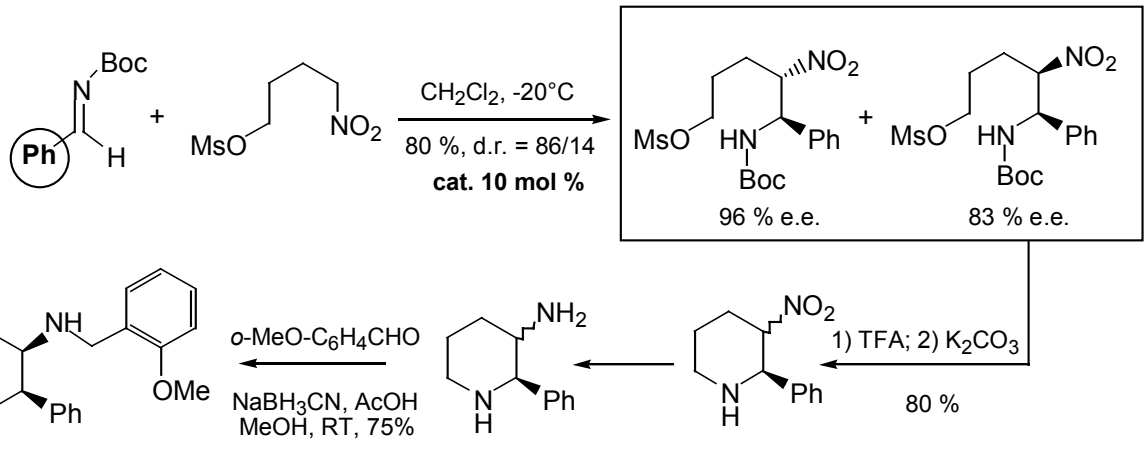
Ar = 1-Napht, 2-Napht, 4-Cl-C_6H_4, 2-Br-C_6H_4, 4-MeO-C_6H_4, 2-Thienyl, 2-Furyl

82-94 % e.e.

L. Bernardi, F. Fini, R.P. Herrera, A. Ricci, V. Sgarzani, *Tetrahedron*, **2006**, *62*, 375, *Symposium in print on Organocatalysis*

Synthesis of a potent neurokinin receptor antagonist via aza-Henry reaction

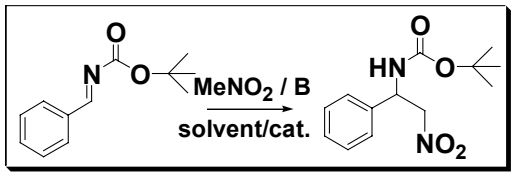


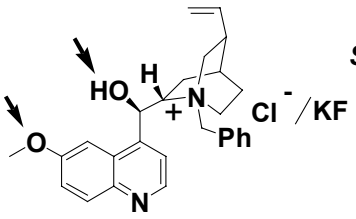


(-)CP-99,994

X. Xu; T. Furukawa; T. Okino; H. Miyabe; Y. Takemoto, *Chem. Eur. J.* **2006**, *12*, 466

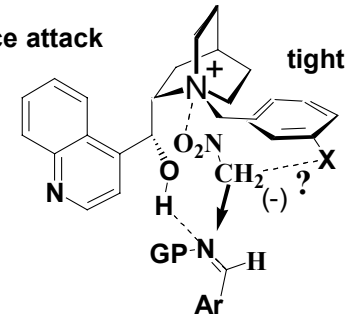
Organocatalyzed aza-Henry reaction under 'phase transfer' conditions.

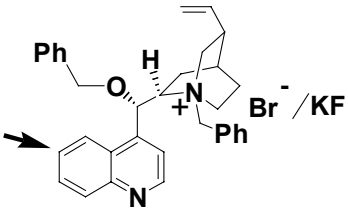




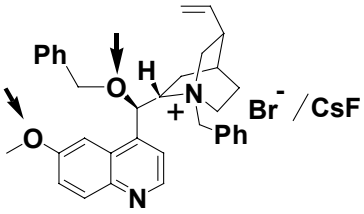
81 % yield, 73 % e.e. (r.t.)
58 % yield, 80 % e.e. (0°C)

Si face attack





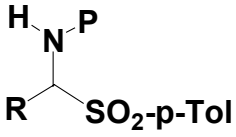
78% yield 0 % e.e.



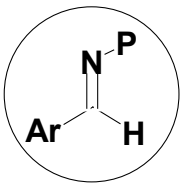
68 % yield, 35 % e.e.

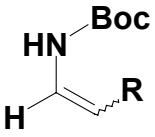
A novel lesson from an 'old' reaction

the evolution of the concept of imine
greatly expands the scope of the nucleophilic addition to the azomethine motif

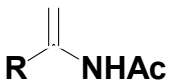


enamides



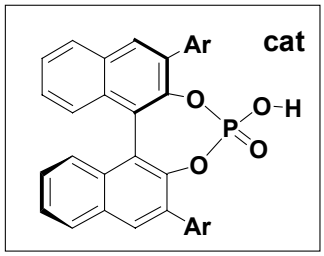


enecarbamates



sulphonamides

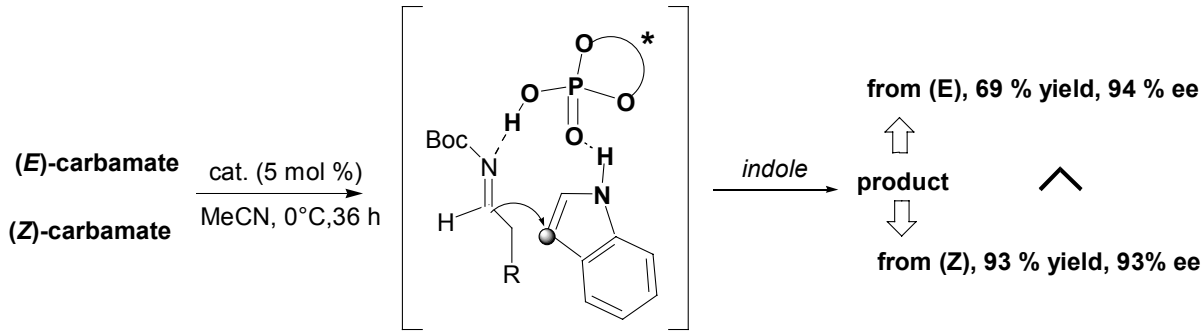
Enecarbamates as electrophiles



R= H, Me, Bn, *i*-Pr

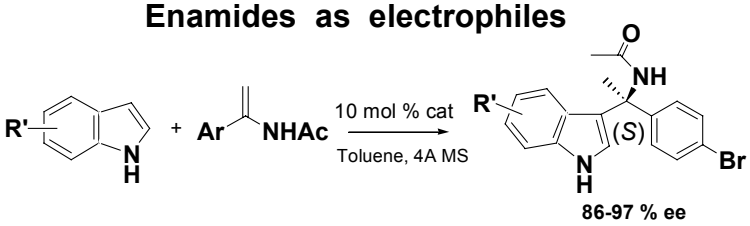
70-91 % yield,
90-94 % ee

***in situ* generation of activated aliphatic imines**
by protonation of the ene-carbamate



M. Terada, K. Sorimachi, *J. Am. Chem. Soc*. **2007**, *129*, 292

Enamides as electrophiles



86-97 % ee

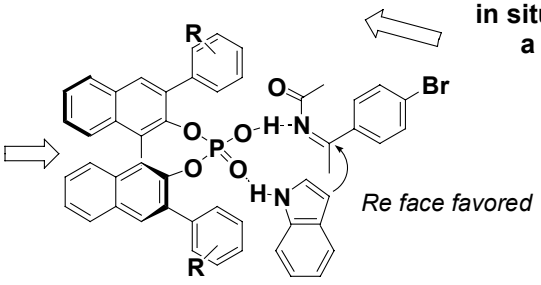
construction of a quaternary stereogenic center

a reaction model calls for the chiral phosphoric acid catalysts
to activate the indole and the enamide moieties
through two hydrogen bonds

enamide ⟷ ketimine

in situ generation of
a ketimine

no reaction with
N-methyl indole



Re face favored

Y.-X. Jia, J. Zhoung, S.-F. Zhu, C.-M. Zhang, Q!.-L. Zhou, *Angew. Chem. Int. Ed.* **2007**, *46*, 5565

a real advancement would require

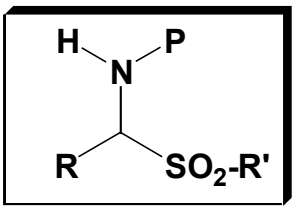
a scenario in which the host-guest interaction between "in situ" generated electrophiles and nucleophiles and bifunctional organocatalysts will be effective

in

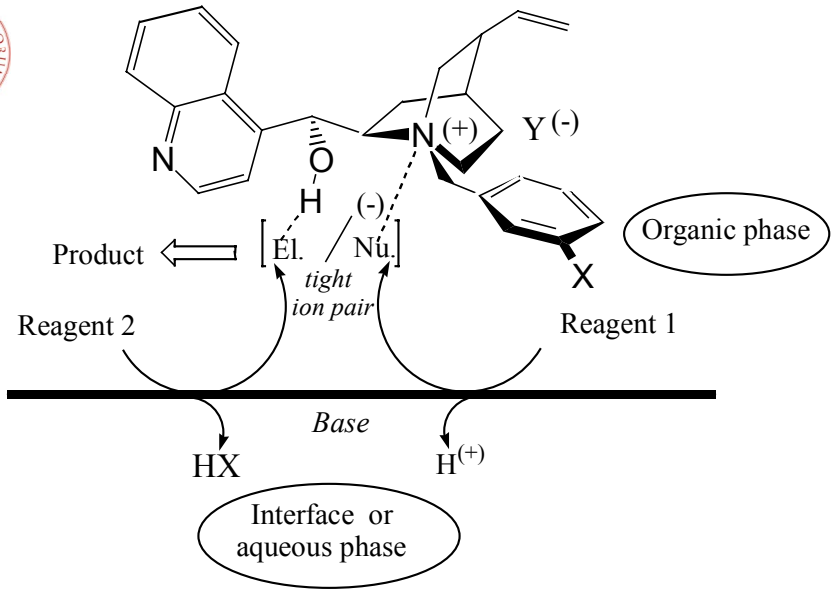
the transfer of chirality during the nucleophile/electrophile assembly

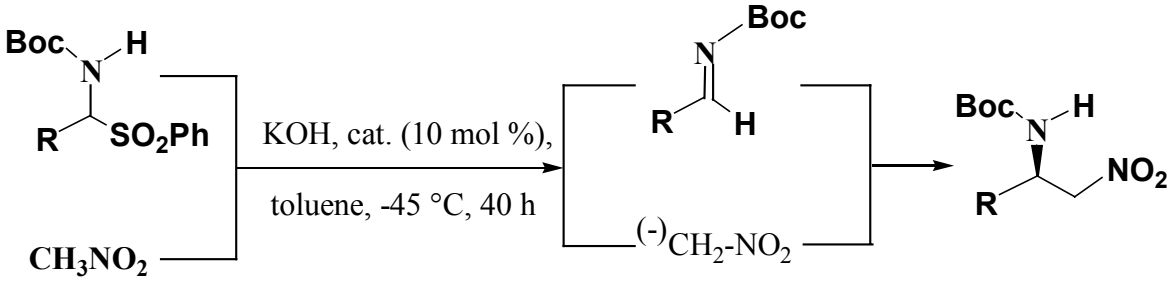
⇩

the amido sulphone game



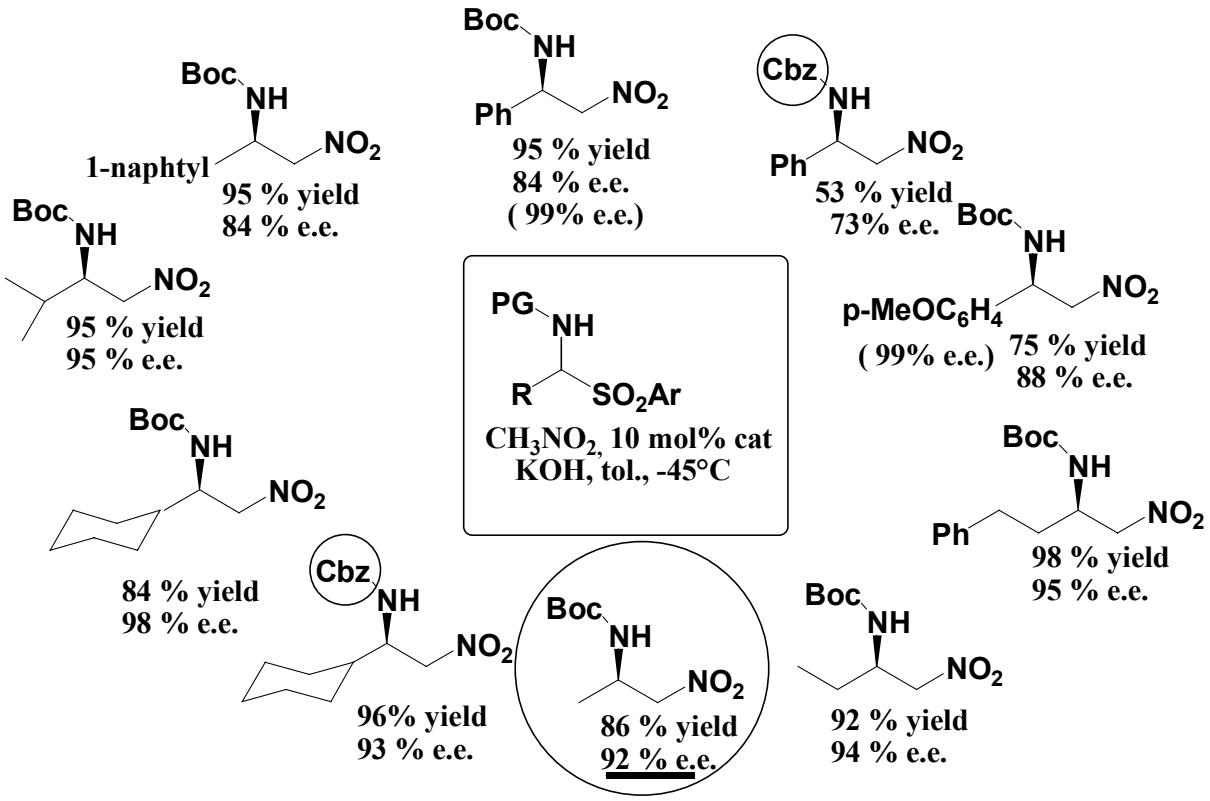
Base-promoted *in situ* formation of the nucleophile and of the electrophile





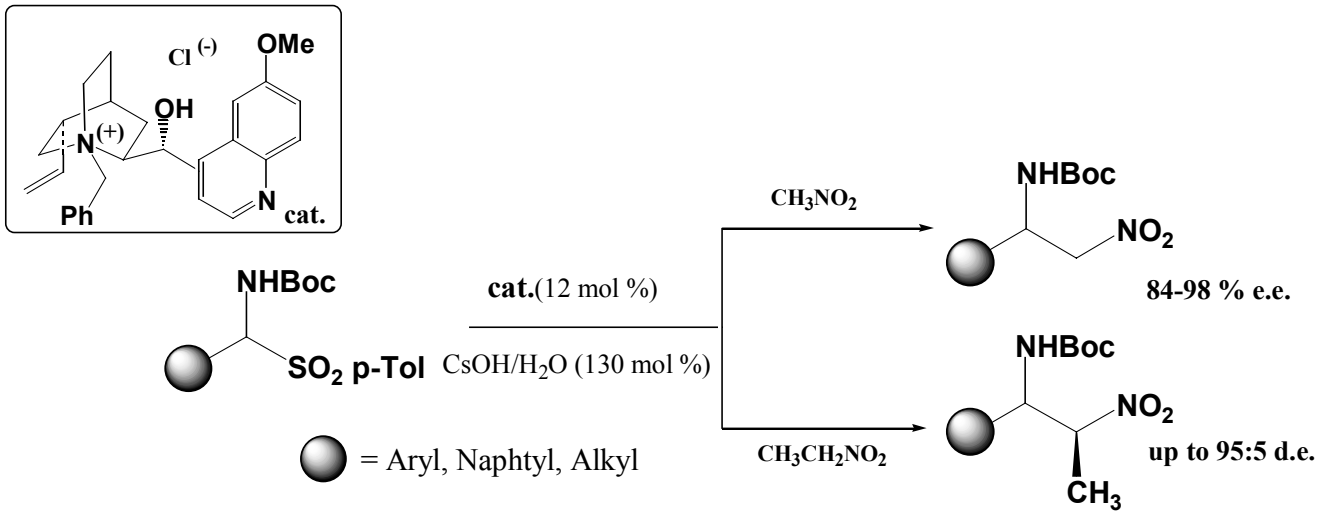
R = Ph, 1-Napthyl, Me, Et, Ph-CH_2-CH_2, *i*-Pr, Cy

Scope of the amido sulphone-mediated organocatalysed aza-Henry reaction



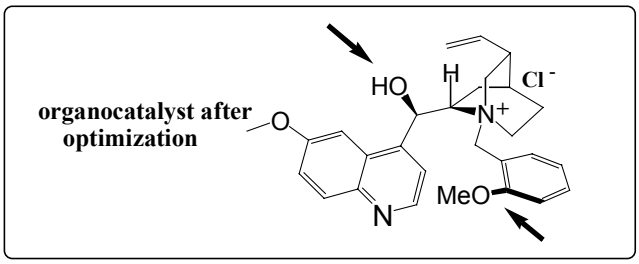
F. Fini ; V. Sgarzani; D. Pettersen; R.P. Herrera; L. Bernardi; A. Ricci, *Angew. Chem. Int. Ed*. **2005**, *44*, 7975

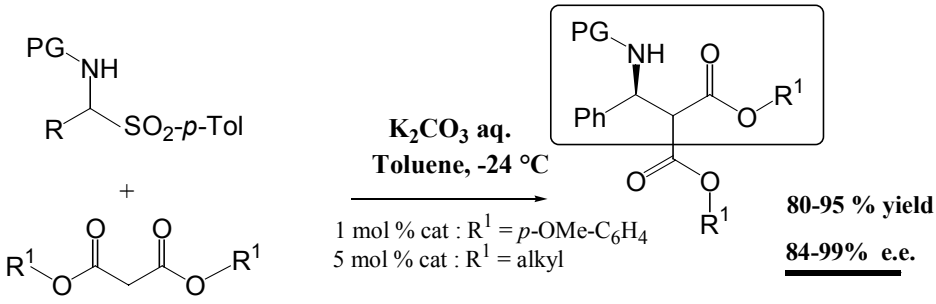
Catalytic enantioselective Aza-Henry reaction with broad substrate scope.



C. Palomo; M. Oiarbide; A. Laso; R. Lòpez, *J. Am. Chem. Soc.* **2005**, *127*, 17622

PTC ORGANOCATALYZED ENANTIOSELECTIVE MANNICH REACTION OF MALONATES WITH α-AMIDO SULFONES



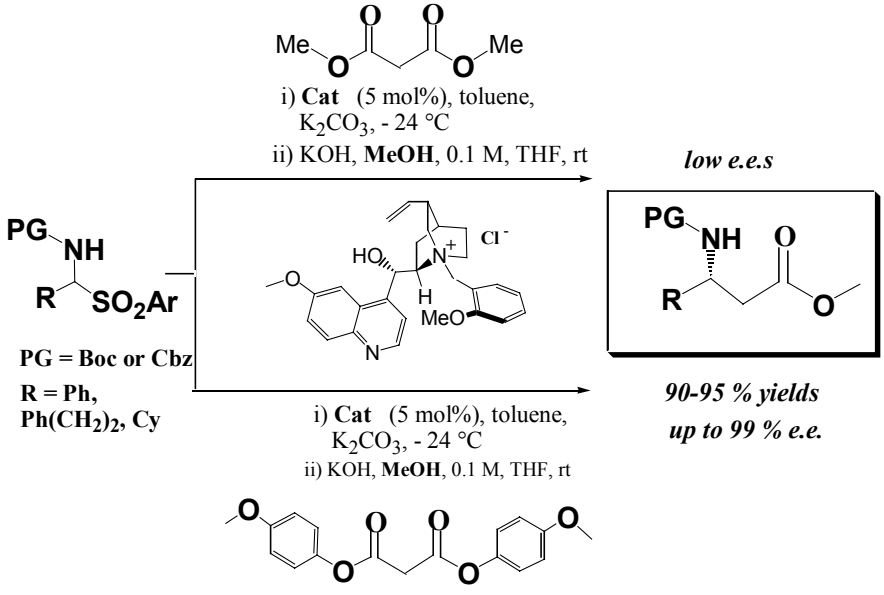


PG = Boc, Cbz

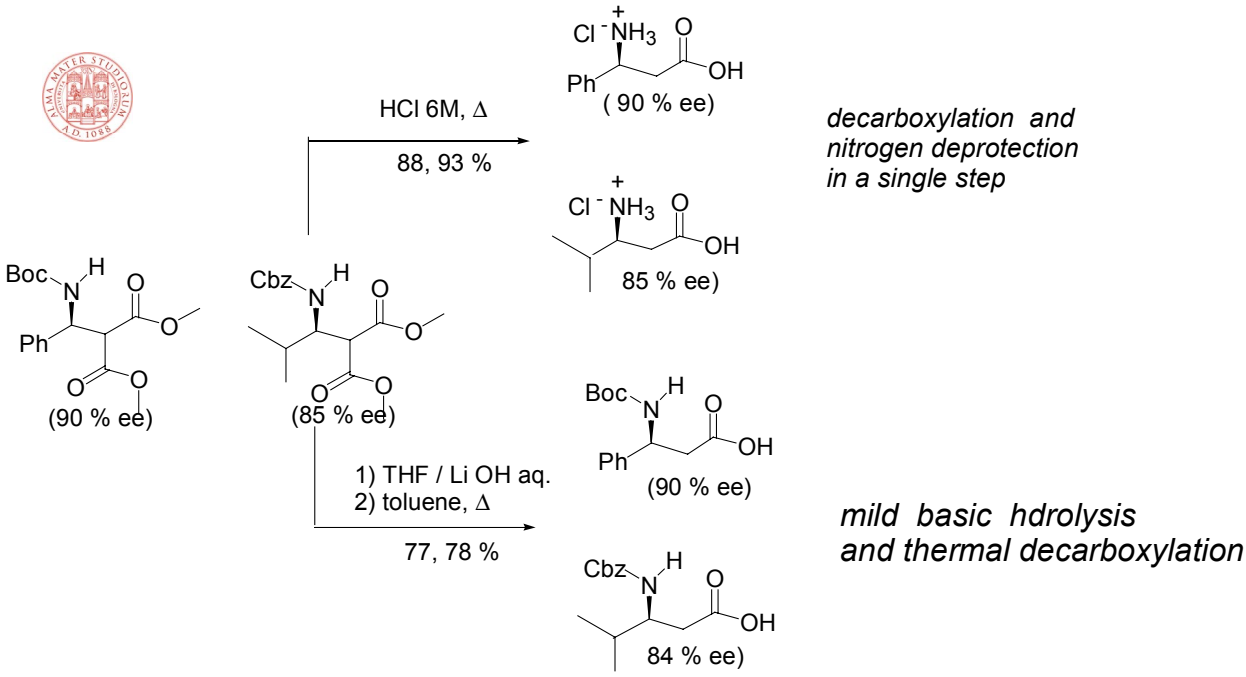
R = Ph, 1- and 2-naphthyl, p-MeO-C_6H_4, *o*-Br-C_6H_4, *p*-Cl-C_6H_4, Me, Et, Ph-CH_2-CH_2-, *i*-Pr, Cy

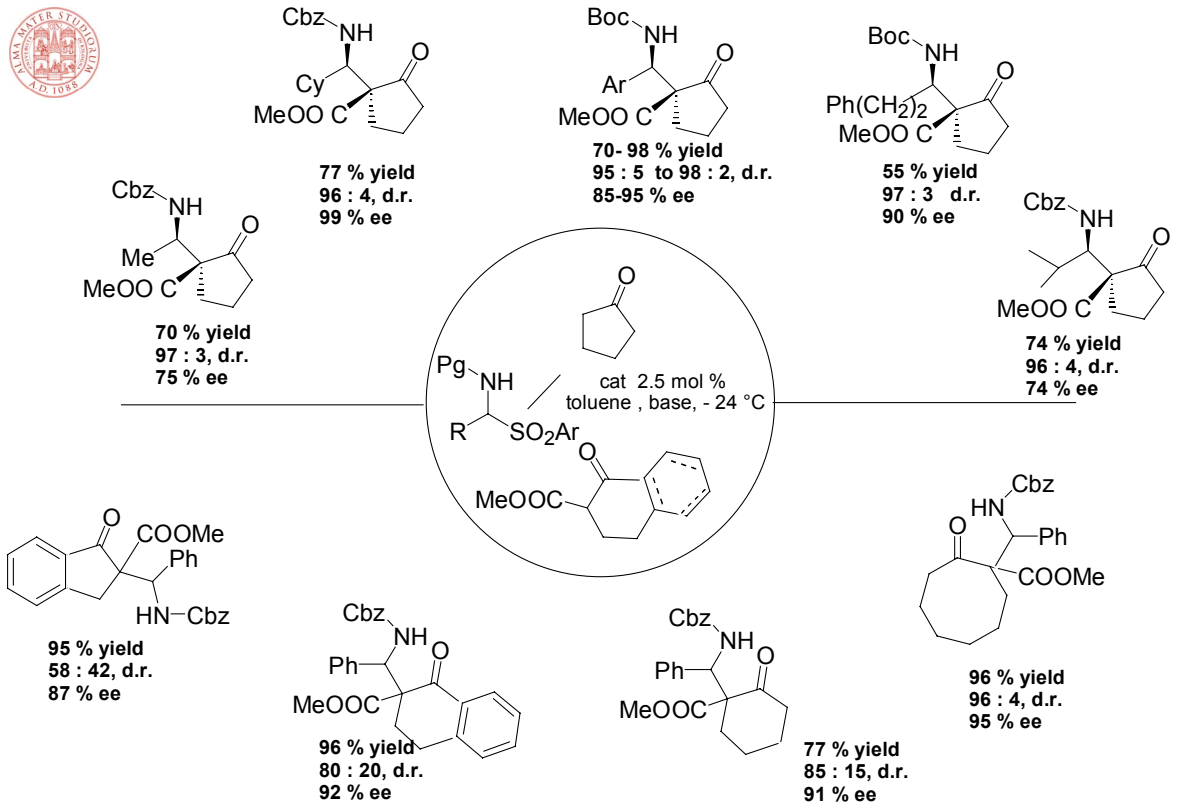
F. Fini, L. Bernardi,R. P. Herrera, D. Pettersen, A. Ricci, V. Sgarzani, *Adv. Synth. & Cat*, **2006**, 348, 2043

access to the antipodal Mannich adduct



A direct route to prepare β^3–amino acids with orthogonal carbamate protecting groups





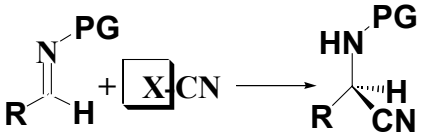
O. Marianacci, G. Micheletti, L. Bernardi, F. Fini, M. Fochi, D. Pettersen, V. Sgarzani, A. Ricci, *Chem. Eur. J.* **2007**, *13*, 8338

Principles of different types of Strecker reactions

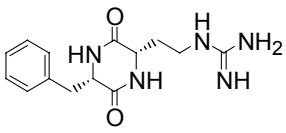
(1850)

Adolf Strecker

Organocatalysts used in the Strecker reaction



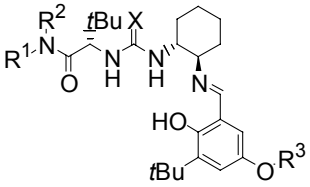
joint characteristics: the presence of an imino moiety beneficial to the catalytic performances



M.S. Iyer, K.M. Glstad, N.D. Namdev, M. Lipton, *J. Am. Chem. Soc.*, **1996**, *118*, 4910

Limited scope: no heteroaromatic and aliphatic aldimines.

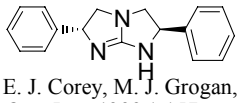
HCN, MeOH, PG = $CHPh_2$, R = Ar, 82-97% yield, , 80-99% ee



M.S. Sigman, P. Vachal, E. Jacobsen, *Angew. Chem. Int. Ed.* **2000**, *39*, 1279.

broad reaction scope: suitable for aromatic, and branched aliphatic imines and for ketimines

HCN, toluene, PG =Bn, All, R = Ar, Alk., 45-100% yield, 77-95 % ee.



E. J. Corey, M. J. Grogan, *Org. Lett.* **1999**,1,157

Suitable for aromatic and branched aliphatic imines.Recycle of the catalyst

HCN, toluene, PG = $CHPh_2$, R = Ar, Alk., 80-99% yield, 50-88% ee

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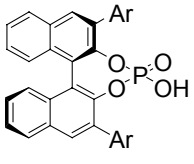
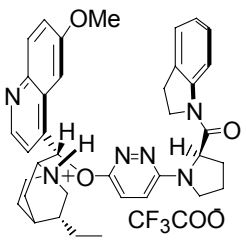
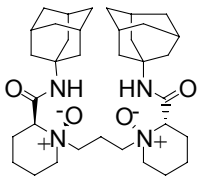


Ar = 9-phenanthryl

HCN, toluene, PG = Bn, R = Ar, 59-97% yield, 85-99% ee

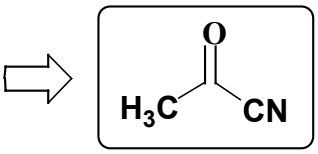


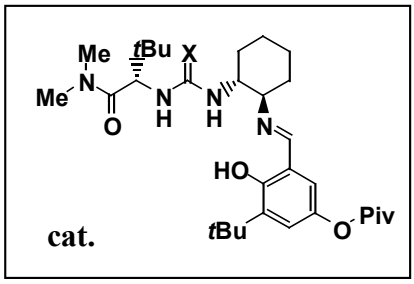
HCN, CH_2Cl_2, PG = All, R = all., 85-98% yield, 79-99% ee



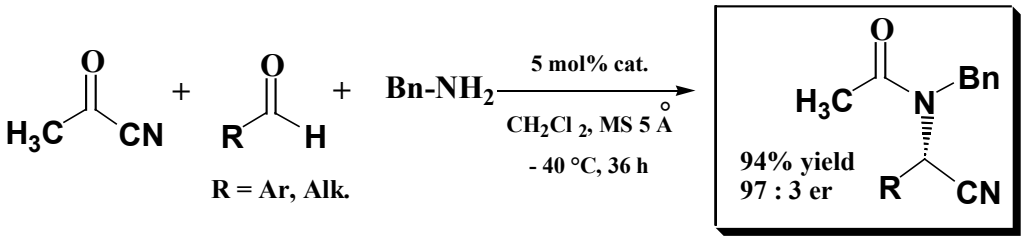
TMSCN, toluene, PG = $P(O)Ph_2$, R = Ar, *t*-Bu, 90-99% yield, 72-92 % ee

Replacing the highly toxic and volatile CN $^{(-)}$ ion sources

acetyl cyanide 



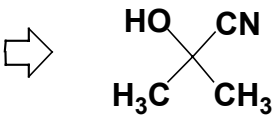
The three-component acyl-Strecker reaction



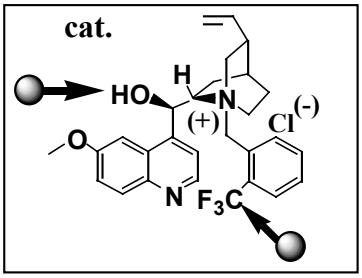
Pan, S. C.; Zhou, J.; List, B. *Angew. Chem. Int.Ed.* **2007**, *46*, 612

Pan, S. C.; List, B. *Org. Lett*. **2007**, *9*, 1149

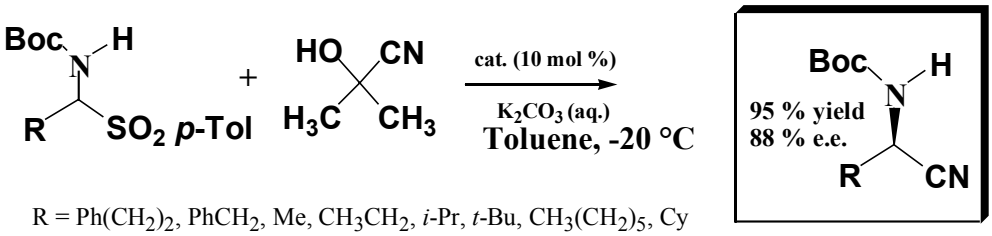
Replacing the highly toxic and volatile CN $^{(-)}$ ion sources

acetone cyanohydrin 

an alternative, safer
and more convenient cyanide source



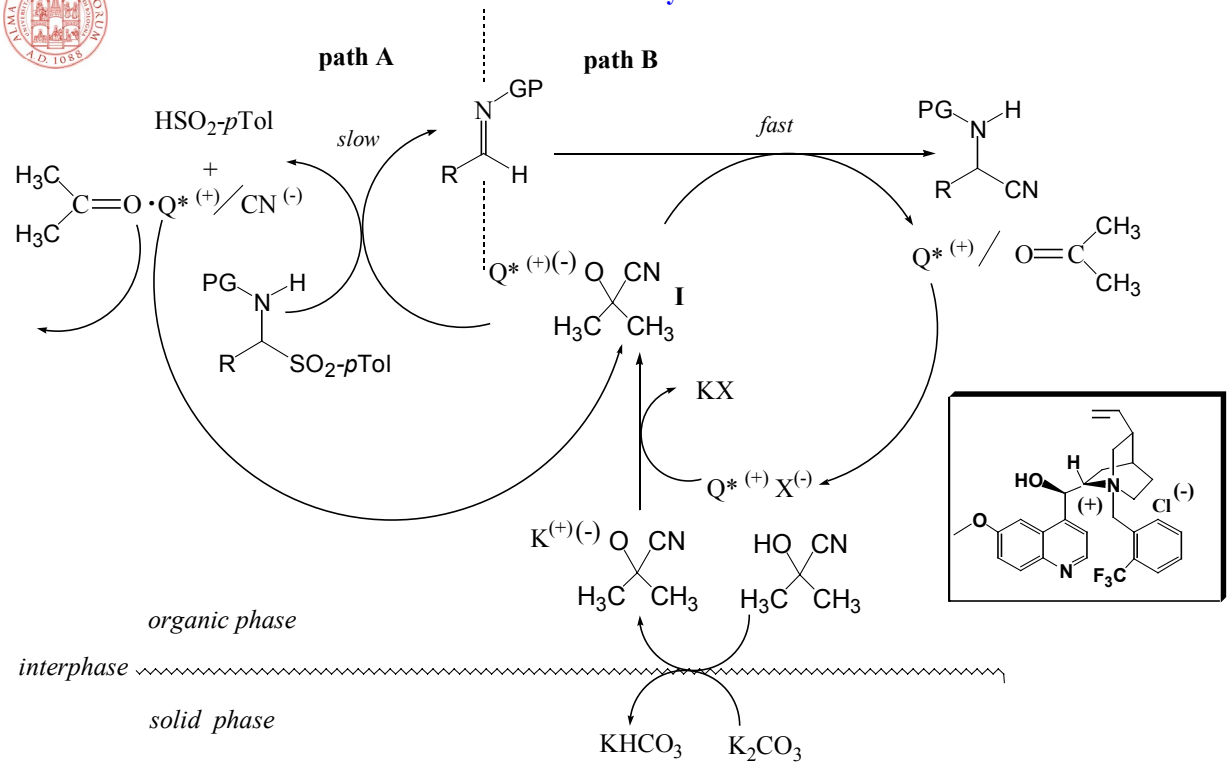
an easily available quinine-derived catalyst, under PTC conditions,



R = $Ph(CH_2)_2$, $PhCH_2$, Me, CH_3CH_2, *i*-Pr, *t*-Bu, $CH_3(CH_2)_5$, Cy

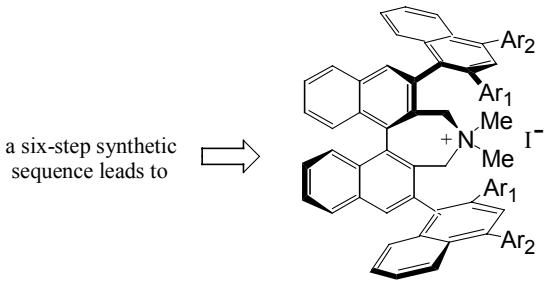
Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Fini, F.; Pettersen, D.; Ricci, A., *J. Org. Chem.* **2006**, *71*, 9869

Assumed mode of action of the catalyst in the Strecker reaction

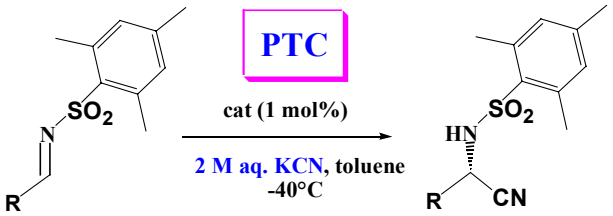


Further advancements:

design and synthesis of a chiral quaternary ammonium salt with the ability to accomplish a facile extraction of the nucleophilic cyanide ion from the aqueous to the organic layer wherein the Strecker reaction occurs with a precise enantiofacial discrimination.



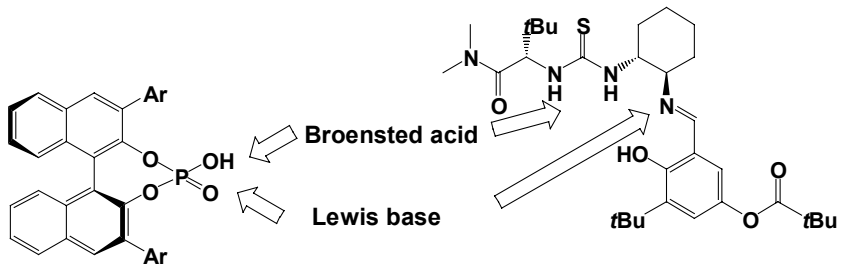
Ar_1, Ar_2 = *p*-CF_3-C_6H_4



R =c-oct, *i*-Pr, $Ph(CH_2)_2$, *t*-Bu, $Ph(CH_3)_2C$
81-98% yield, 88-98% ee

T. Ooi, Y. Uematsu, K. Maruoka, *J. Am. Chem. Soc*. **2006**,*128*, 2548.

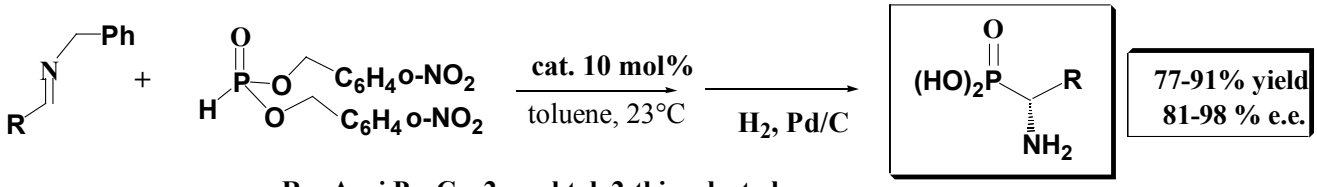
Organocatalysts used in the hydrophosphonylation of imines



Ar = 3,5-$(CF_3)_2C_6H_3$

Previous organocatalysed hydrophosphonylation of imines

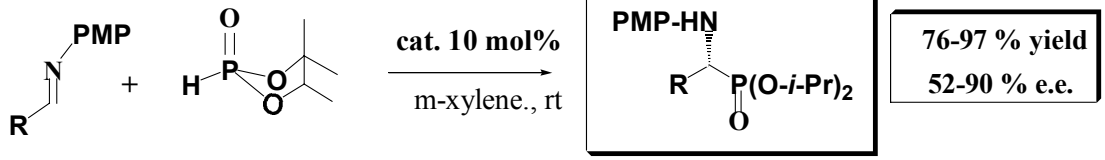
Thiourea-catalysed



R = Ar, *i*-Pr, Cy, 2-naphtyl, 2-thienyl, et al

G. D., Joly, E.N. Jacobsen, *J. Am. Chem. Soc*. **2004,** *126*, 4102.

Chiral Broensted acid catalysed

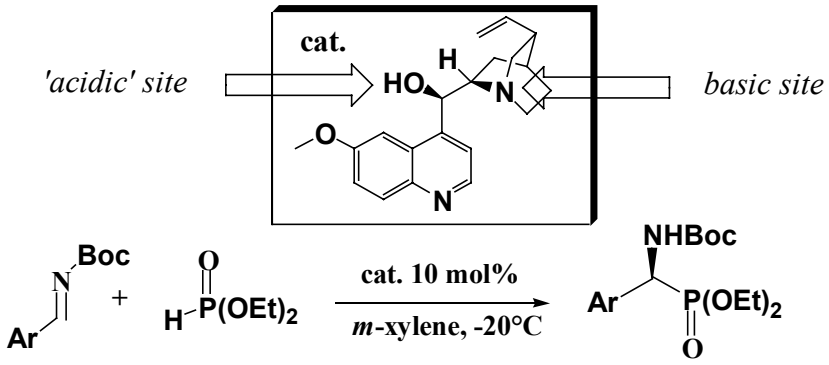


R = Ar, CH=CH-C_6H_5, 1-Napthyl, et al

T. Akiyama, H. Morita, J. Itoh, K. Fuchibe, *Org. Lett*. **2005,** *7*, 2583

Quinine Organocatalysed Hydrophosphonylation of Imines

moving towards a simpler organocatalytic approach

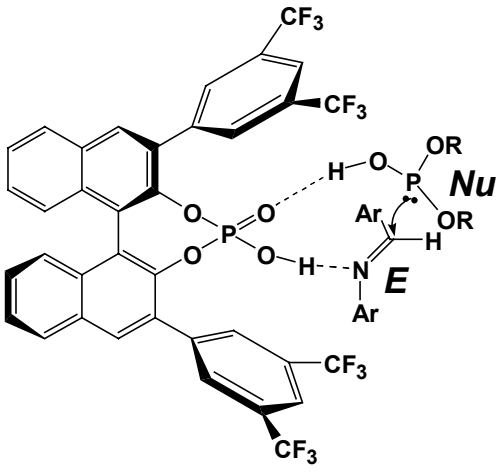


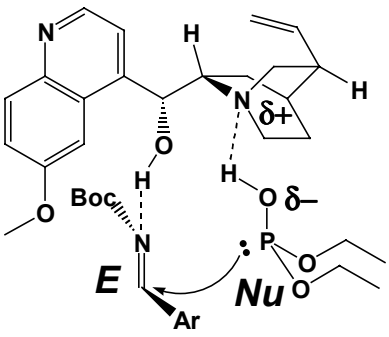
Ar = C_6H_5, *m*-Me-C_6H_4, *p*-Me-C_6H_4, *p*-MeO-C_6H_4, *p*-Cl-C_6H_4, 2-napthyl

60-83% yield
88-94% e.e.

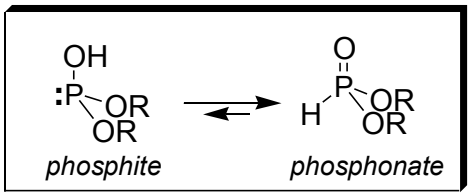
D. Pettersen, M. Marcolini, L. Bernardi, F. Fini, P.R. Herrera,V. Sgarzani, A. Ricci, *J. Org. Chem.* **2006**, *71*, 6269.

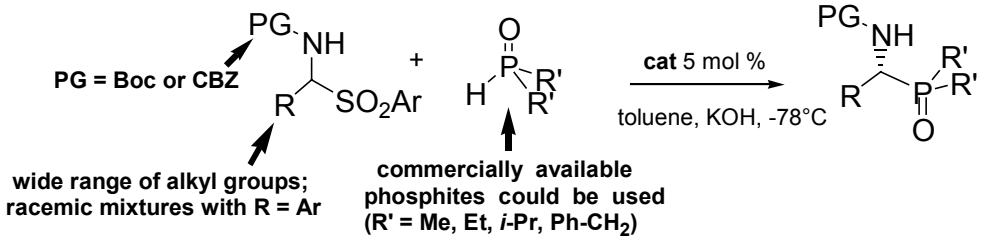
Proposed models for the organocatalysed hydrophosphonylation of imines

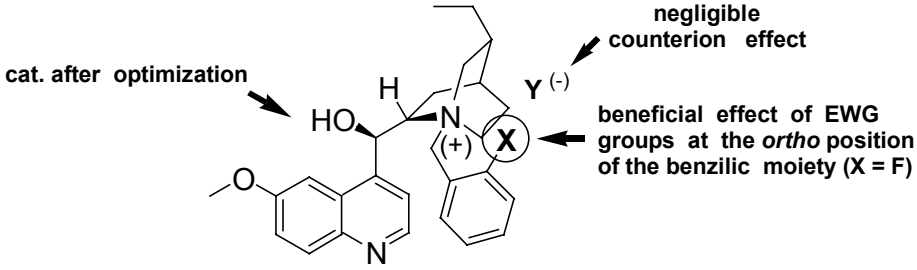




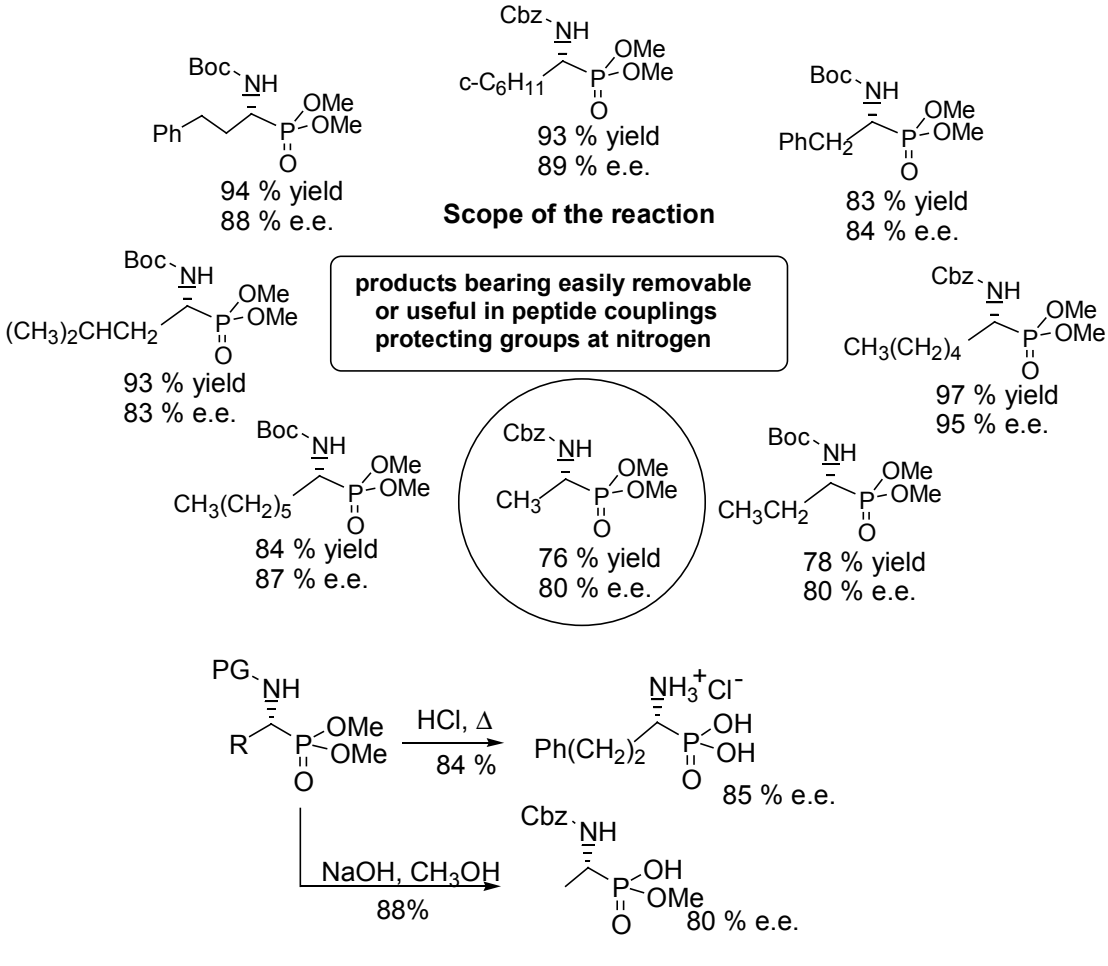
α-Amino phosphonic acids using phase-transfer organocatalysis



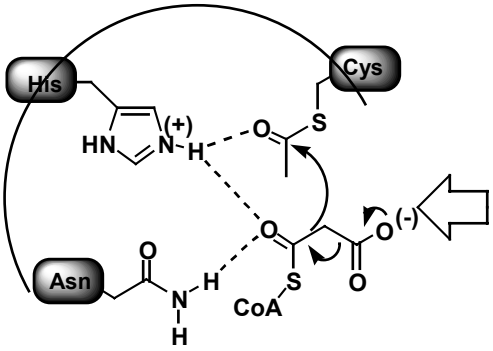




F. Fini, G. Micheletti, L. Bernardi, D. Pettersen, M. Fochi, A. Ricci, *Chem. Commun*., **2008**, 4345.



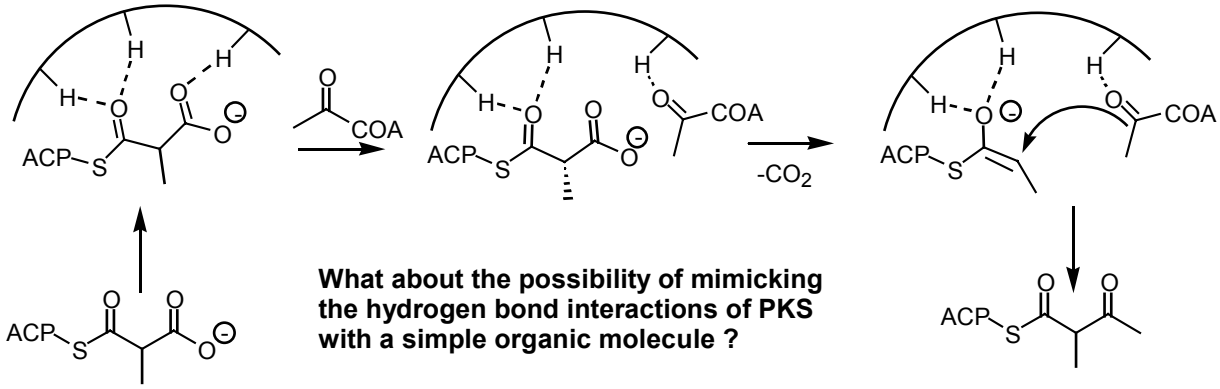
Active Syte of Polyketide Synthase



biosynthesis of fatty acids and polyketides

*within the catalytic triad the **His-Asn** motive is responsible for activating the CoA-bound deprotonated MAHT that reacts with a second **Cys**-bound thioester*

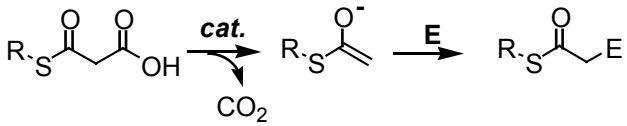
Symplified PKS mechanism

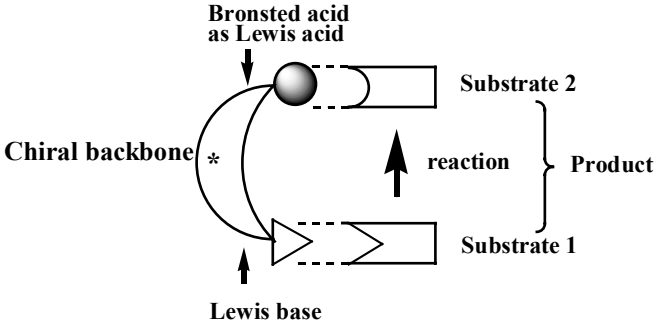


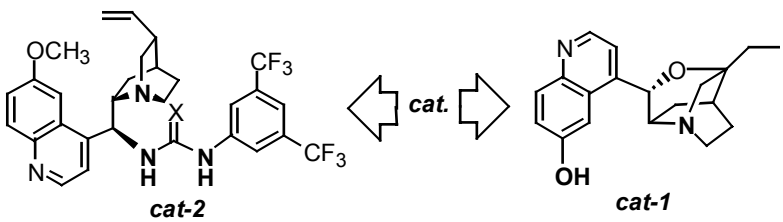
What about the possibility of mimicking the hydrogen bond interactions of PKS with a simple organic molecule ?

M.M. Benning, T. Haller, J. A. Gerlt, H.M. Holden , *Biochemistry*, **2000**, *39*, 4630

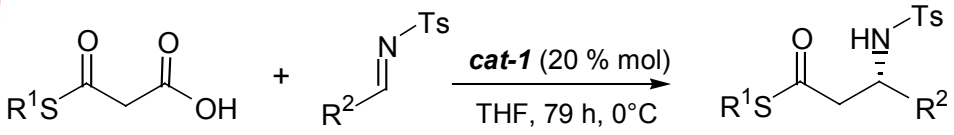
Organocatalysed mimicry of polyketide synthase





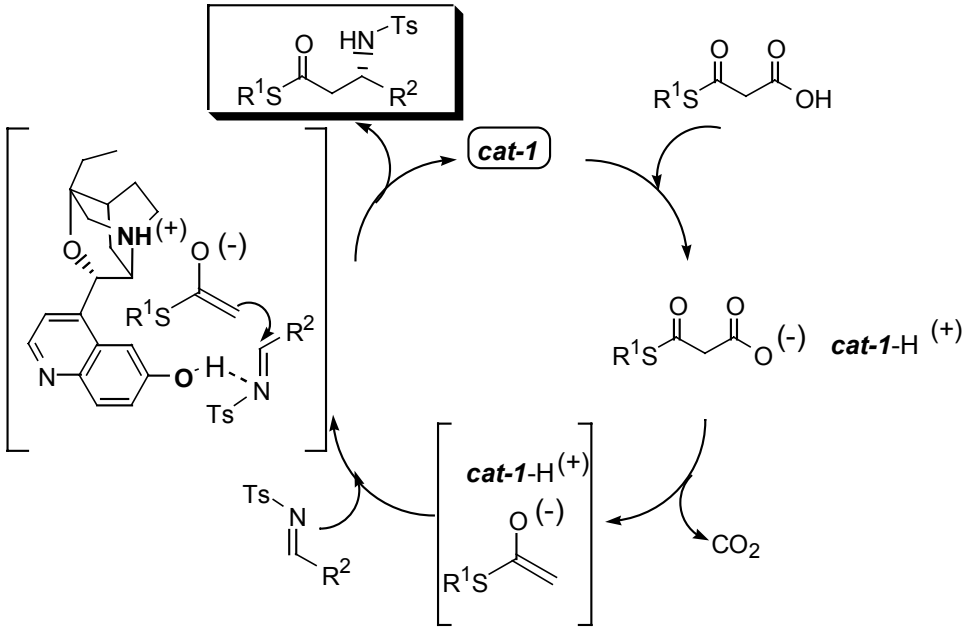


cat-2 ***cat-1***

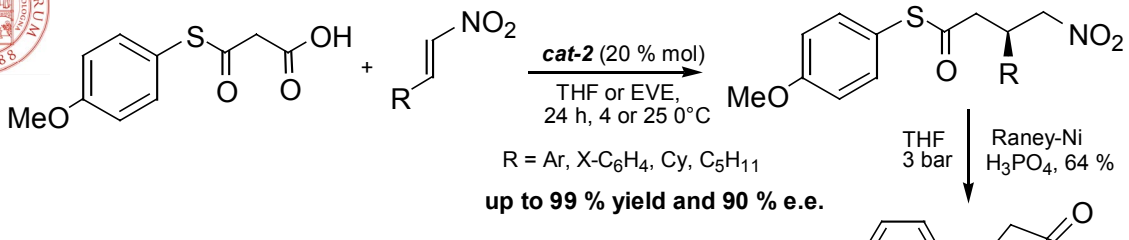


R^1 = Ar; R^2 = C_6H_5, X-C_6H_4, c-C_6H_{11}, 1-naphtyl, C_6H_5-CH_2-CH_2

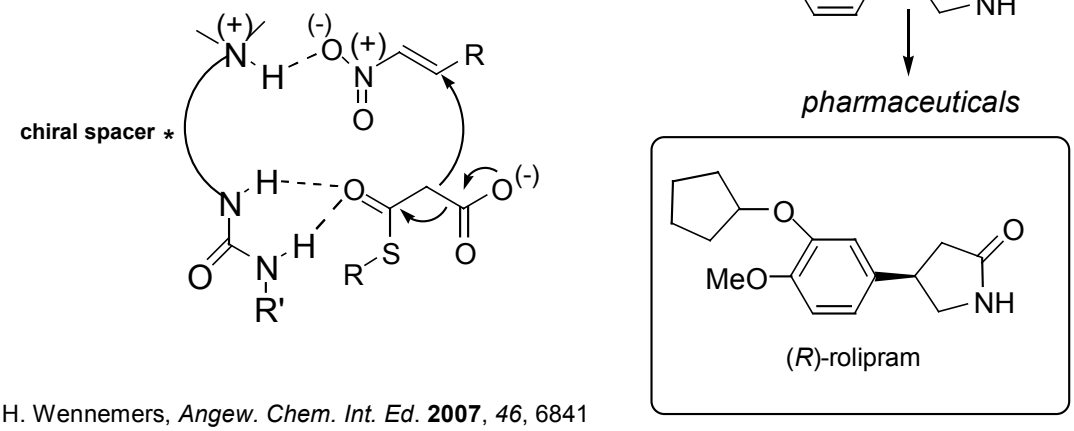
up to 83 % yield and 79 % e.e.



A. Ricci, D. Pettersen, L. Bernardi, F. Fini, M. Fochi, R. P. Herrera, V. Sgarzani, *Adv. Synth. Catal.* **2007**, *349,* 1037



up to 99 % yield and 90 % e.e.

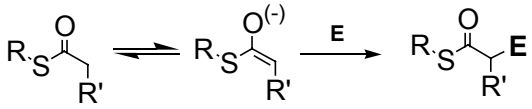


J. Lubkoll, H. Wennemers, *Angew. Chem. Int. Ed*. **2007**, *46*, 6841

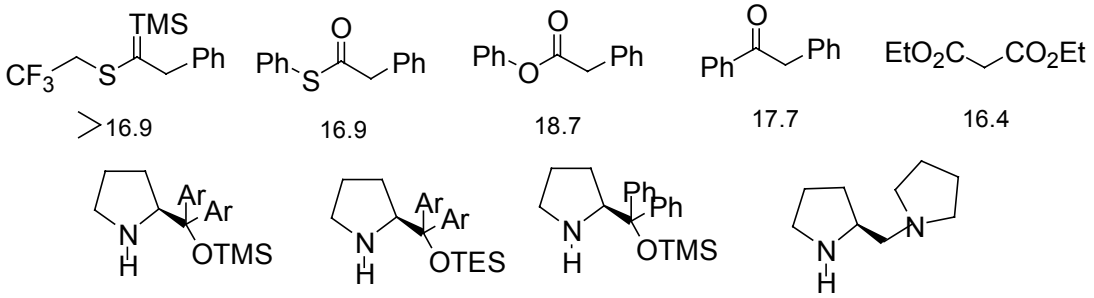
Simplicity is the ultimate sophistication ⇨ **A more atom economical approach that would not require decarboxylation of MATH**

The principle of Occam's razor

α-proton removal by electronic tuning at the thioester: the equilibrium approach



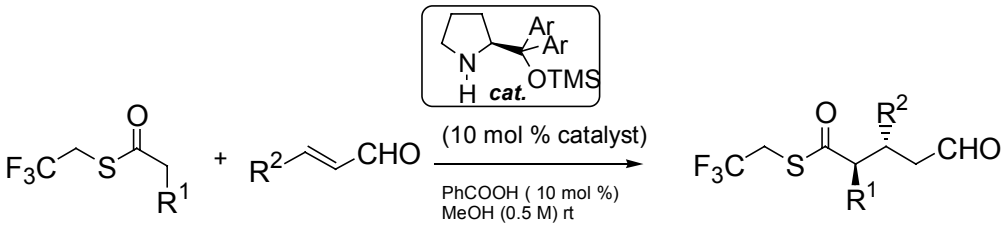
direct organocatalytic methods based on amine catalysis have a functional pK_a barrier for nucleophilic activation that lies between the pK_a values of 16 and 17



Ar = 3,5-$(CF_3)_2C_6H_3$

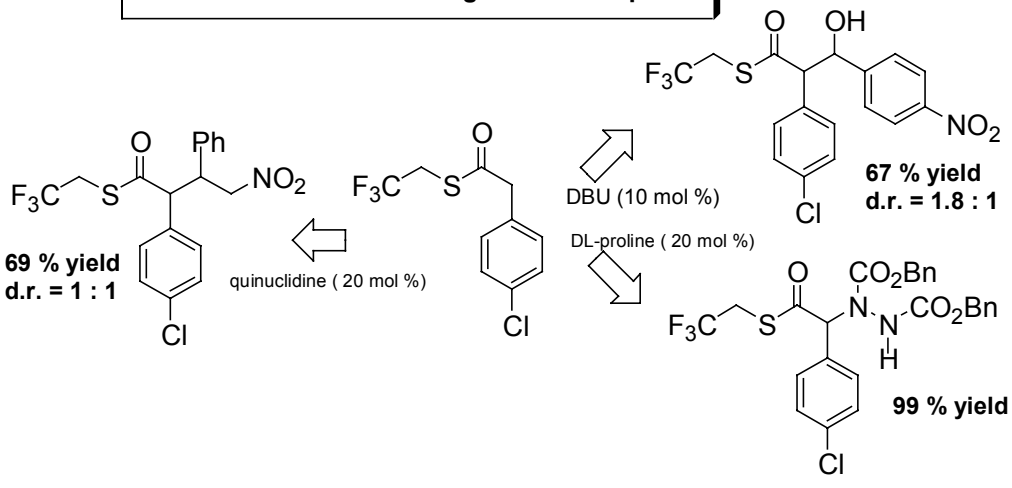
D. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem. Int. Ed*. **2008**, *47*, 4588

Thioester addition reaction to α–β-unsaturated aldehydes



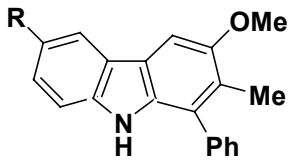
R ^{1} = Ph, X-C_6H_4, 1-napthyl, 2-thienyl, PhCH=CH; 50-88 % yield, up to 86:14 *anti*/*syn* ratio, 66-98% e.e.

extension to a wider range of electrophiles

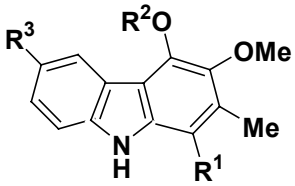


Pharmacologically active structures

carbazoles ⇨

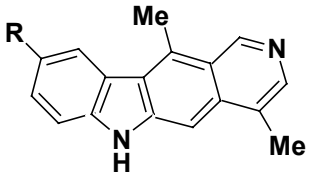


natural product from algae

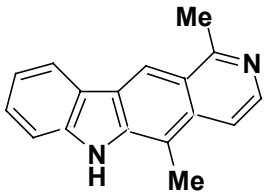


antibiotic action

pyrido carbazoles ⇨

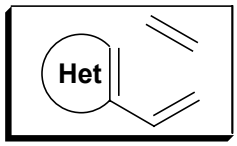


antitumor action

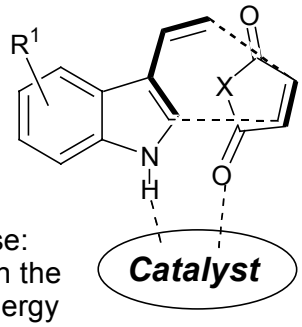


antitumor action

Synthetic elaboration of vinyl indole derivatives ⇨ **Cycloadditions**



A scenario where a suitable bifunctional acid-base organic catalyst coordinates through H-bond interactions both diene and dienophile



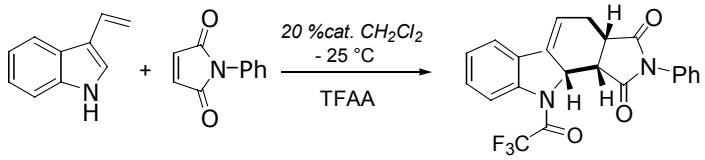
Lewis Base: increase in the HOMO energy

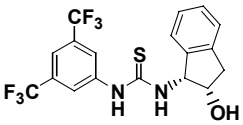
Broensted Acid: lowering in the LUMO energy

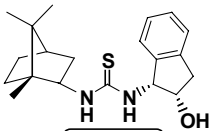
⇩

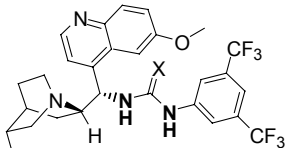
highly organised transition state

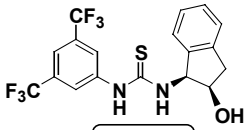
Survey of the organocatalysts

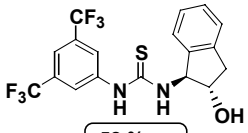


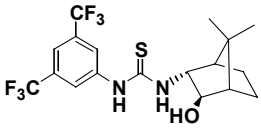

61 % ee

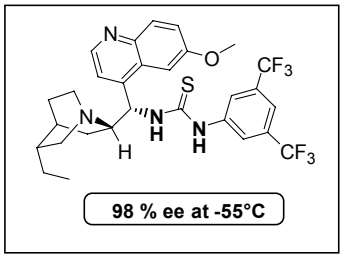

22 % ee


X =S, O: 91 % ee

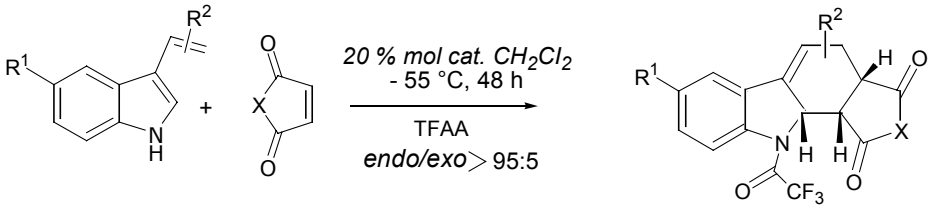

63 % ee

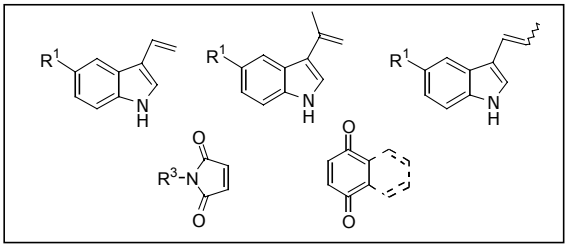

52 % ee

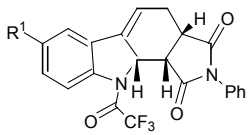

racemic

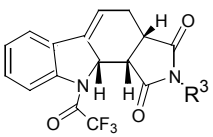

98 % ee at -55°C

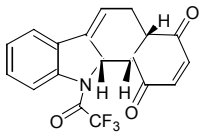
Scope of the reaction

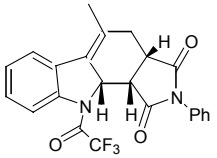


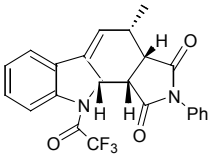


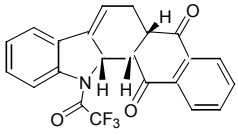

R^1 = H, 91 % yield, 98 % e.e.
R^1 = Br, 86 % yield, 90 % e.e.
R^1 = OMe, 77 % yield, 96 % e.e.


R^3= Me, 89 % yield, 98 % e.e.
R^3= Bn, 89 % yield, 96 % e.e.
R^3 = *t*-Bu, 81 % yield, 88 % e.e.


83 % yield, 99 % e.e.

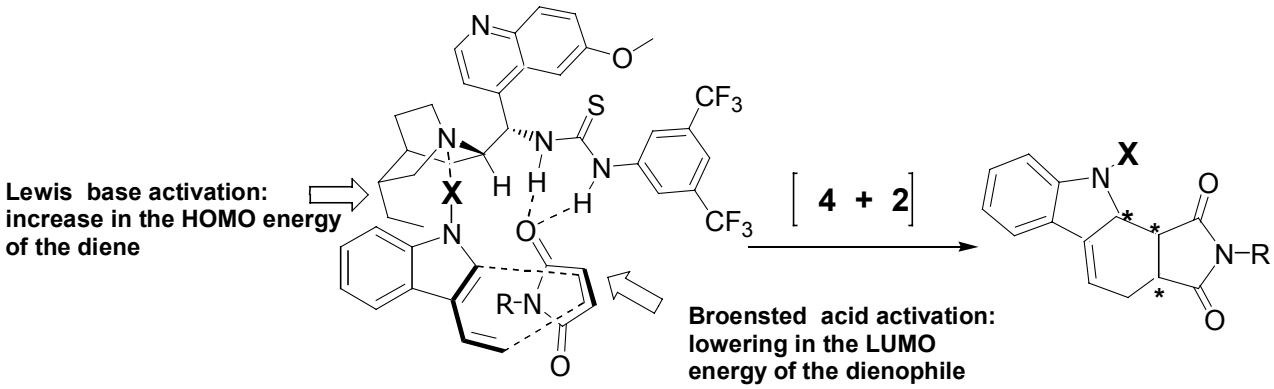

79 % yield, 96 % e.e.


58 % yield, 92 % e.e.


77% yield, 96 % e.e.

Angew. Chem. Int. Ed., ***2008,*** *in press*

Bifunctional action of the organocatalytic species: proposed working model



X = Boc, Ts or Me : racemic mixtures
X = H : high enantioselectivities

Hydrogen bonding acts as a ubiquitous glue to sustain intricate architectures and functionality of proteins nucleic acids and many supramolecular assemblies. This weak interaction can accomplish even by using simple organic molecules, what has previously been considered to be in the domain of enzymes , catalytic antibodies and chiral metal-based Lewis acids.