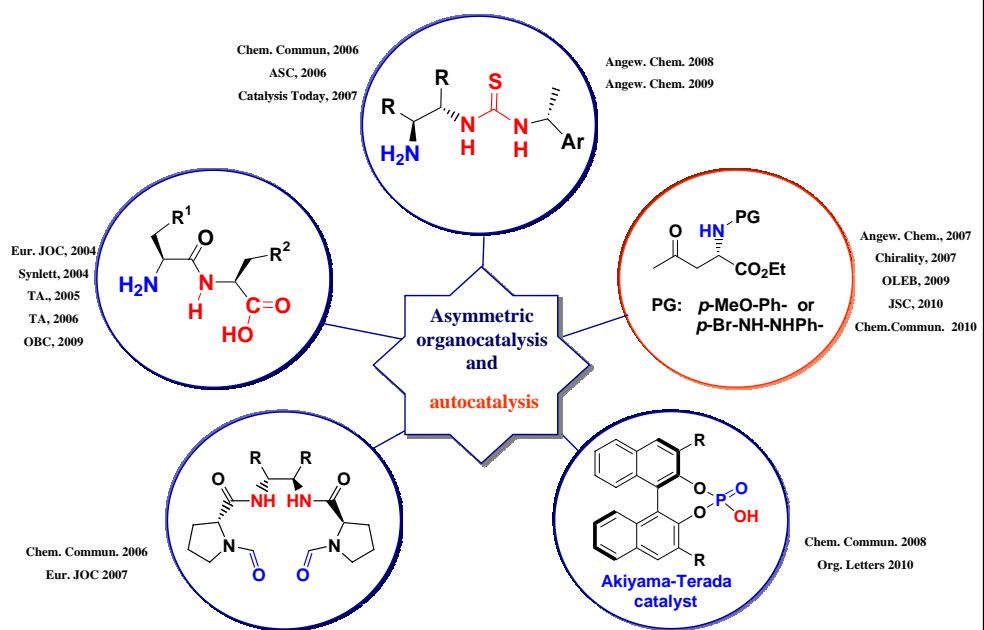
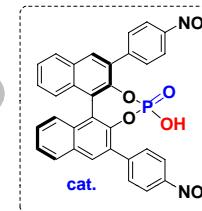


## An overview of selected organocatalysts applied in our group

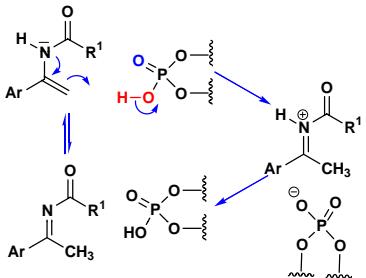


## BINOL-phosphate catalyzed self-coupling reaction

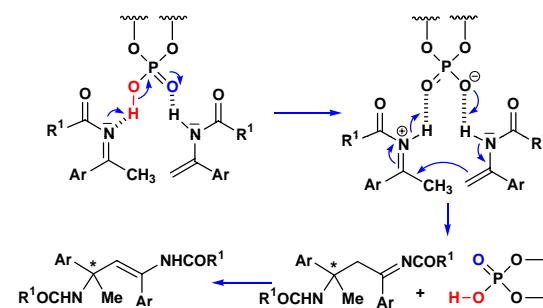


### Proposed reaction mechanism

#### a) Enamide / ketimine equilibrium

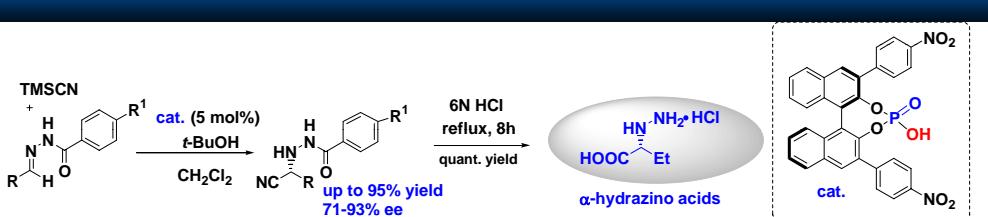


#### b) Aza-ene type pathway

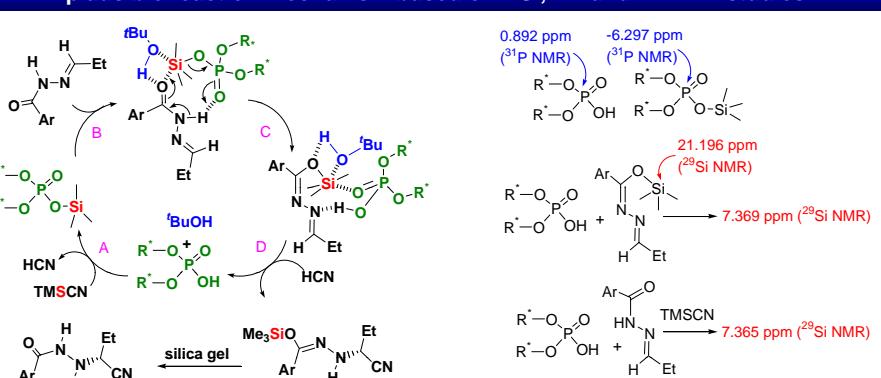


C. Baudequin, A. Zamfir, S. B. Tsogoeva, *Chem. Commun.* 2008, 4637

## Asymmetric organocatalytic hydrocyanation reactions

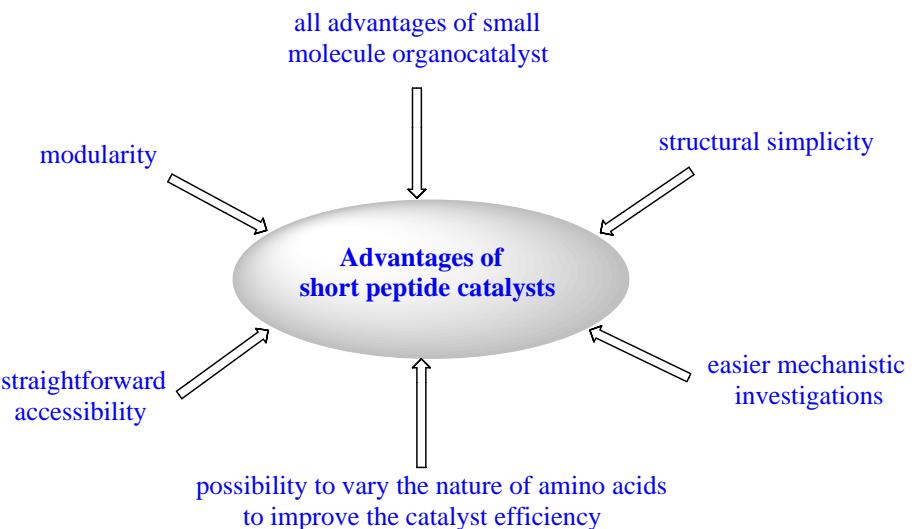


### A plausible reaction mechanism based on $^{29}\text{Si}$ , $^{31}\text{P}$ and $^1\text{H}$ NMR studies

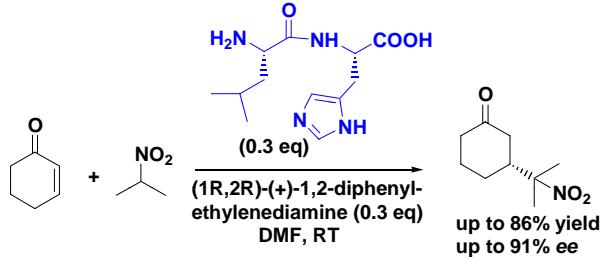


A. Zamfir, S. B. Tsogoeva, *Org. Lett.* 2010, 12, 188

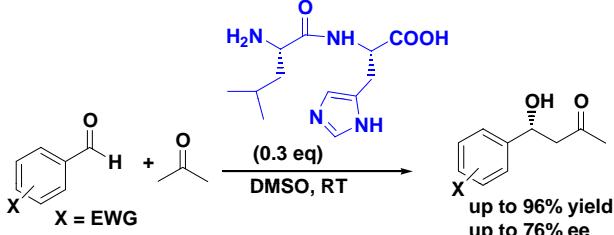
## Some advantages of the “Oligopeptide Approach”



## N-terminal primary amino dipeptide catalyzed 1,4-conjugate addition and aldol reaction



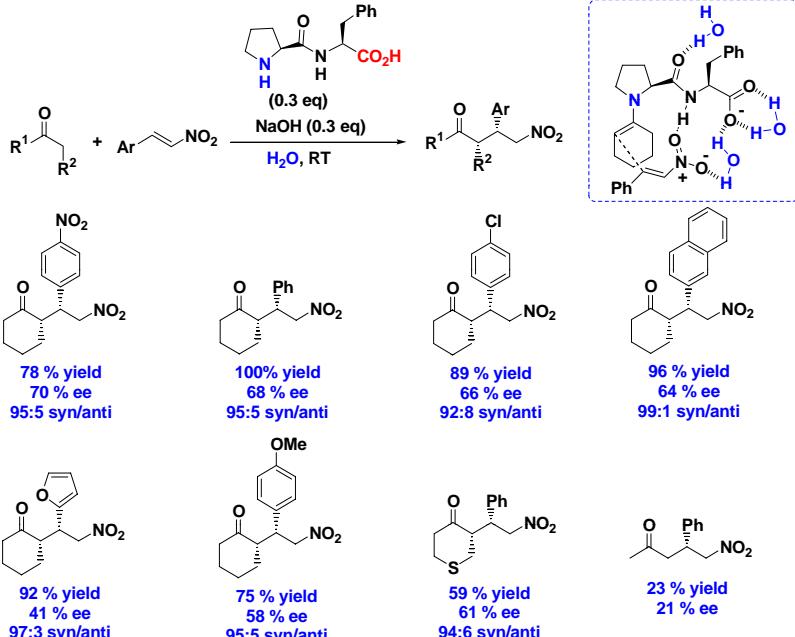
Tsogoeva, S. B.; Jagtap, S. B. *Synlett.* 2004, 2624



Tsogoeva, S. B.; Wei, S.-W. *Tetrahedron: Asymmetry*, 2005, 16, 1947

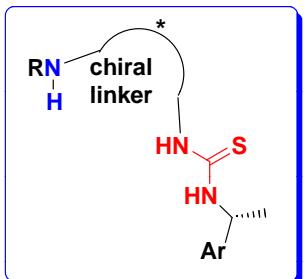
"Most Cited Paper 2005-2008 Award"

## Substrate scope

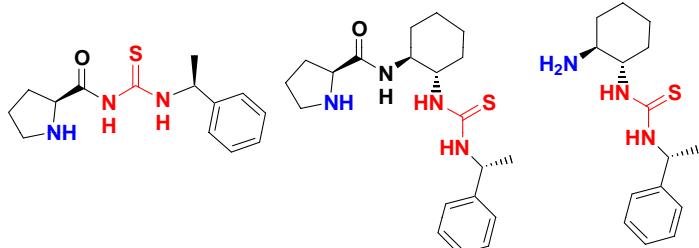


Freund, M.; Schenker, S.; Tsogoeva, S. B. *Org. Biomol. Chem.* 2009, 7, 4279

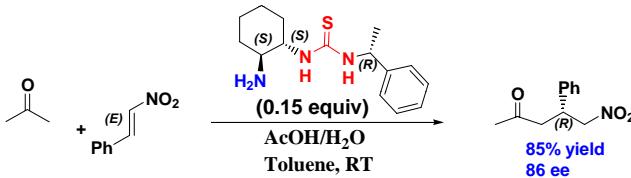
## Design of bifunctional organocatalysts



## New chiral thiourea based bifunctional organocatalysts

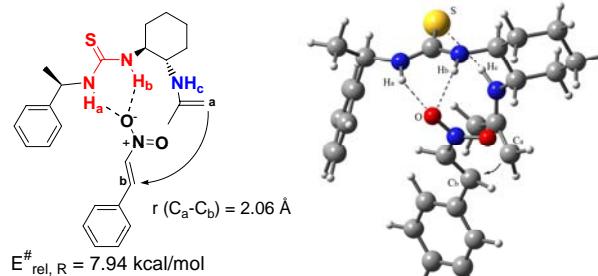


## Asymmetric nitro-Michael reactions catalyzed by thiourea-amine



Tsogoeva, S. B.; Wei, S.-W. *Chem. Commun.* 2006, 1451

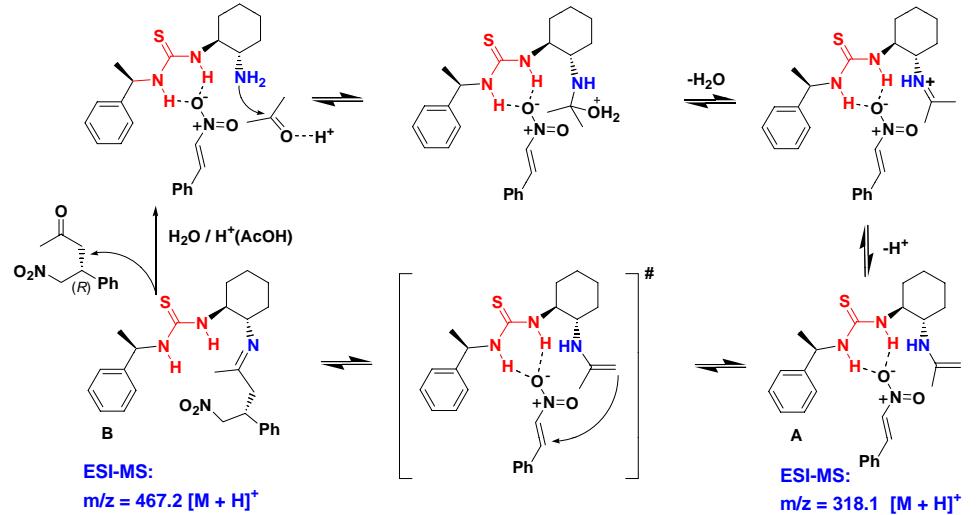
## DFT quantum-chemical calculations (B3LYP/6-31G(d))



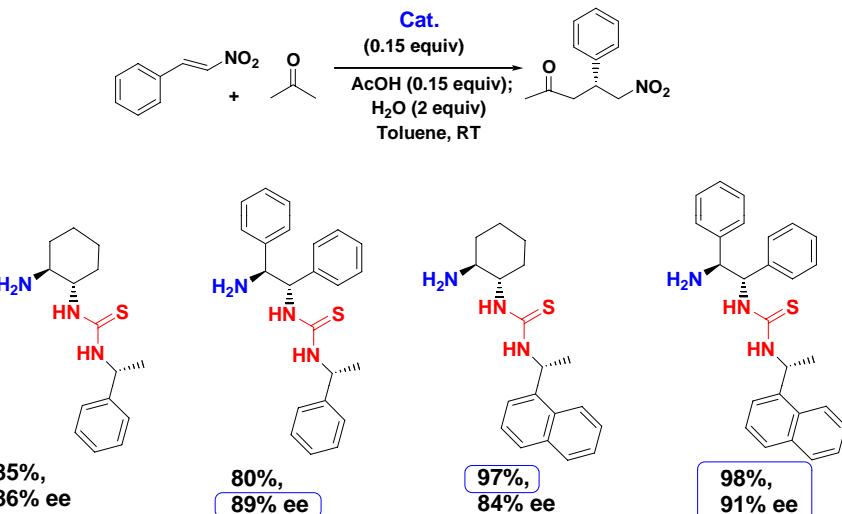
Transition state structure for the formation of the *R* enantiomer.

Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Adv. Synth. Catal.* 2006, 348, 826

### Plausible multistep chiral thiourea-amine catalysis

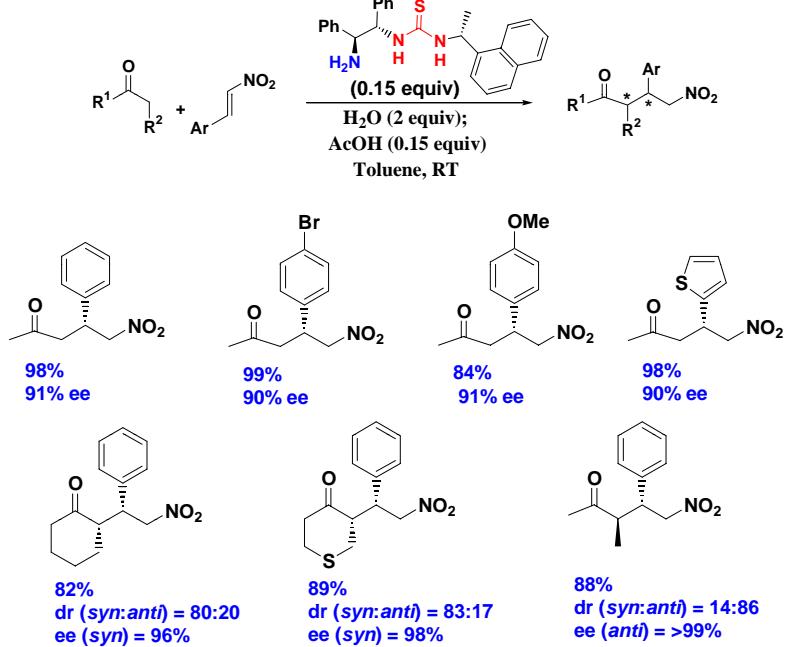


### Nitro-Michael addition catalyzed by derivatives of the new bifunctional catalyst

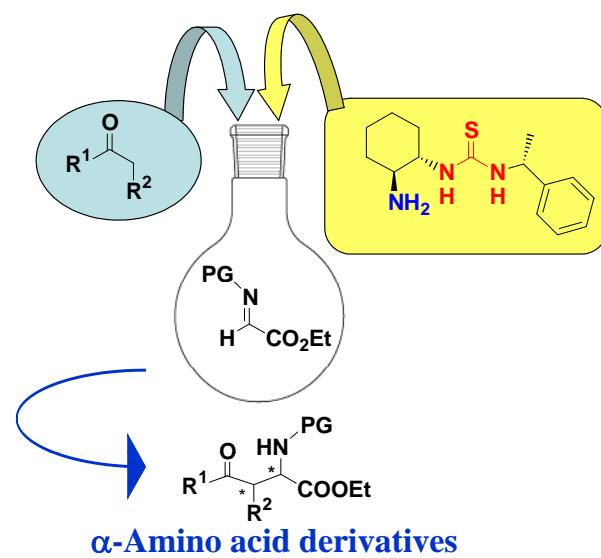


Wei, S.-W.; Yalalov, D. A.; Tsogoeva, S. B.; Schmatz, S. *Catalysis Today* 2007, 121, 151

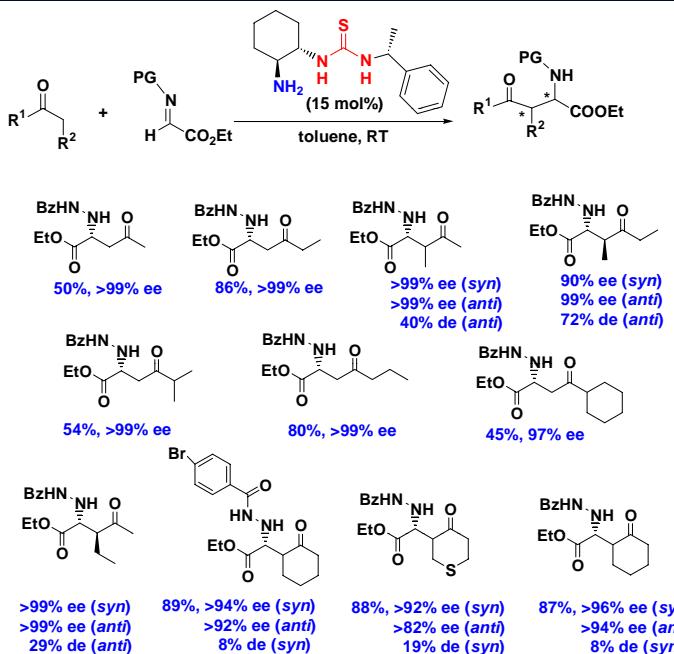
### Scope of reactions



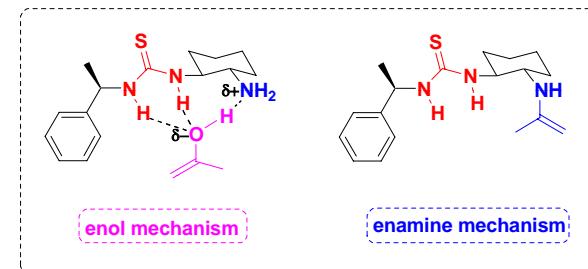
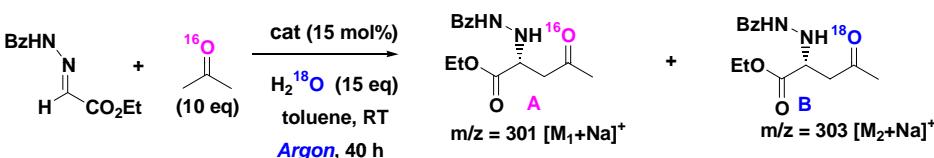
### Further applications for the new thiourea-amine catalysts



## Scope of Mannich-type reactions catalyzed by thiourea-amine

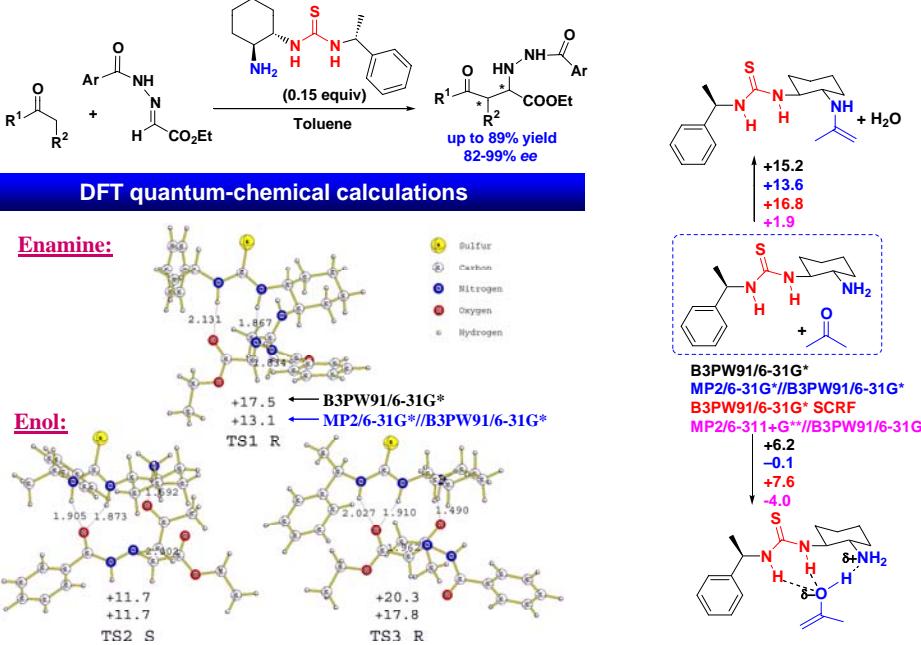


## <sup>18</sup>O-incorporation experiment studied by ESI-MS

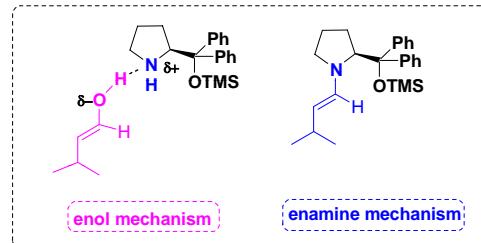
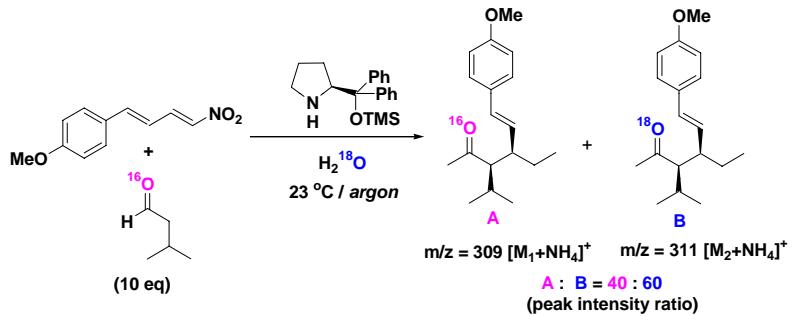


Yalalov, D. A.; Tsogoeva, S. B.; Shubina, T. E.; Clark, T. *Angew. Chemie Int. Ed.* 2008, 47, 6624

## Computational studies of asymmetric Mannich-type reaction

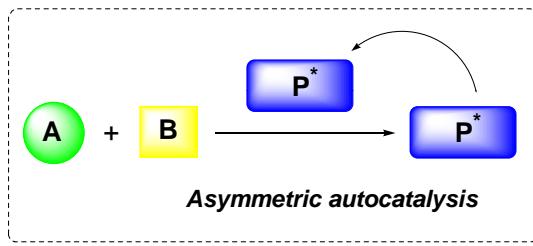
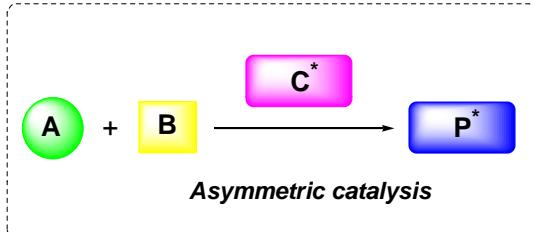


## <sup>18</sup>O-marker experiment studied by ESI-MS



S. Belot, A. Quintard, N. Krause, A. Alexakis. *Adv. Synth. Catal.* 2010, 352, 667.

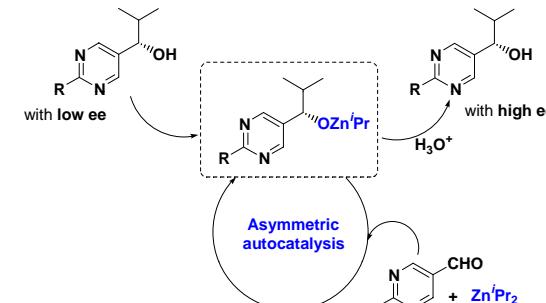
## Asymmetric catalysis vs. Asymmetric autocatalysis



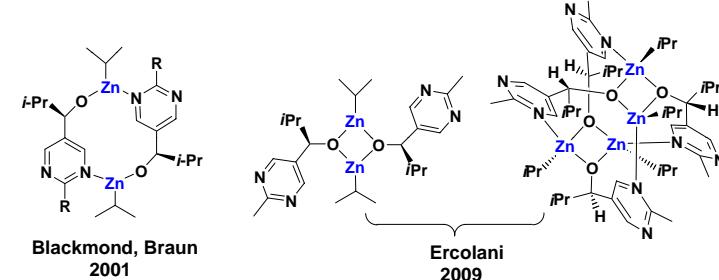
**"Asymmetric autocatalysis is a process whereby a chiral reaction product is the catalyst in its own formation from achiral reactants."**

H. Wynberg  
1989

## Asymmetric autocatalysis

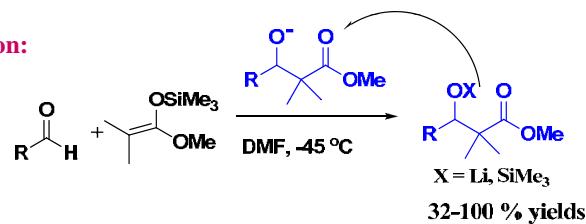


Via dimeric or tetrameric Zn-complexes as active catalysts:



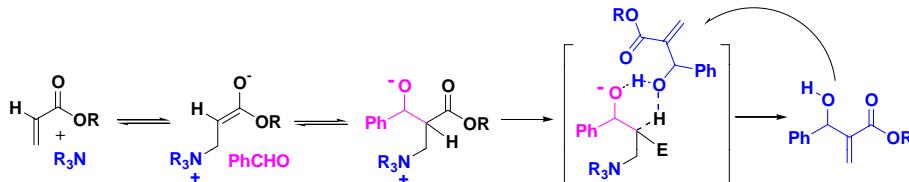
## Non-enantioselective organo-autocatalysis

### Aldol Reaction:



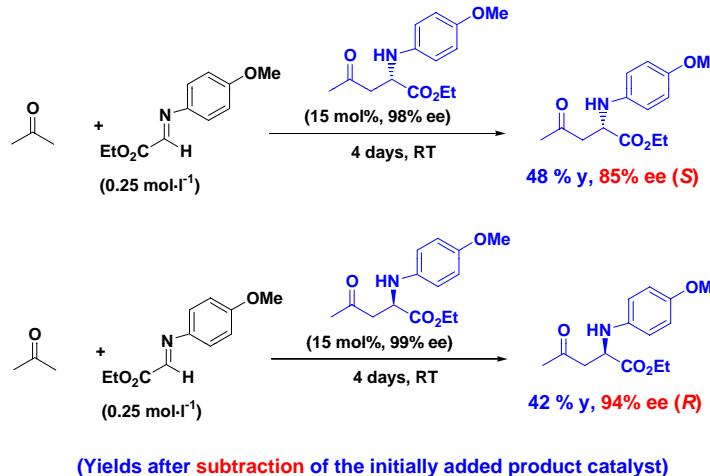
H. Fujisawa, T. Nakagawa, T. Mukaiyama, *Adv. Synth. Catal.* 2004, 346, 1241

### Baylis-Hillman Reaction:



V. K. Aggarwal, S. Y. Fulford and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2005, 44, 1706

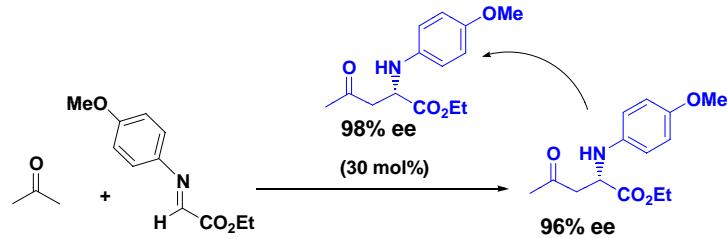
## When chiral product and catalyst are the same



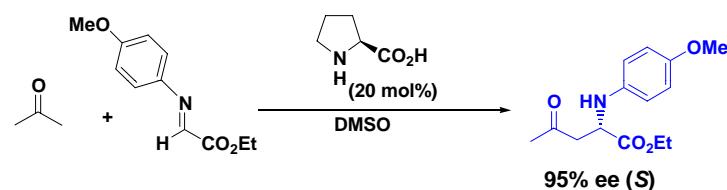
M. Mauksch, S. B. Tsogoeva, I. M. Martynova, S.-W. Wei. *Angew. Chem. Int. Ed.* 2007, 46, 393

- Promoted to "Hot Paper".
- Highlighted in *SYNFORM*, *Synlett*, Issue 8, 2007.

### Product catalysis vs. Proline catalysis

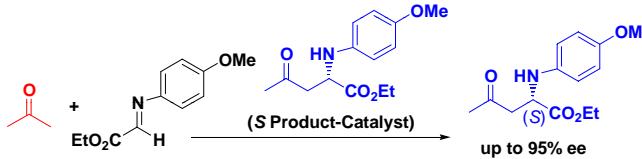


M. Mauksch, S. B. Tsogoeva, I. M. Martynova, S.-W. Wei. *Angew. Chem. Int. Ed.* 2007, 46, 393

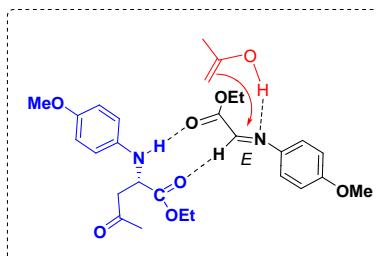
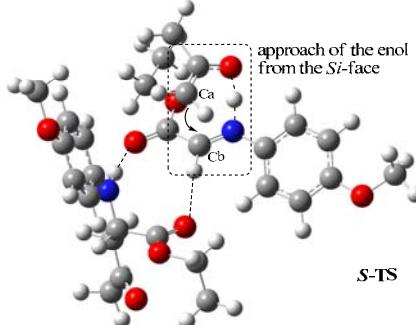


A. Cordova, W. Notz, G. Zhong, J.M. Betancort C. F. Barbas III. *J. Am. Chem. Soc.* 2002, 124, 1842

### When product and catalyst are the same



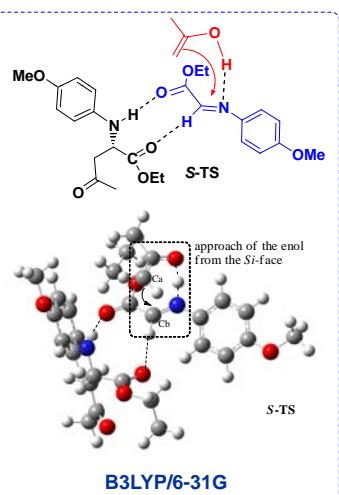
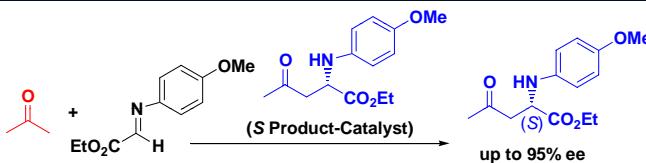
DFT Calculations with Gaussian03 Program Package at B3LYP/6-31G level:



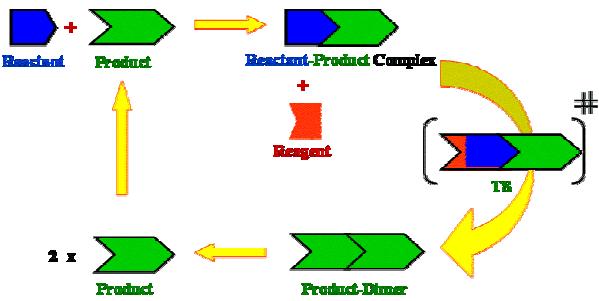
Transition state structure for the formation of the *S* enantiomer of Mannich Product

M. Mauksch, S. B. Tsogoeva, I. M. Martynova, S.-W. Wei. *Angew. Chem. Int. Ed.* 2007, 46, 393

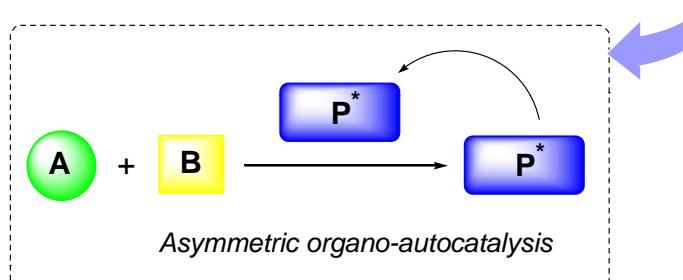
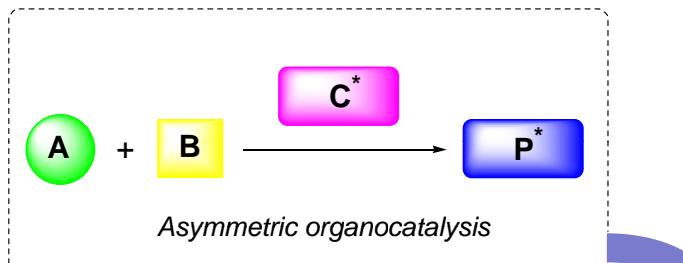
### Asymmetric organoautocatalysis via product-templates



Template + Autocatalysis = Self-Replication



### Organoautocatalysis as a natural extension to organocatalysis

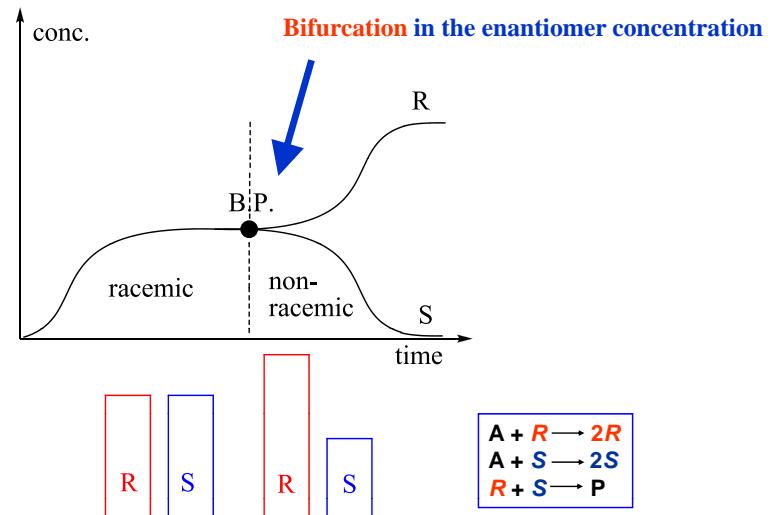


## "Absolute Asymmetric Synthesis" and "Spontaneous Mirror Symmetry Breaking"

**"Absolute Asymmetric Synthesis is the formation of enantiomerically enriched products from achiral precursors without the intervention of chiral chemical reagents or catalysts"**

Kurt Mislow  
Collect. Czech Chem Commun. 2003

## The Frank model of mirror symmetry breaking in enantioselective autocatalysis



Kondepudi and Nelson Phys A, 1984

Crusats et al, ChemPhysChem, 2009  
Mauksch et al, OLEB, 2009

### Asymmetric Organo-autocatalytic Mannich Reaction

### Symmetry Breaking: Mannich reaction under achiral conditions

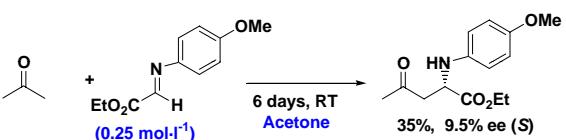


## Symmetry breaking: Mannich reaction under achiral conditions

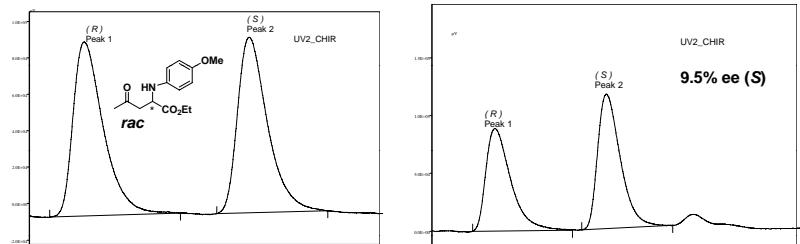
Entry	Reaction Time (days)	Yield (%)	ee (%)	ee (%)
			by HPLC	by <sup>1</sup> H-NMR with Eu(tfc) <sub>3</sub>
1	2	20	9.0 (S)	-
2	2	11	1.5 (R)	2.4 (R)
3	2	18	9.1 (S)	9.1 (S)
4	4	35	0.5 (S)	-
5	4	13	2.1 (R)	2.2 (R)
6	4	31	9.4 (S)	8.2 (S)
7	4	34	6.8 (S)	-
8	4	33	7.4 (S)	-
9	4	32	2.6 (S)	-
10	6	35	9.5 (S)	-
11	6	32	3.8 (S)	3.9 (S)
12	8	36	2.6 (S)	-
13	8	33	2.0 (S)	2.4 (S)

M. Mauksch, S. B. Tsogoeva, S.-W. Wei, I. M. Martynova, Chirality, 2007, 19, 816

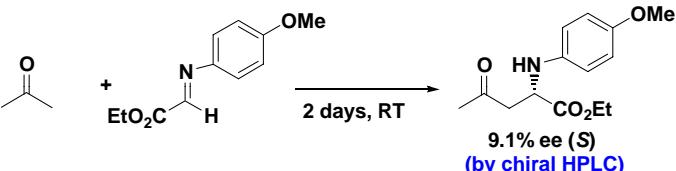
## Measurement of product enantiomeric excess in the Mannich reaction, run under achiral conditions



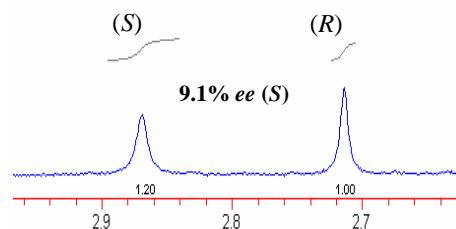
### HPLC chromatograms (chiral OD column)



## Measurement of product enantiomeric excess in the Mannich reaction, run under achiral conditions

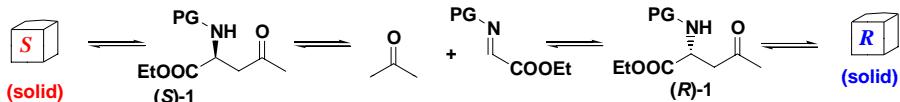


<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) signals of CH<sub>3</sub>CO group in (*R*)- and (*S*)- enantiomers in presence of Eu(tfc)<sub>3</sub> complex

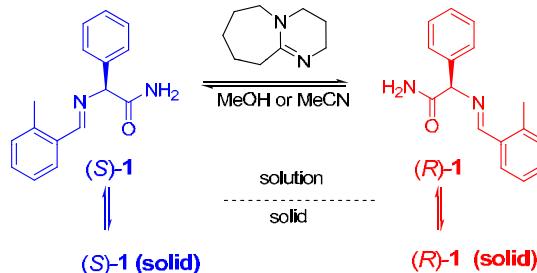


## Asymmetric Autocatalysis in Homogenous System

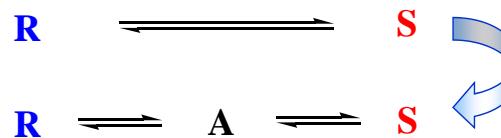
## Asymmetric Autocatalysis in Heterogenous System



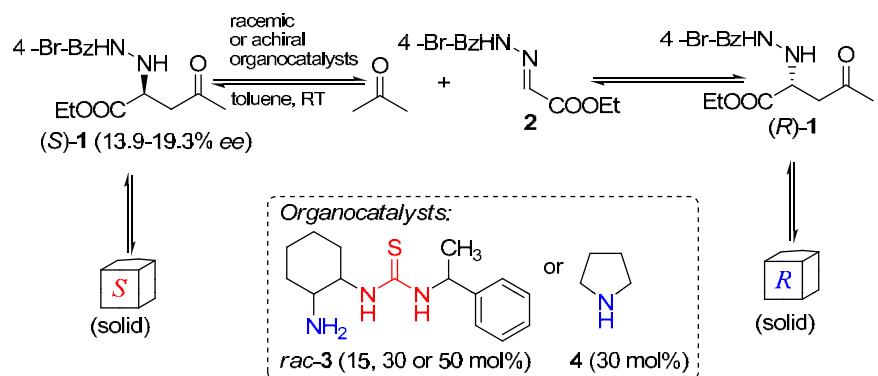
## Deracemization in heterogenous system



W. L. Noorduin, et al, *JACS*, 2008, 130, 1158; *Angew. Chem. Int. Ed.*, 2008, 47, 6445.

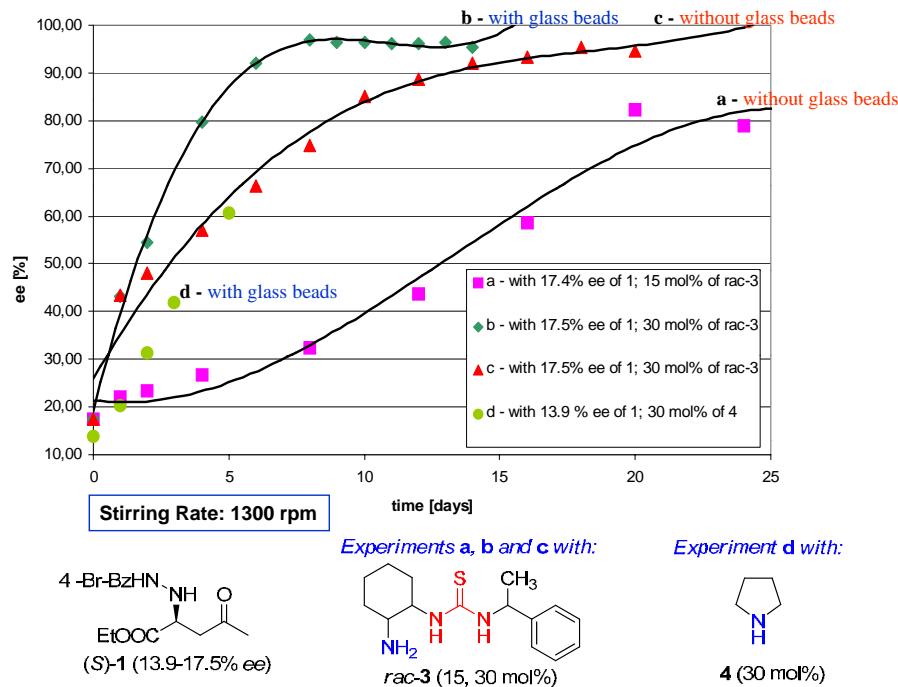


### Deracemization experiments with a Mannich-type reaction

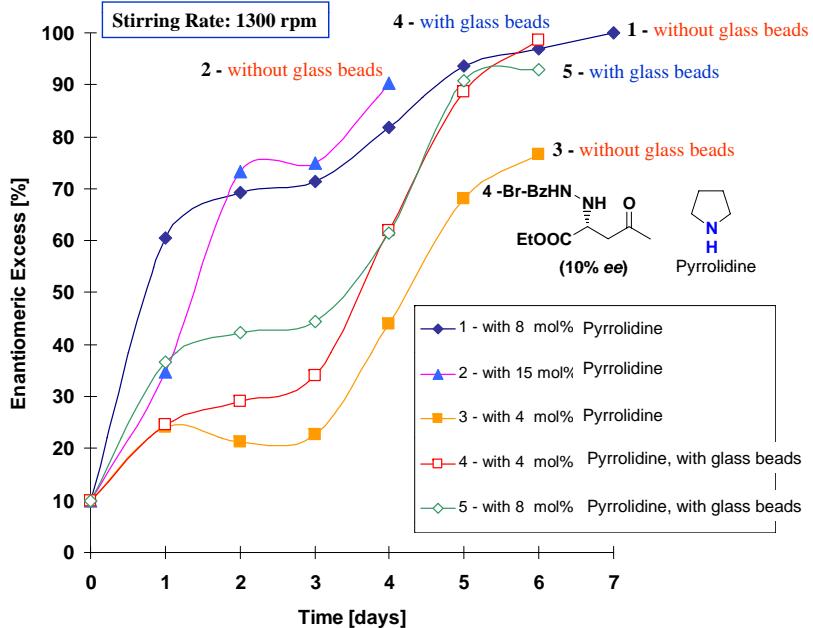


S. B. Tsogoeva, S.-W. Wei, M. Freund, M. Mauksch, *Angew. Chemie Int. Ed.* 2009, 48, 590

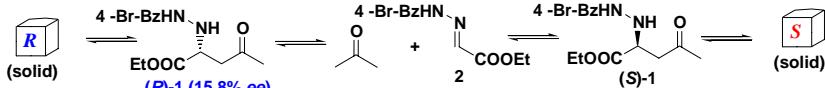
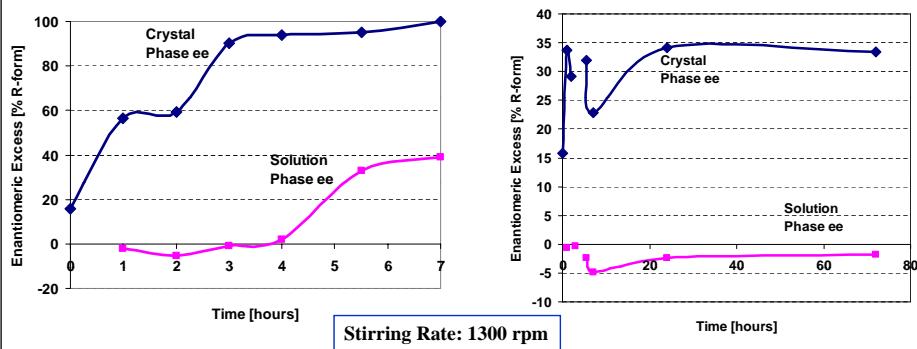
### Deracemization process in the Mannich-type reaction at RT



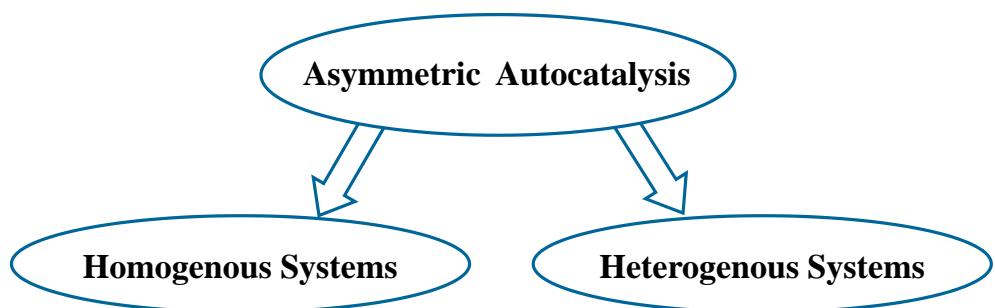
### Deracemization process with an achiral catalyst at RT



### Deracemization process in the Mannich-type reaction at 40°C



S.-W. Wei, M. Mauksch, S. B. Tsogoeva, *Chem. Eur. J.* 2009, 15, 10255



**“Asymmetric Autocatalysis  
is the major challenge in future Asymmetric Synthesis.”**

*H. Wynberg, Chimia, 1989, 43, 150*