# Supramolecular Catalysis

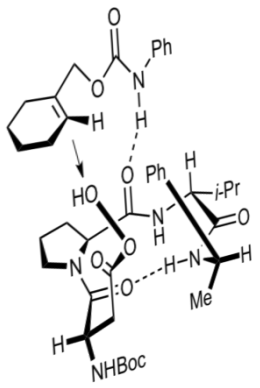
Sergey Pronin
Shenvi Group

*"…organic catalysts of the future will combine binding and orientation with cooperativity between catalytic functional groups."*

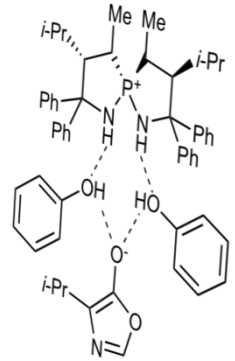
*Donald J. Cram, 1983*

Small-molecule enzyme mimics

Miller
Jacobsen
Crabtree

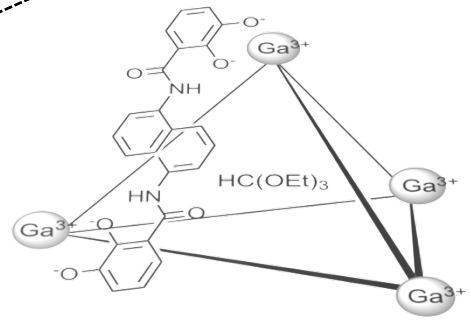


Supramolecular catalysis



Self-assembled catalytic species

Breit
Reek
Ooi



Host-guest complexes

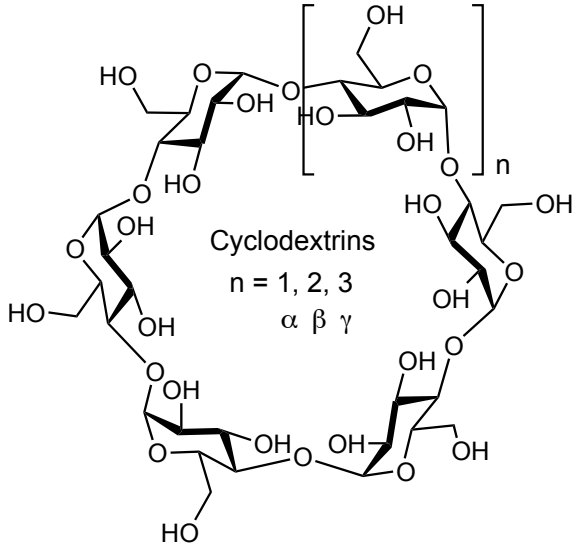
Breslow Lehn Raymond

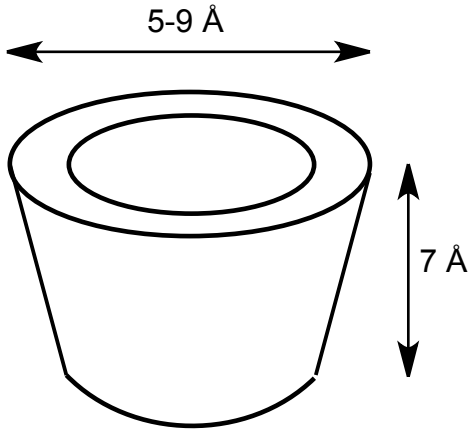
Assembly of reactive complexes by harnessing multiple weak molecular interactions

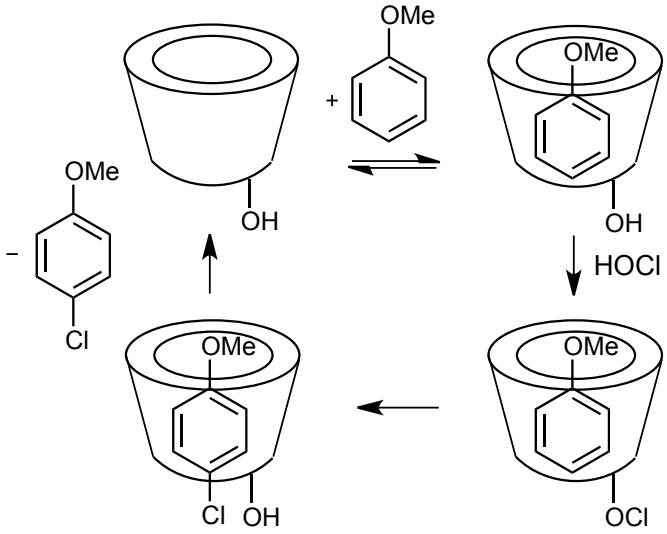
# Supramolecular Catalysis: Host-Guest Chemistry

Sergey Pronin
Shenvi Group

Ronald Breslow

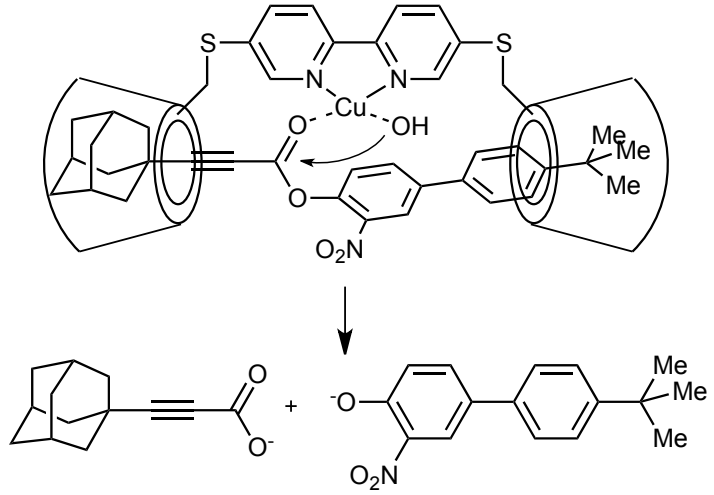



Single regioisomer

R. Breslow and P. Campbell *J. Am. Chem. Soc.* **1969**, *91*, 3085.



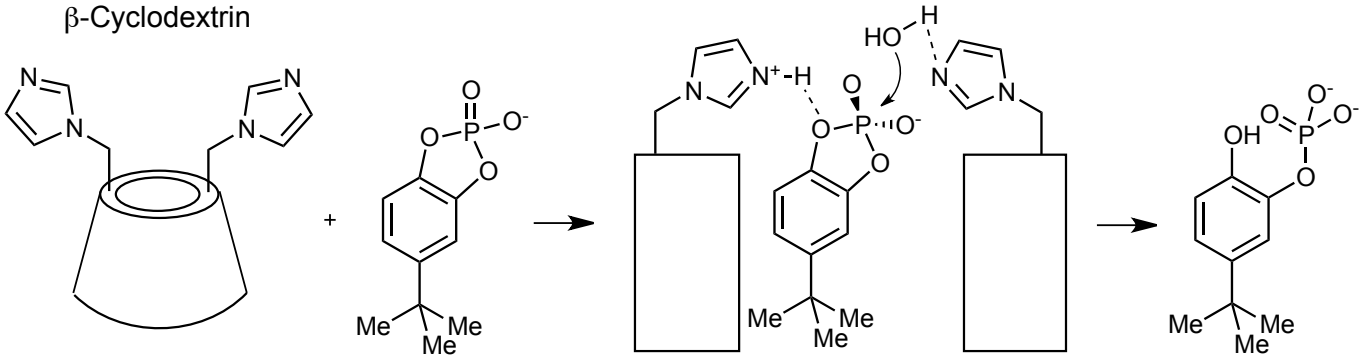

$k_{cat}/k_{uncat} = 1.45\times10^7$

B. Zhang and R. Breslow *J. Am. Chem. Soc.* **1997**, *119*, 1676.

# Supramolecular Catalysis: Host-Guest Chemistry

Sergey Pronin
Shenvi Group

β-Cyclodextrin



*Ribonuclease mimics*

*Single regioisomer*
$k_{cat}/k_{uncat}$ = 120

R. Breslow et al. *J. Am. Chem. Soc.* **1978**, *100*, 3227; **1996**, *118*, 6601.

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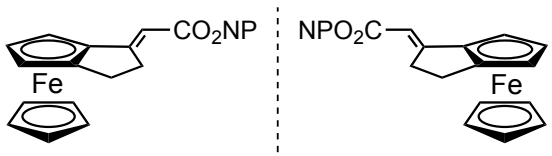
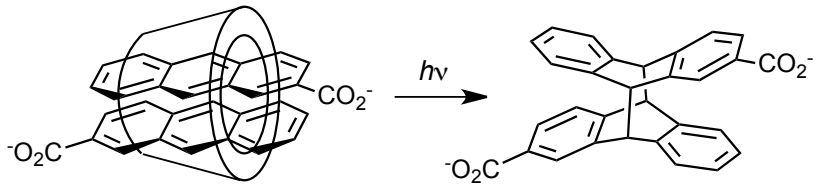
*"Optimization of metallocene substrates for β-cyclodextrin reactions"*



Hydrolysis of ferrocene esters:
*left:* $k_{cat}/k_{uncat}$ = 5900000
*right:* $k_{cat}/k_{uncat}$ = 95000
62:1 enantioselectivity

R. Breslow et al. *J. Am. Chem. Soc.* **1983**, *105*, 2739.

γ-Cyclodextrin



*plus achiral dimer*

*32% ee*

A. Nakamura and Y. Inoue *J. Am. Chem. Soc.* **2002**, *125*, 966.

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*Substrates always have to be tuned!*

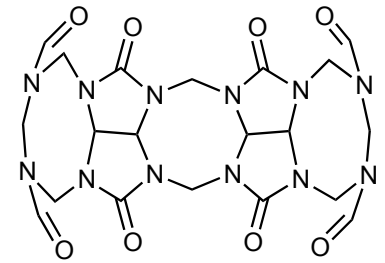
*For more information see:* R. Breslow *Science*, **1982**, *218*, 532;
R. Breslow *Acc. Chem. Res.*, **1995**, *28*, 146;
R. Breslow and S. D. Dong *Chem. Rev.*, **1998**, *98*, 1997.

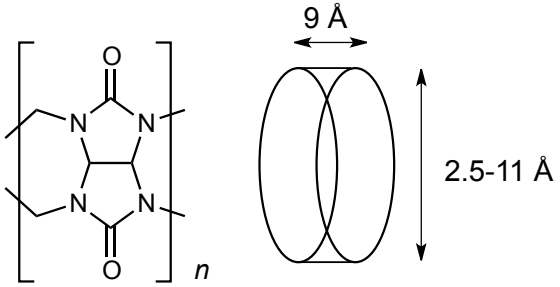
# Supramolecular Catalysis: Host-Guest Chemistry

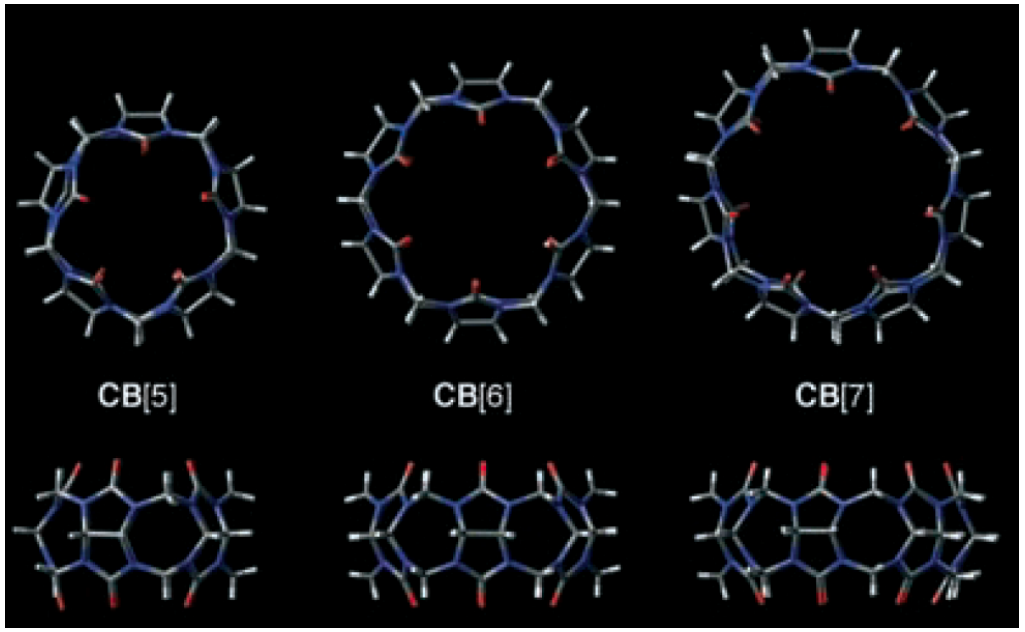
Sergey Pronin
Shenvi Group

Cucurbit[*n*]urils

*n* = 5-10



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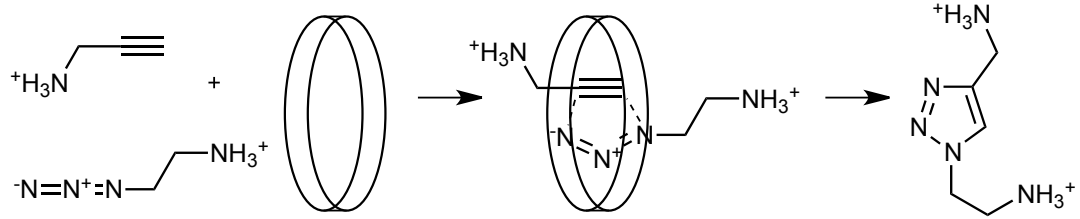
Cucurbit[6]uril



*Completely regioselective; $k_{cat}/k_{uncat}$ = 55000*
*Enzyme kinetics: saturation effect,*
*rate-limiting product release, substrate inhibition*

W. L. Mock et al. *J. Org. Chem.:* **1983**, *48*, 3619;
**1989**, *54*, 5302.

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*For more information see:* J. Lagona et al. *Angew. Chem. Int. Ed.* **2005**, *44*, 4844.

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# Supramolecular Catalysis: Host-Guest Chemistry

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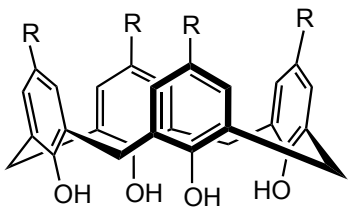
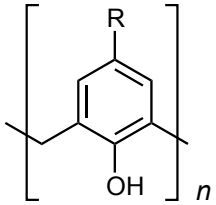
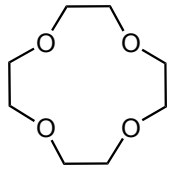
Shenvi Group

Calix[*n*]arenes

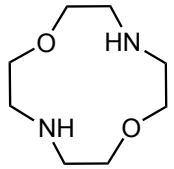


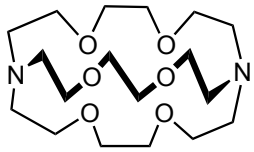

Crown ethers



Macrocyclic polyamines




Cryptands




C. J. Pederson *J. Am. Chem. Soc.* **1967**, *89*, 7017; D. J. Cram *Science* **1983**, *219*, 1177; J. M. Lehn *Science* **1985**, *227*, 849.

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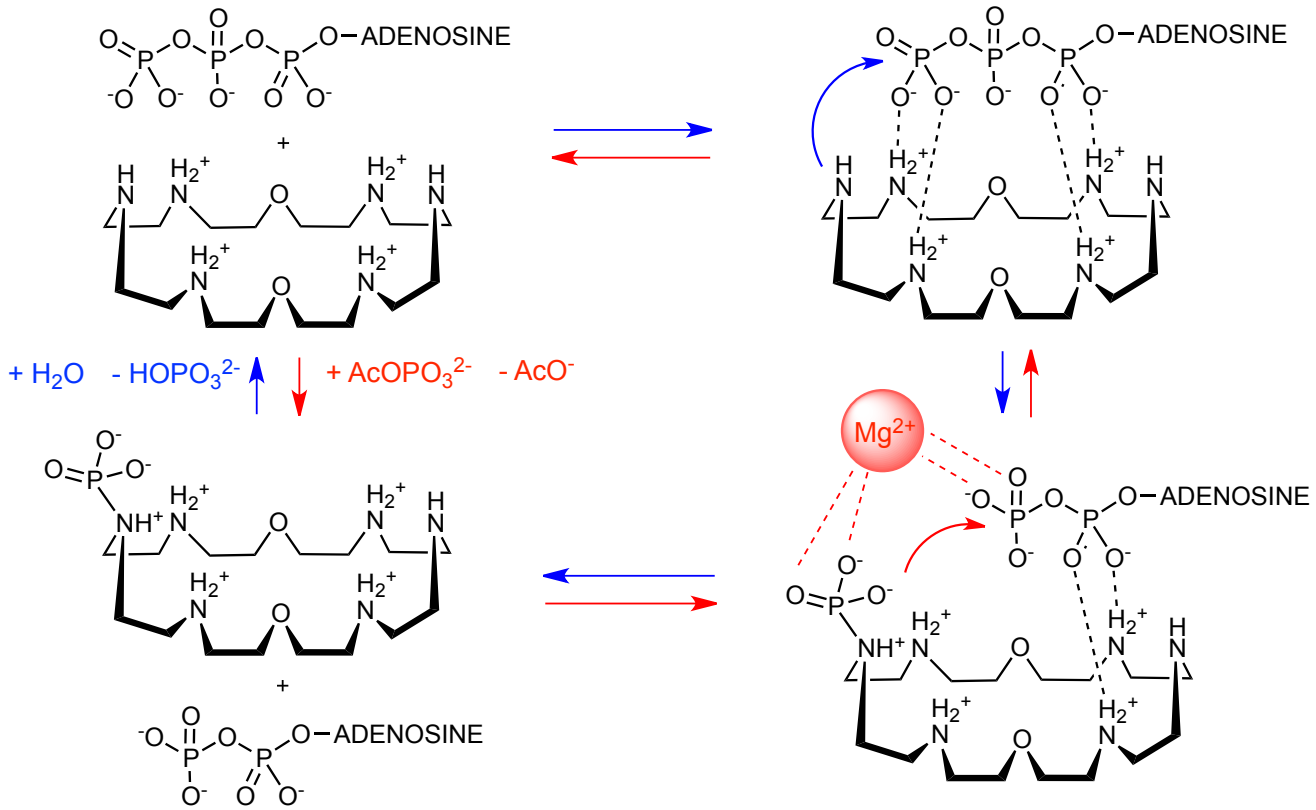


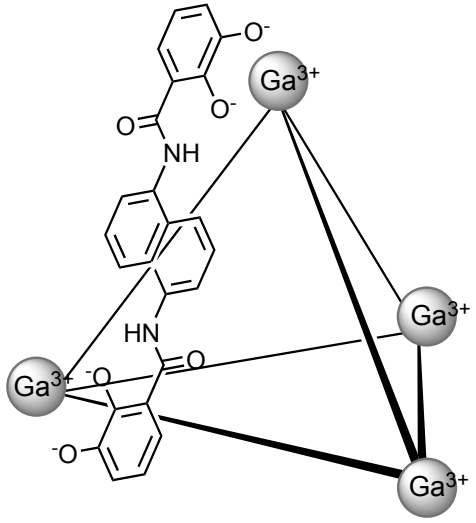

ATP hydrolysis, *p*H = 7
M. W. Hosseini et al.
*JACS* **1989**, *111*, 6330.

*ATPase and ATP synthase mimics*

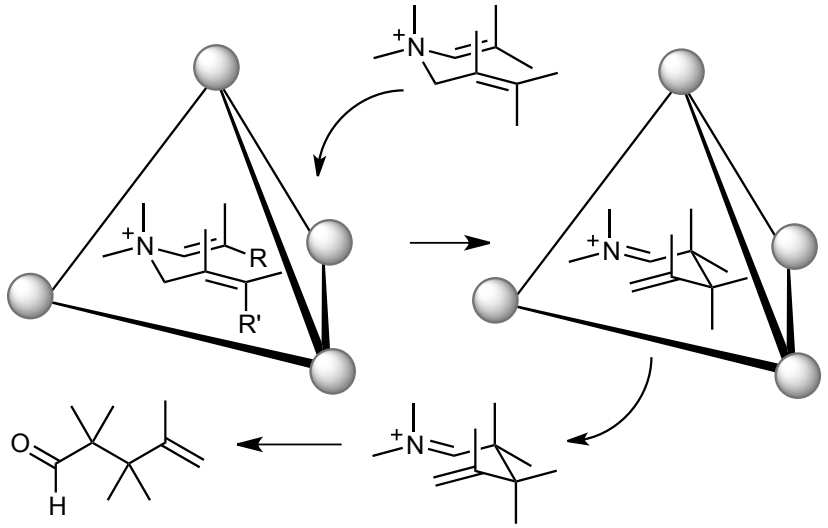
ATP synthesis, *p*H = 7
M. W. Hosseini and J. M. Lehn
*JCS Chem. Com.* **1991**, 451.

# Supramolecular Catalysis: Host-Guest Chemistry

Sergey Pronin
Shenvi Group

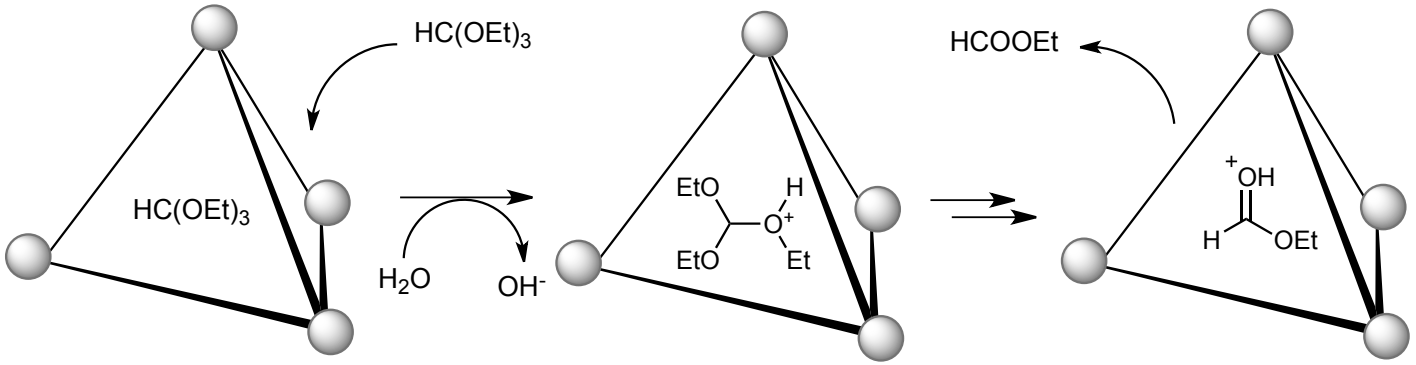



Pluth, Bergman, and Raymond
*Acc. Chem. Res.* **2009**, *42*, 1650




Ground-state preorganization: strong NOE between R and R'
$k_{cat}/k_{uncat}$ *up to 854*

D. Fiedler et al. *Angew. Chem. Int. Ed.*, **2004**, *43*, 6748;
D. Fiedler et al. *J. Am. Chem. Soc.* **2006**, *128*, 10240.

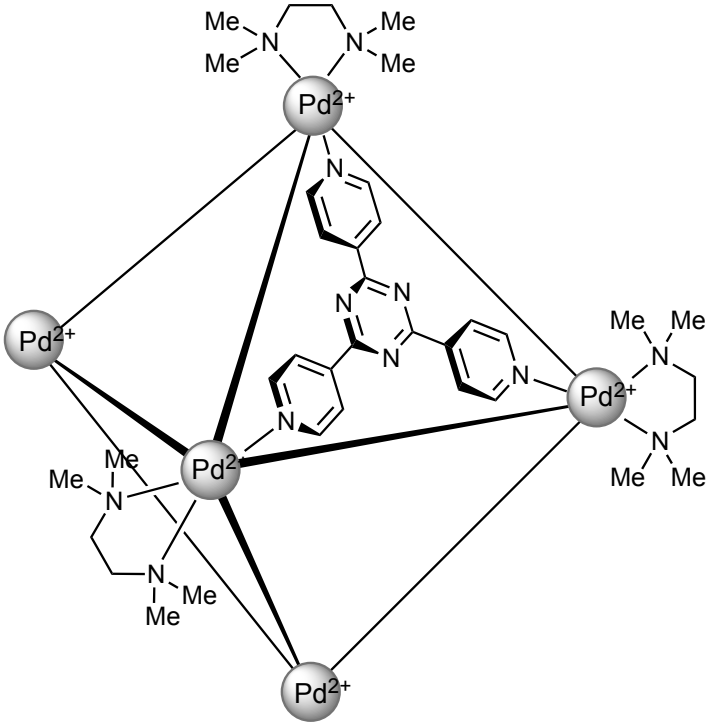



$t_{½(orthoformate)}$ *~ 12 min at pH = 11.0*

M. D. Pluth, R. G. Bergman, K. N. Raymond *Science* **2007**, *316*, 85.

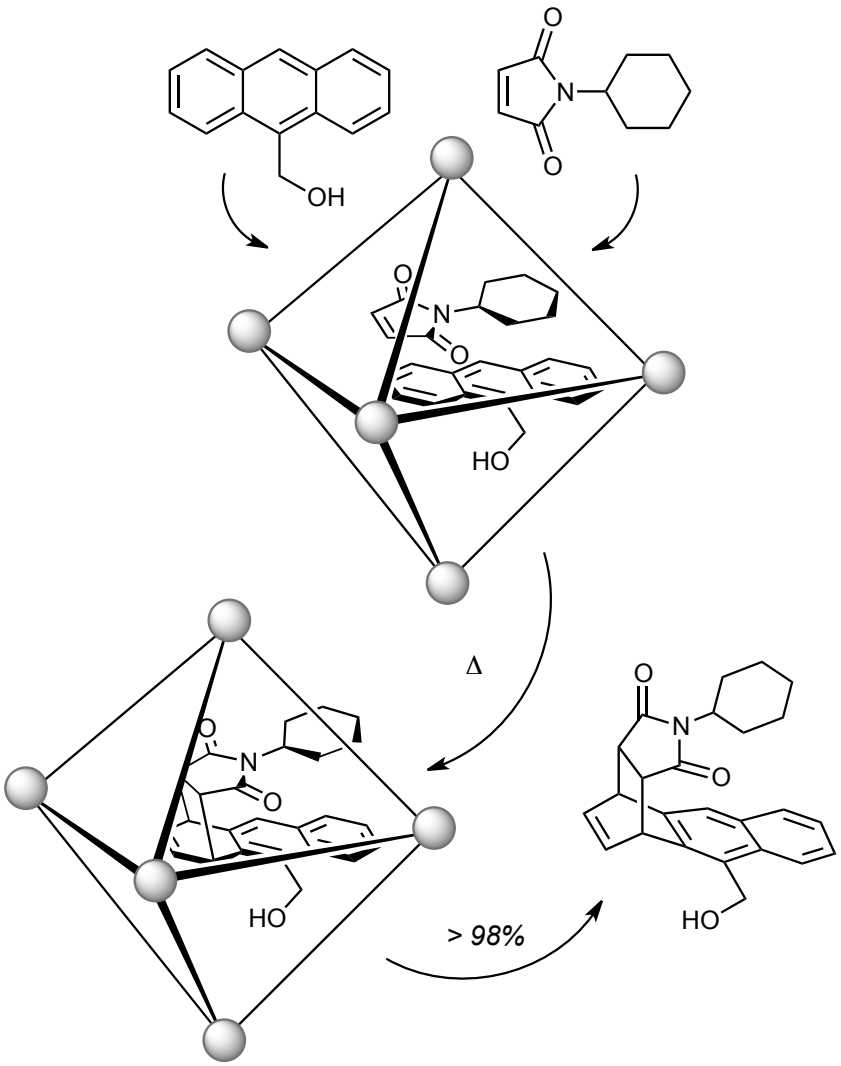
# Supramolecular Catalysis: Host-Guest Chemistry

Sergey Pronin
Shenvi Group




Fujita et al. *Nature* **1995**, *378*, 469;
S. Y. Yu et al. *J. Am. Chem. Soc.* **2000**, *122*, 2665.

None of the conventional
Diels-Alder product is observed




M. Yoshizawa, M. Tamura, M. Fujita *Science* **2006**, *312*, 251.

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# Supramolecular Catalysis: Self-Assembly

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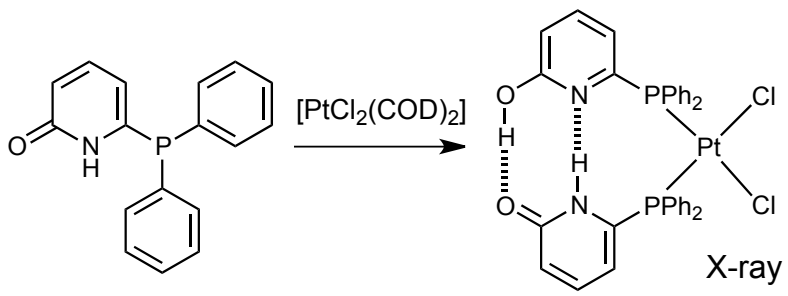
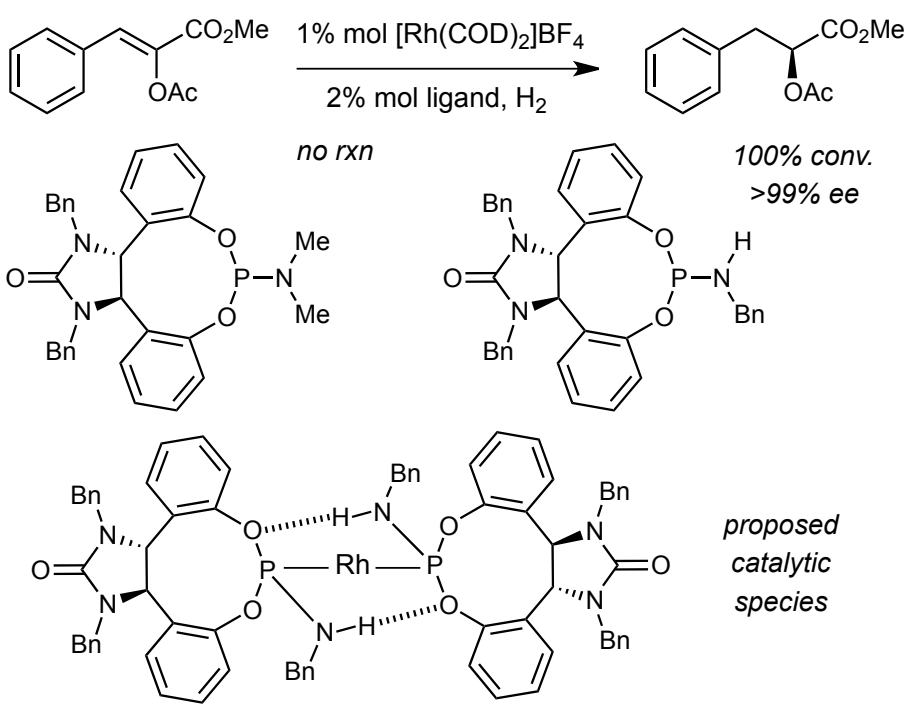
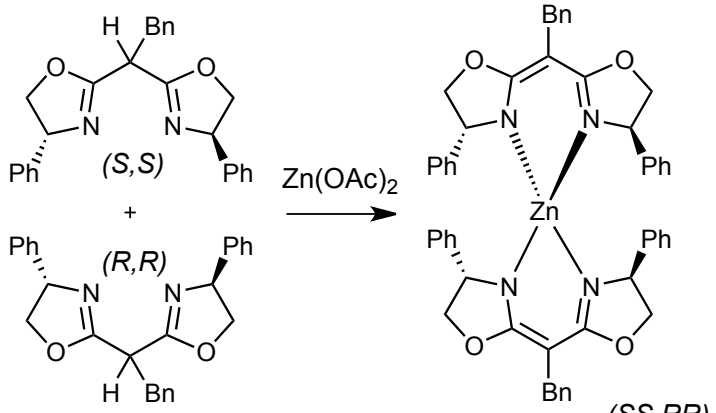
Shenvi Group

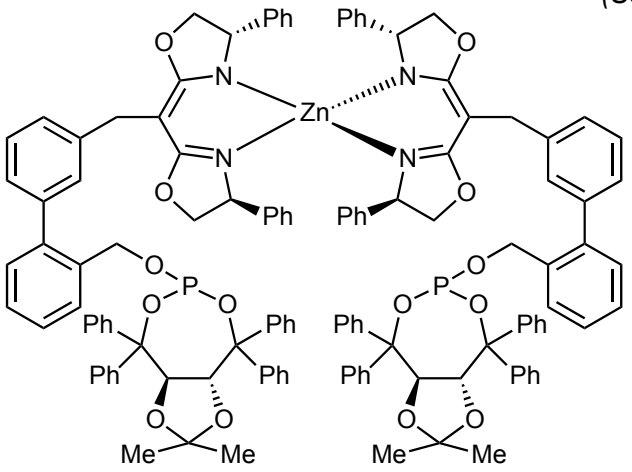


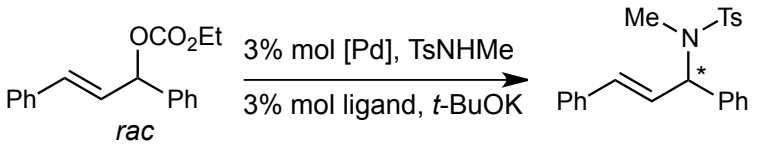

B. Breit and W. Seiche *J. Am. Chem. Soc.* **2003**, *125*, 6608.




Y. Liu et al. *J. Am. Chem. Soc.* **2006**, *128*, 14212.






*Library of 50 chiral diphosphites from 13 scaffolds gave ee values from 20% to >99%*

J. M. Takacs et al. *J. Am. Chem. Soc.* **2004**, *126*, 4494.

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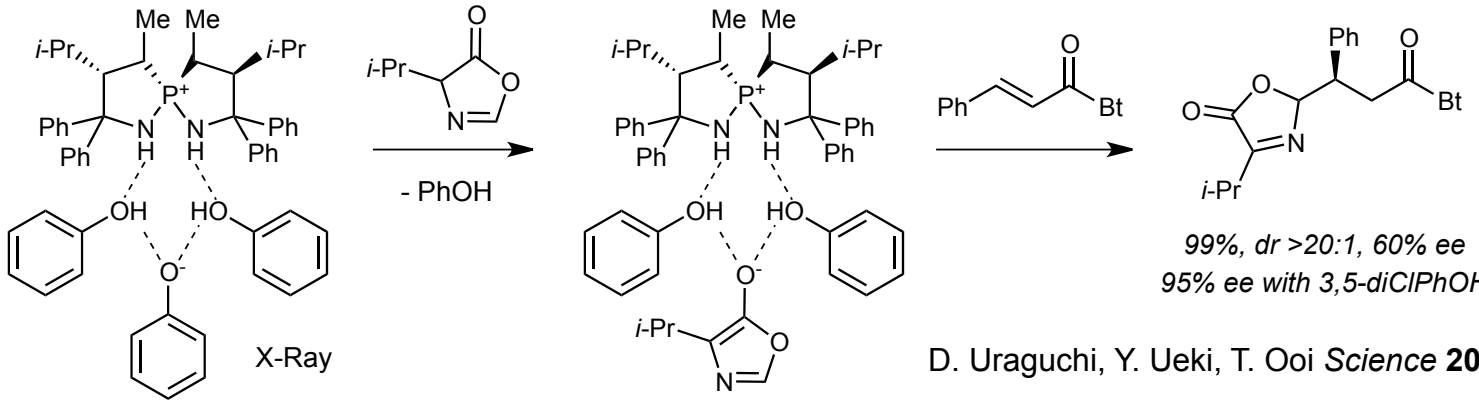
*March 8, 2011*

# *Supramolecular Catalysis: Self-Assembly*

*Sergey Pronin*
*Shenvi Group*




D. Uraguchi, Y. Ueki, T. Ooi *Science* **2009**, *326*, 120.

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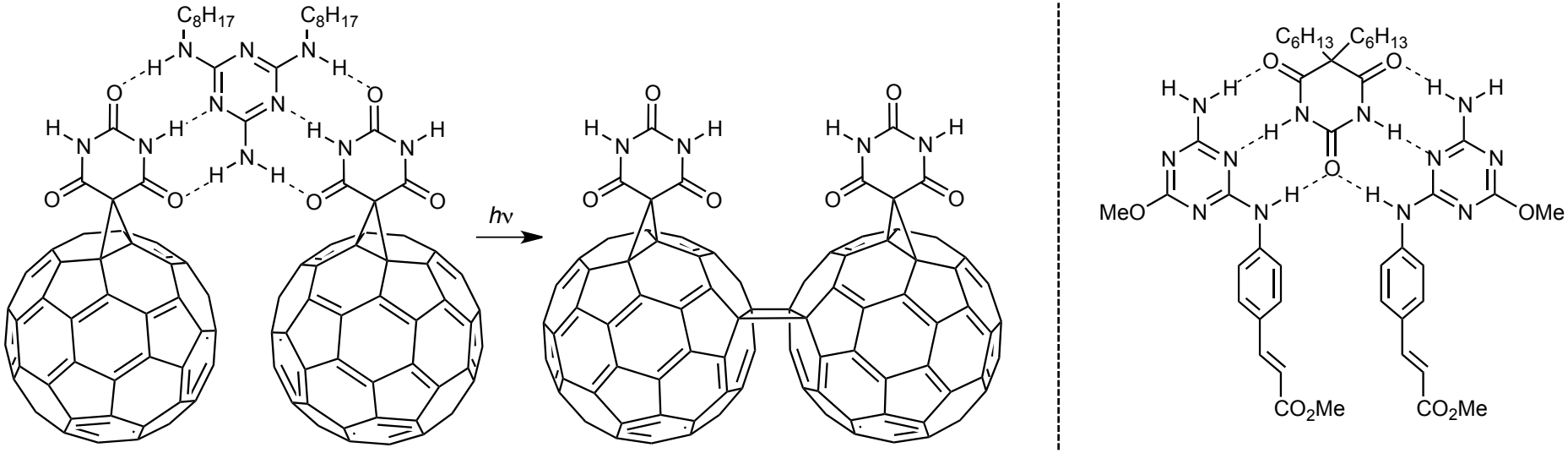


N. D. McClenaghan et al. *J. Am. Chem. Soc.* **2003**, *125*, 13004; D. M. Bassani et al. *J. Am. Chem. Soc.* **2000**, *122*, 8795.

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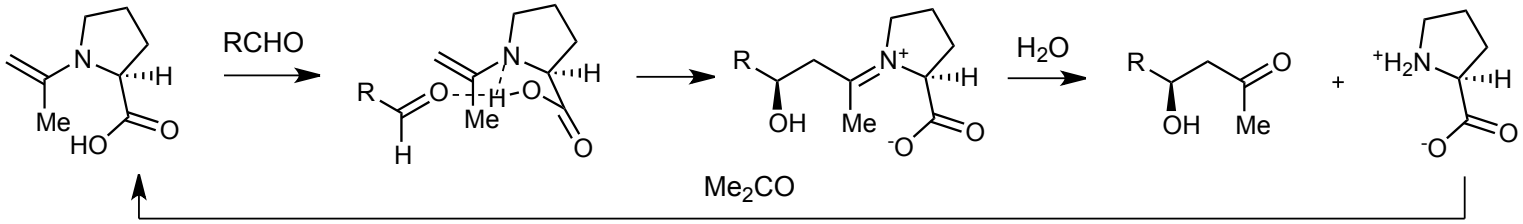
*For more information see:* J. Meeuwissen and J. N. H. Reek *Nat. Chem.* **2010**, *2*, 615.

# Supramolecular Catalysis: Enzyme Mimics

Sergey Pronin
Shenvi Group




*Up to 96% ee*
*The simplest enzyme?*

B. List, R. A. Lerner, and C. Barbas III *J. Am. Chem. Soc.* **2000**, *122*, 2395.
See *also:* Z. J. Hajos, D. R. Parrish *J. Org. Chem.* **1974,** *39*, 1615 (Pat. In 1971);
U. Eder, G. Sauer, R. Wiechert *Angew. Chem. Int. Ed.* **1971**, *10*, 496;
S. Mukherjee et al. *Chem. Rev.* **2007**, *107*, 5471.

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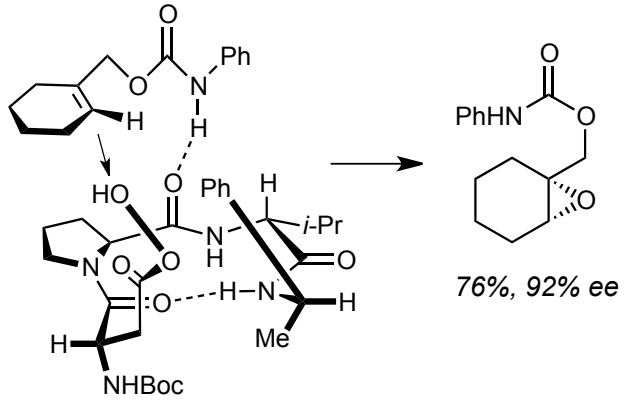

*76%, 92% ee*

G. Peris et al. *J. Am. Chem. Soc.* **2007**, *129*, 8710.

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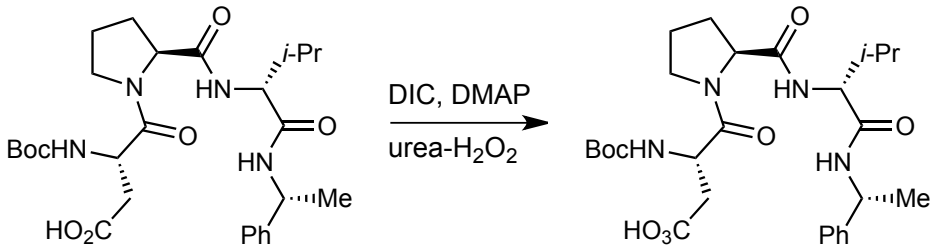


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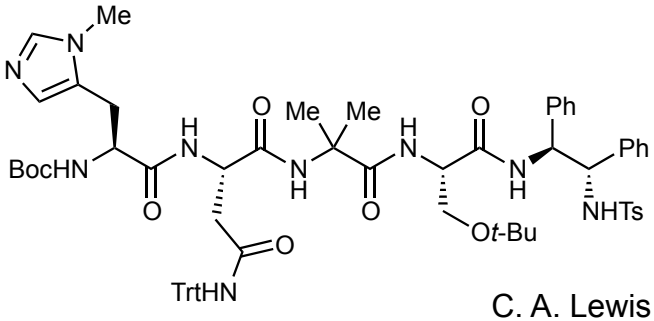

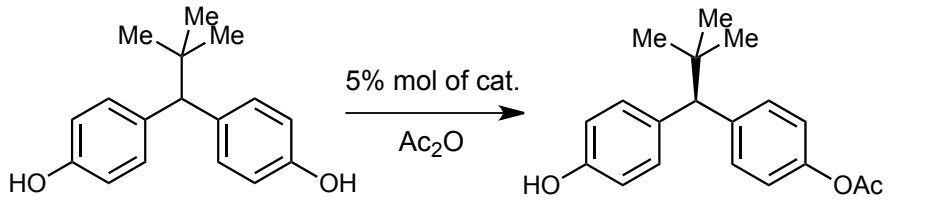


*80%, 95% ee*

*Enzymatic processes were ineffective*

C. A. Lewis et al. *J. Am. Chem. Soc.* **2006**, *128*, 16454.

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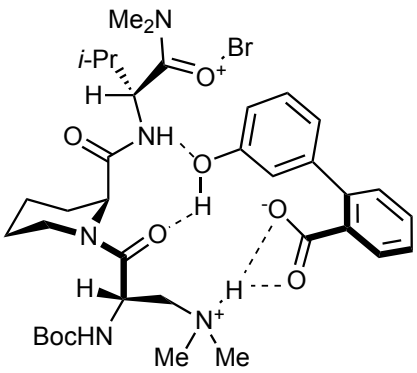
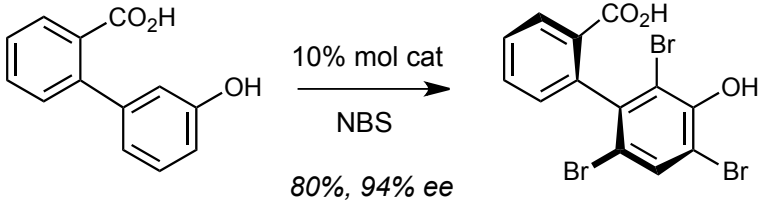
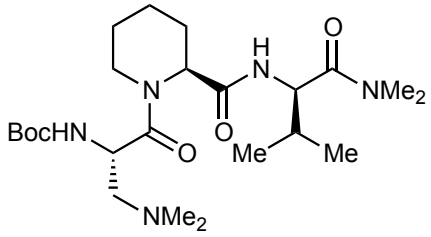
# Supramolecular Catalysis: Enzyme Mimics

Sergey Pronin
Shenvi Group





*15% yield without amide catalyst*

*2-carboxy-3'-hydroxybiphenyl core is critical to reactivity*

J. L. Gustafson, D. Lim, S. J. Miller *Science* **2010**, *328*, 1251

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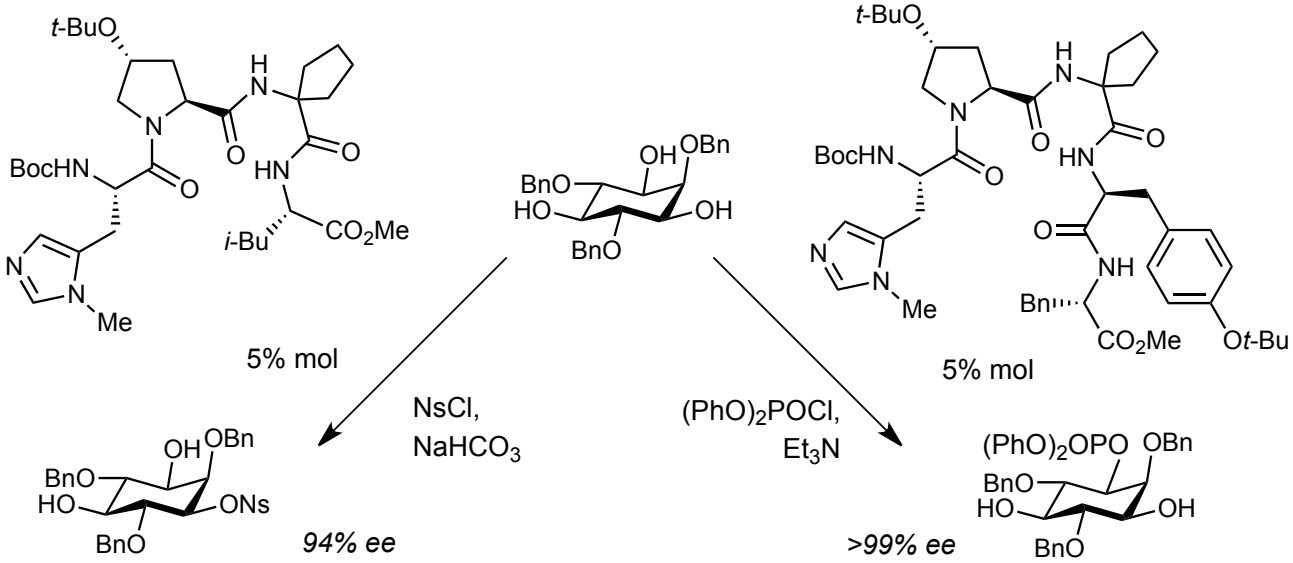


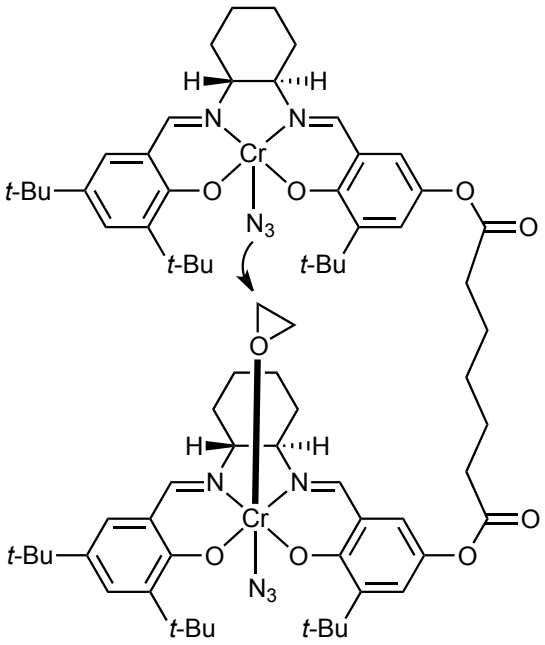

*Like in enzymatic transformations, minor changes can lead to a complete selectivity switch*

*See also*: G. T. Copeland et al. *J. Org. Chem.* **1998**, *63*, 6784

K. W. Fiori, A. L. A. Puchlopek and S. J. Miller *Nat. Chem.* **2009**, *1*, 630.

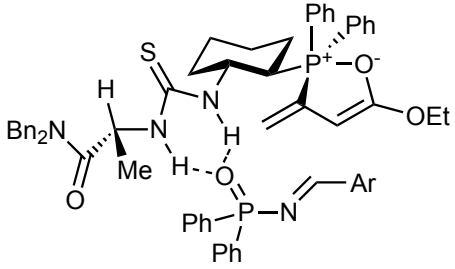
# Supramolecular Catalysis: Cooperative Reactivity

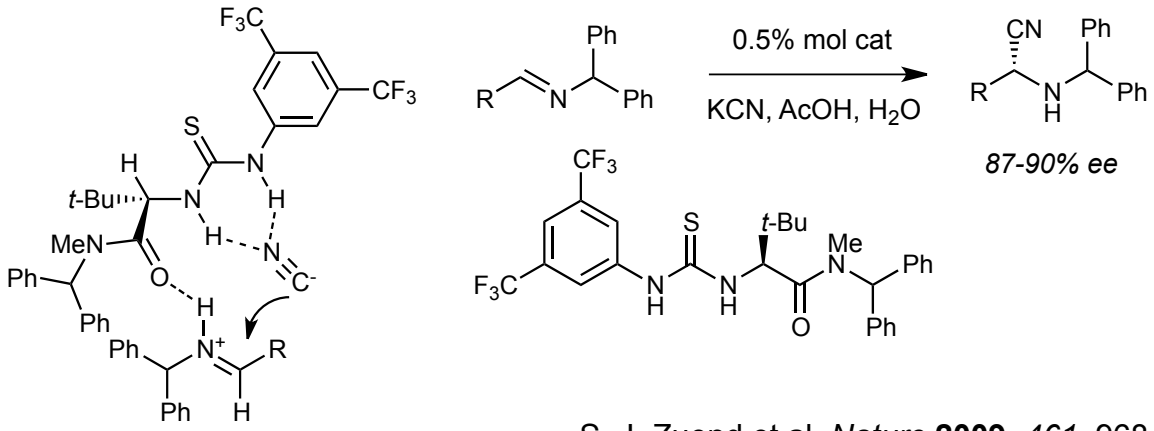
Sergey Pronin
Shenvi Group



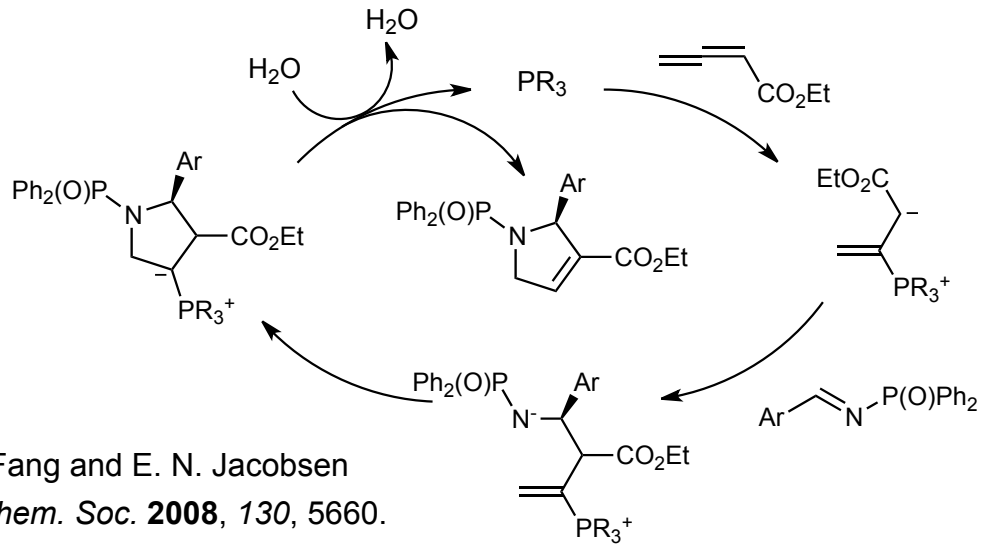
*Linear correlation between ee's of catalyst and product*

R. G. Konsler, J. Karl and E. N. Jacobsen
*J. Am. Chem. Soc.* **1998**, *120*, 10780.





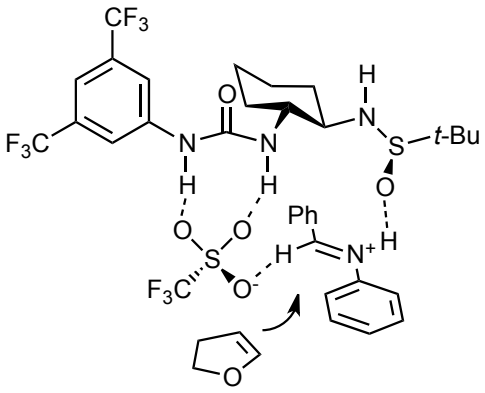
S. J. Zuend et al. *Nature* **2009**, *461*, 968.
*See also*: S. J. Zuend and E. N. Jacobsen *J. Am. Chem. Soc.* **2007**, *129*, 15872.



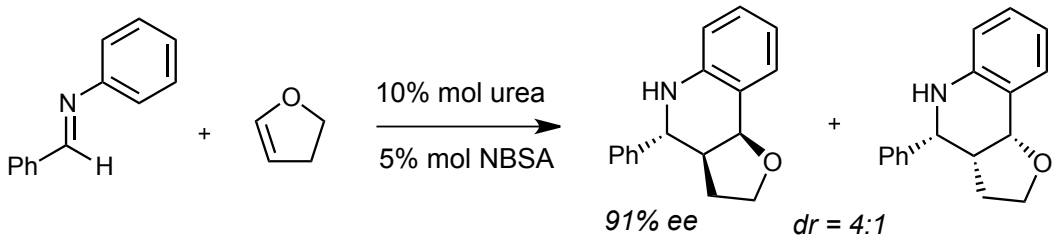
Y. Q. Fang and E. N. Jacobsen
*J. Am. Chem. Soc.* **2008**, *130*, 5660.

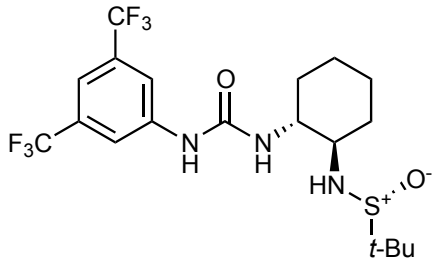
# *Supramolecular Catalysis: More Ureas*

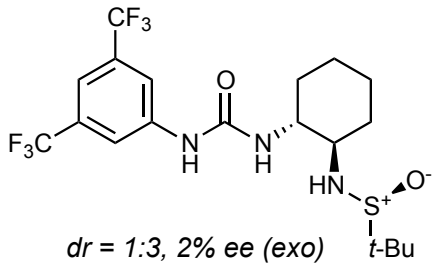
*Sergey Pronin*
*Shenvi Group*



H. Xu et al. *Science* **2010**, *327*, 986.



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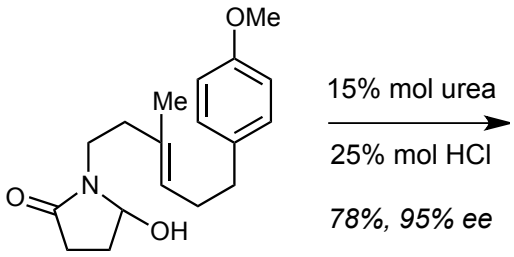
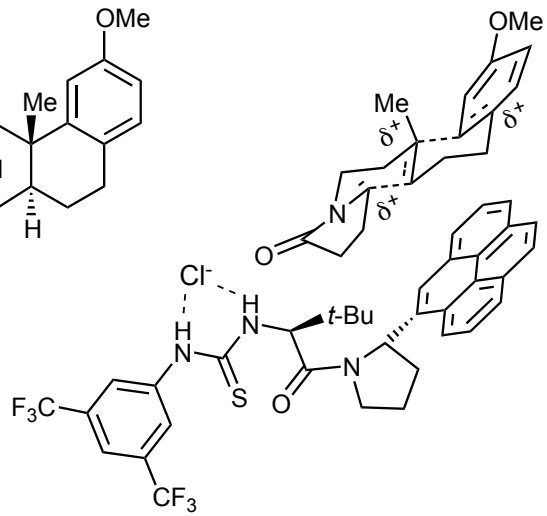
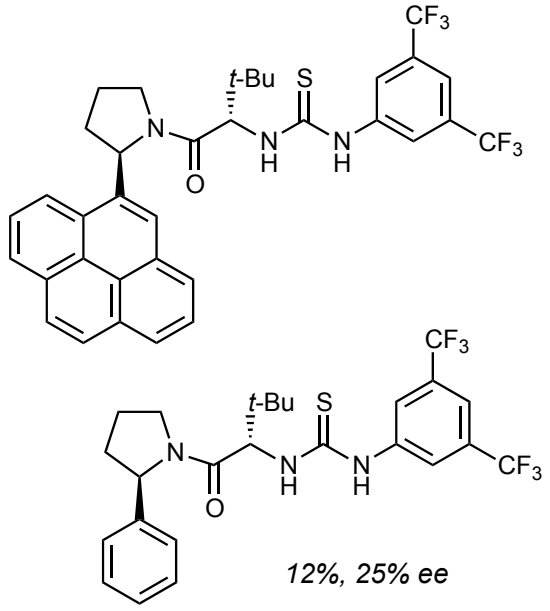


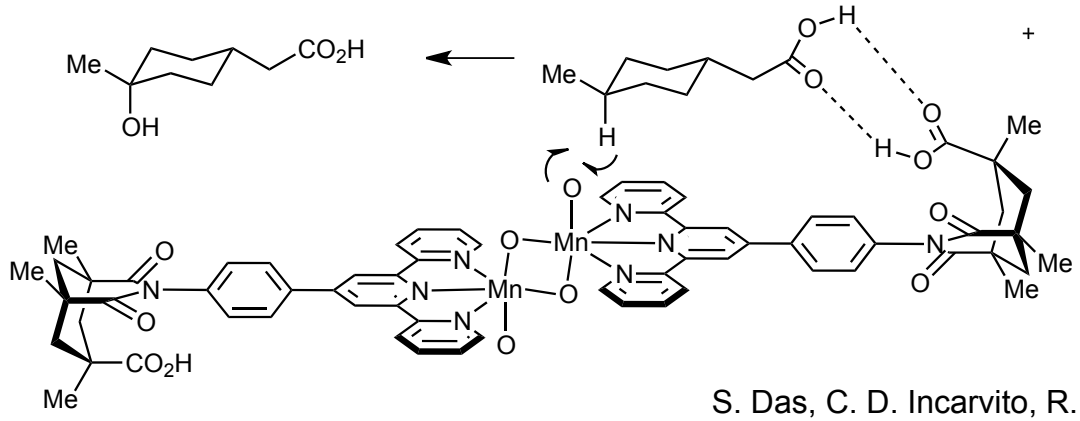

R. R. Knowles, S. Lin, and E. N. Jacobsen
*J. Am. Chem. Soc.* **2010**, *132*, 5030.





# Supramolecular Catalysis: Last but not Least

Sergey Pronin
Shenvi Group



*Only one product observed*
*Catalyst loading: 0.1% mol*

S. Das, C. D. Incarvito, R. H. Crabtree, G. W. Brudvig *Science* **2006**, *312*, 1941.

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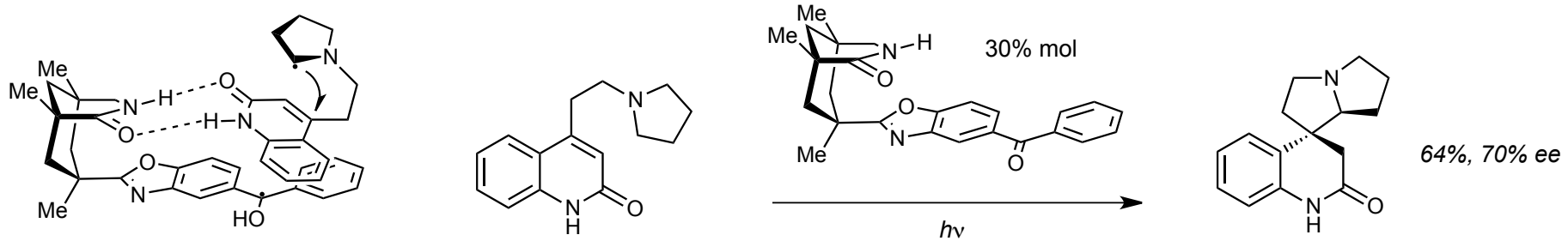


A. Bauer, F. Westkamper, S. Grimme and T. Bach *Nature* **2005**, *436*, 1139.