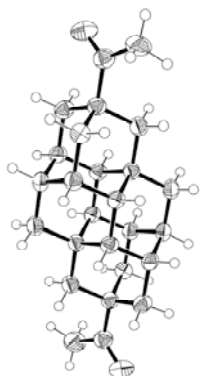


Organocatalysis – From Revelation to Revolution

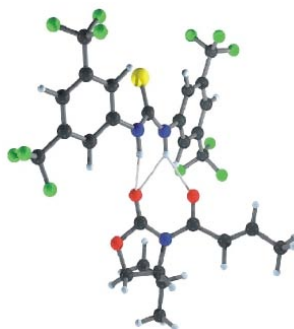
Gruppenseminar
17. October 2008

Peter R. Schreiner

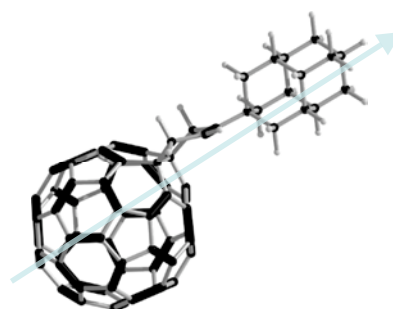
Institut für Organische Chemie, Justus-Liebig-Universität Gießen



Nanodiamonds
Carbon-rich materials



Organocatalysis



Molecular
Electronics

Die organischen Katalysatoren und ihre Beziehungen zu den Fermenten

Von

Dr. Wolfgang Langenbeck

o. Prof. an der Universität Rostock

Zweite Auflage

Mit 8 Textabbildungen

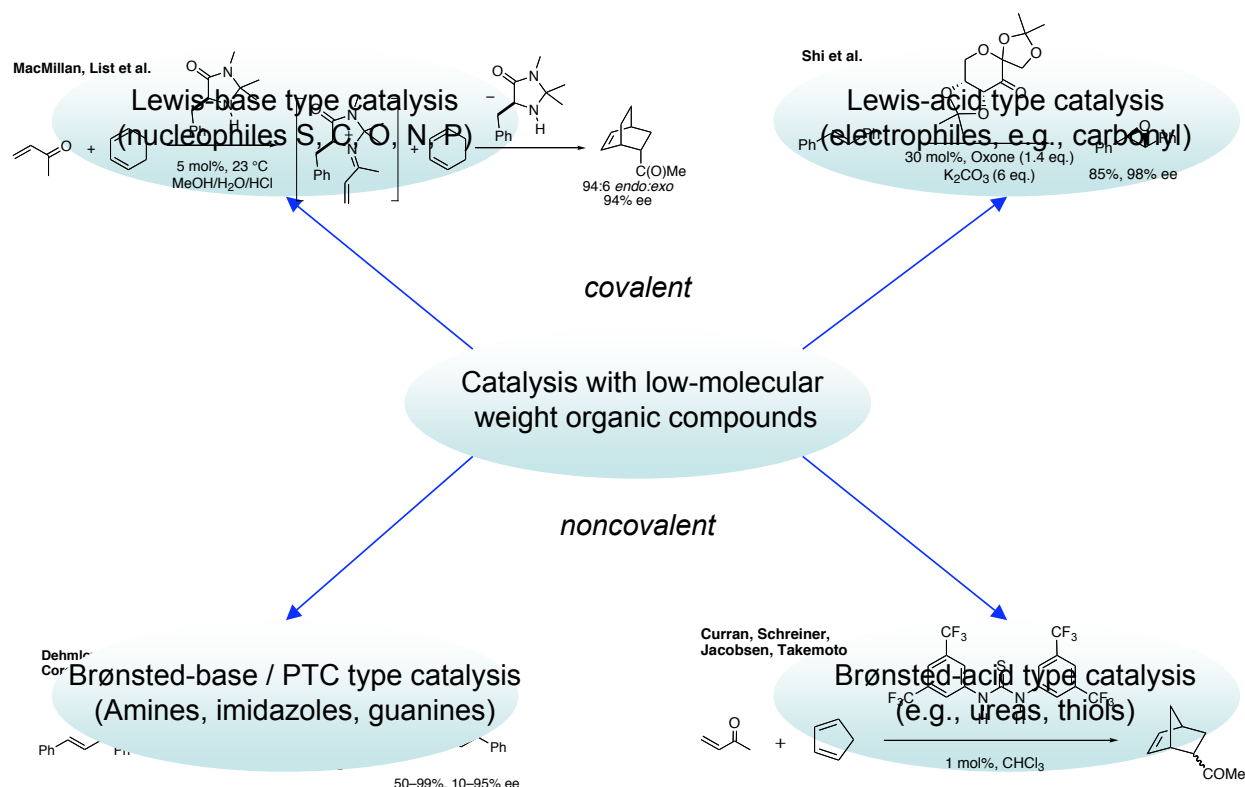


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1949

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Organocatalysis

Metal Catalysis

High, no inert atmosphere,
water often tolerated

Stability

Often low, inert
atmosphere, water-free
conditions

Low molecular weight
purely organic compounds

Synthesis

Inorganic (metallic)-
organic compounds

Often cheap

Cost

Often expensive (e.g.,
noble metals)

Easily separable

Product separation

Often metal contamination

Little to no product
inhibition; but: efficiency
often very low

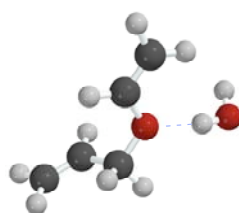
Efficiency

Very high, but: product
inhibition (no catalysis) for
e.g., Lewis-Acids

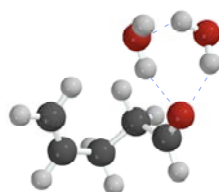
...leads to a catalyst model like^{b,c}

Claisen rearrangement

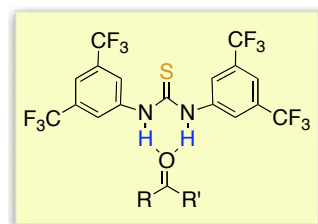
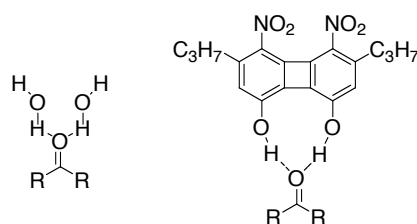
Solvent	Relative rate
Benzene	1
Methanol	5
Water	106



Starting material

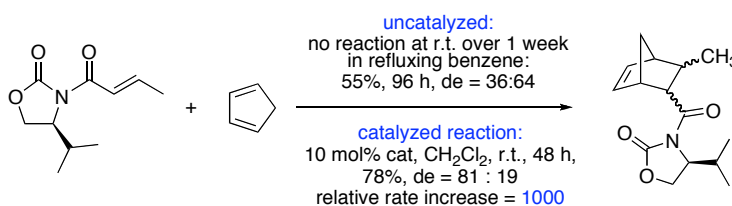


product

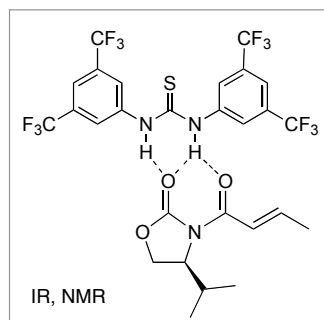


a) Jorgensen, W. L.; Severance, D. L. *J. Am. Chem. Soc.* **1992**, 114, 10966–10968 b) Kelly, T. R.; Meghani, P. Ekkundi, V. S. *Tetrahedron Lett.* **1990**, 31, 3381–3384. c) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, 36, 6647–6650.

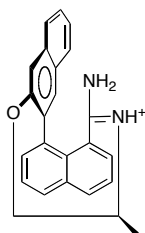
The Beginning: Diels-Alder Reactions



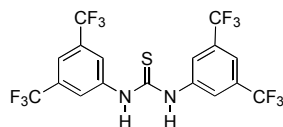
- Proof-of-concept
- Akin to weak Lewis acids
- Carbonyl activation
- Double hydrogen-bonding
- Reactions also in water



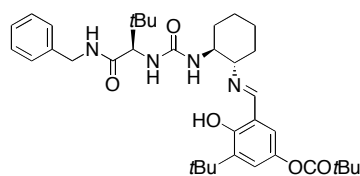
a) A. Wittkopp and P. R. Schreiner *Diels-Alder Reactions Catalyzed by Hydrogen Bonding*, in *The Chemistry of Dienes and Polyenes*, Rappoport, Z., Ed. John Wiley & Sons, Chichester, **2000**, 1029–1088. b) P. R. Schreiner and A. Wittkopp *Org. Lett.* **2002**, 4, 217–220. c) A. Wittkopp and P. R. Schreiner *Chem. Eur. J.* **2003**, 9, 407–414.



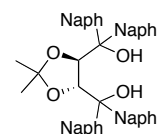
Göbel, 2000



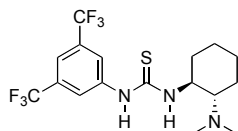
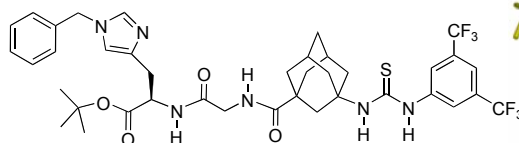
Schreiner, 2000



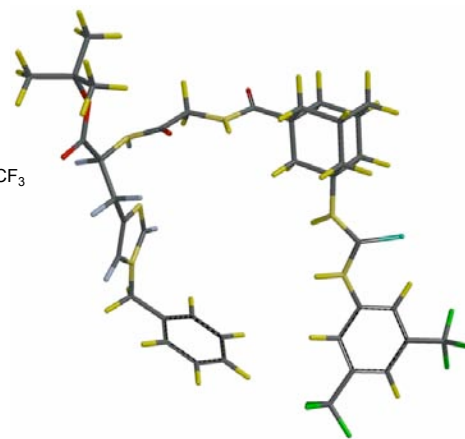
Jacobsen, 2000



Rawal, 2003

Takemoto, 2003
Berkessel, 2005 (urea)

Current developments in our group...

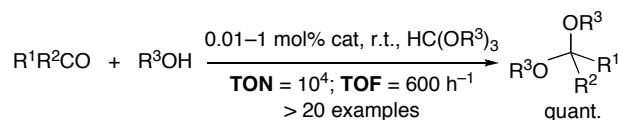


Reviews: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, 32, 289. b) Highlight: P. M. Pihko, *Angew. Chem. Int. Ed.* **2004**, 43, 2062. c) Takemoto, Y. *Org. Biomol. Chem.* **2005**, 3, 4299. c) M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, 45, 1520, and several more...

Recent examples

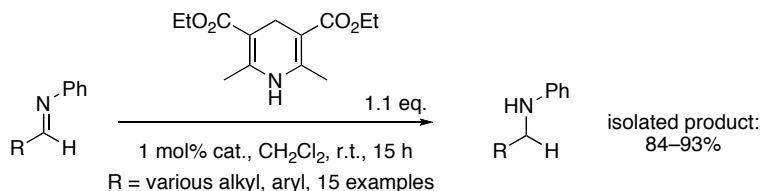


Acetalization



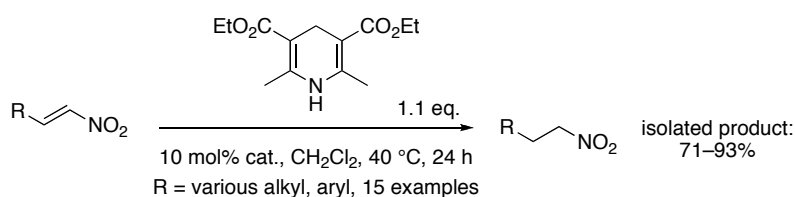
M. Kotke and P. R. Schreiner *Tetrahedron* **2006**, 62, 434–439.

Reduction of aldimines

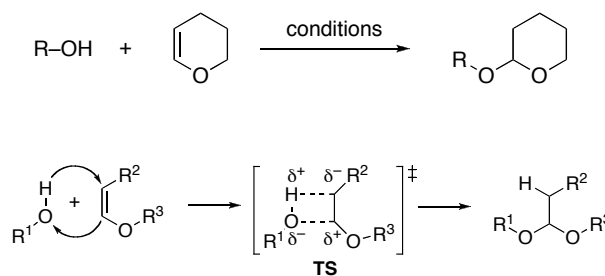


Z. Zhang and P. R. Schreiner *Synlett* **2007**, 1455–1458.

Biomimetic reduction of nitroalkenes

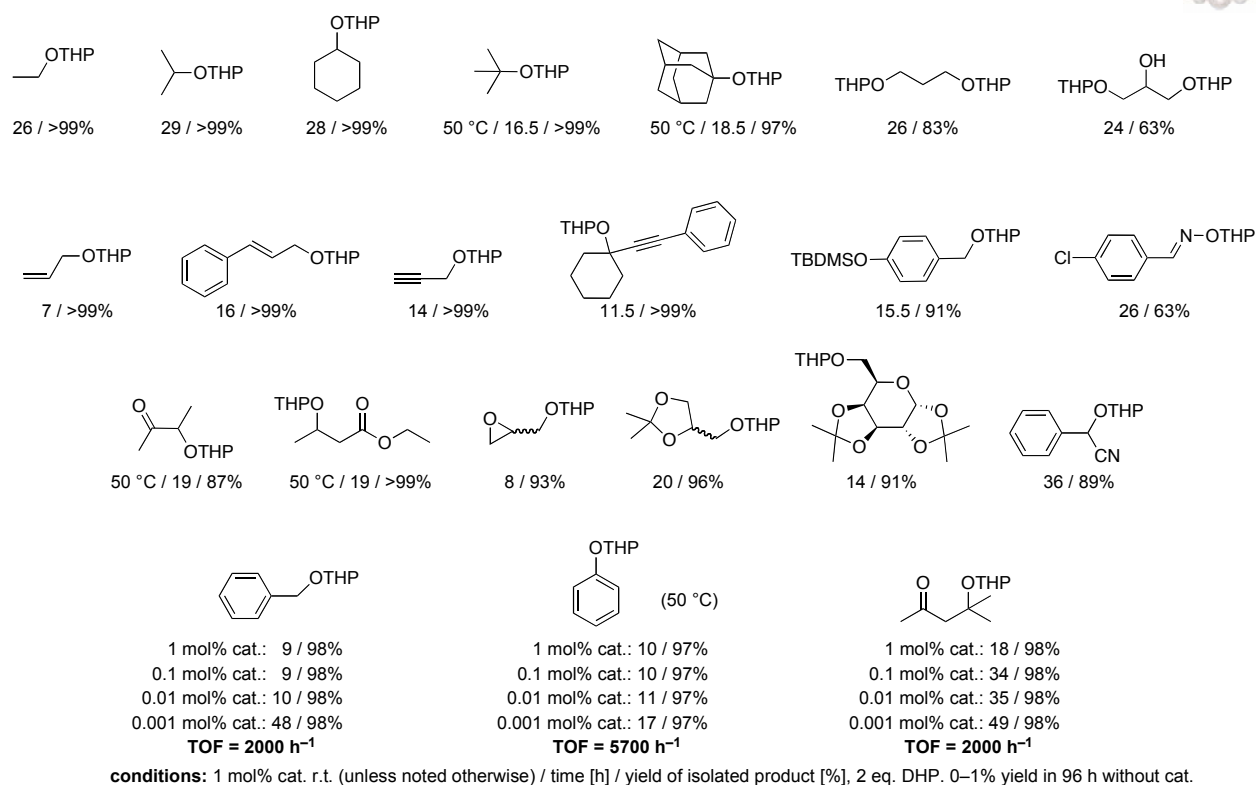


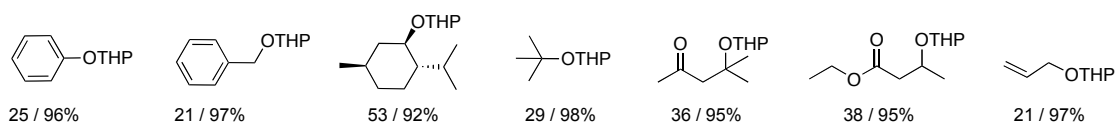
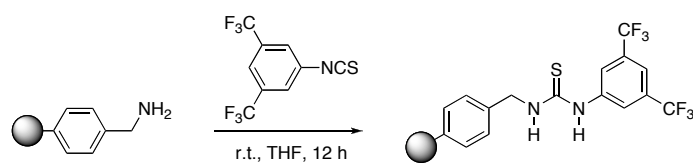
Z. Zhang and P. R. Schreiner *Synthesis* **2007**, 2559–2564.



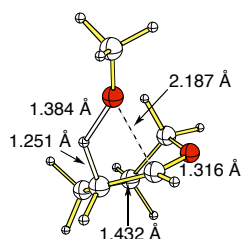
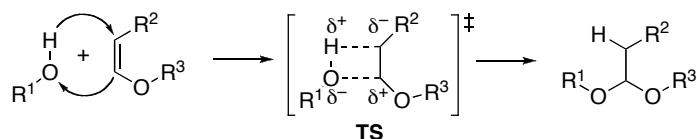
Previous “acid free” methods with:

- 2.5 mol% $\text{BnP}^+\text{Ph}_3\text{Br}_3^-$ or $\text{Bu}_4\text{N}^+\text{Br}_3^-$ – HBr generated *in situ*, yields 75–97%
 Hajibour, A. R.; Pourmousavi, S. A.; Ruoho, A. E. *Synth. Commun.* **2005**, 35, 2889–2804
 Naik, S.; Gopinath, R.; Patel, B. K. *Tetrahedron Lett.* **2001**, 42, 7679–7681
- 27 mol% $\text{VO}(\text{OAc})_2$ – yields 75–97%
 Choudary, B. M. Neeraja, V.; Kantam, M. L. *J. Mol. Cat. A* **2001**, 175, 169–172
- 500 mol% LiClO_4 or 3 mol% $\text{Fe}(\text{ClO}_4)_3$ – poor yields for tertiary substrates
 Babu, B. S.; Balasubramanian, K. K. *Tetrahedron Lett.* **1998**, 39, 9287–9288
 Heravi, M. M.; Behbahani, F. K.; Oskooie, H. A.; Shoar, R. H. *Tetrahedron Lett.* **2005**, 46, 2543–2545
- 5 mol% $\text{Bi}(\text{NO}_3)_3 \cdot 5 \text{H}_2\text{O}$ – yields 73–92%
 Khan, A. T.; Gosh, S.; Choudhury, L. H. *Eur. J. Org. Chem.* **2005**, 4891–4896

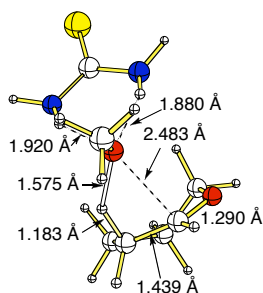




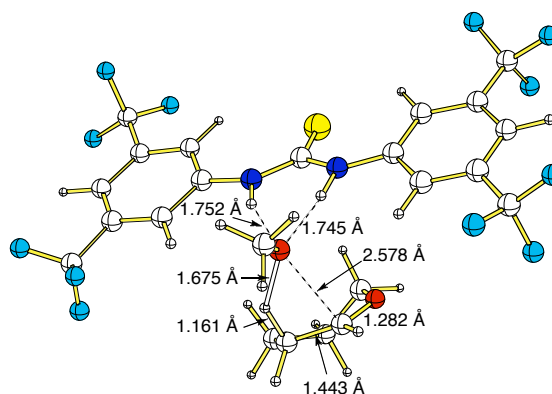
M. Kotke and P. R. Schreiner *feature article in Synthesis*, **2007**, 779–792



$\Delta H_0^\ddagger$ (abs.) = +40.6 kcal mol⁻¹
 $\Delta H_0^\ddagger$ (abs.) = +45.2 kcal mol⁻¹



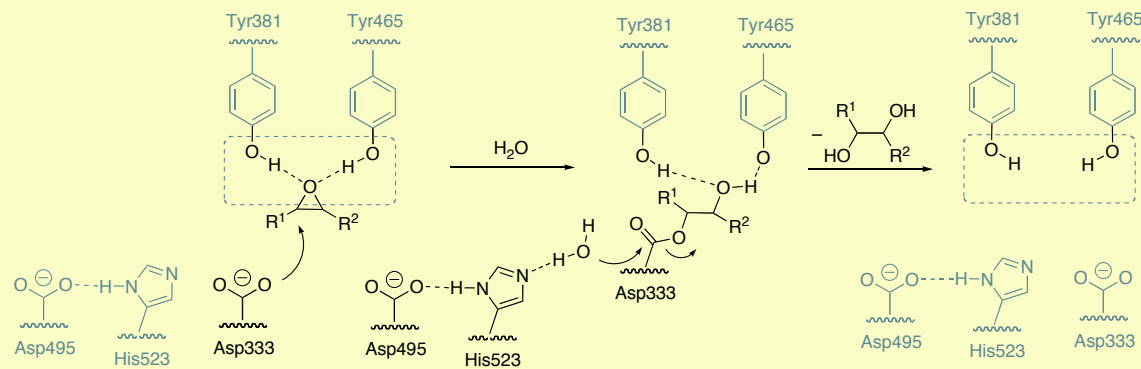
$\Delta H_0^\ddagger$ (abs.) = +23.0 kcal mol⁻¹
 $\Delta H_0^\ddagger$ (abs.) = +25.6 kcal mol⁻¹



$\Delta H_0^\ddagger$ (abs.) = +17.7 kcal mol⁻¹



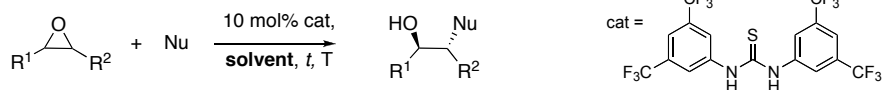
Example: Epoxide hydrolase



- a) M. Arand, H. Wagner, F. Oesch, *J. Biol. Chem.* **1996**, 271, 4223-4229.
 b) G. M. Lacourciere, R. N. Armstrong, *J. Am. Chem. Soc.* **1993**, 115, 10466-10467.

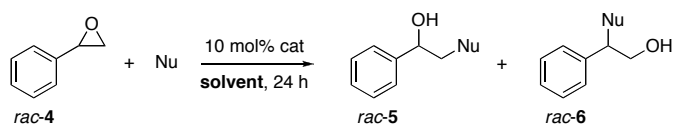
Hydrophobic amplification



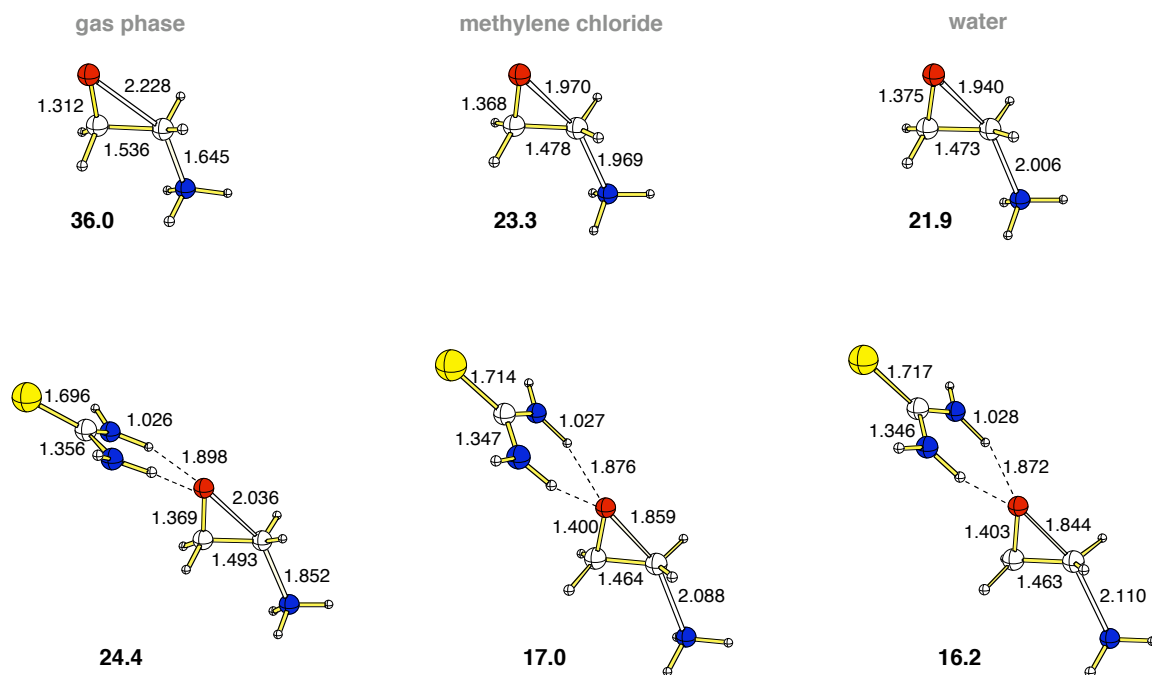


Epoxide	Nucleophile	t (h)	Yield (%) CH ₂ Cl ₂ /no cat.	Yield (%) CH ₂ Cl ₂ /cat.	Yield (%) H ₂ O/ no cat.	Yield (%) H ₂ O/cat.
±2	<i>n</i> -BuNH ₂	21	17	70	33	93
±2	<i>t</i> -BuNH ₂	21	0.5	37	29	94
±2	<i>n</i> -Bu ₂ NH	21	36	48	73	90
±2	<i>n</i> -Pr ₂ NH	36	39	63	30	91
±2	<i>i</i> -Pr ₂ NH	21	0.5	47	30	64
±2	(C ₃ H ₅) ₂ NH	36	9	47	78	87
±2	morpholine	36	52	62	25	83
±2	piperidine	36	45	57	83	87
±2	pyrrolidine	36	52	63	82	90

C. Kleiner and P. R. Schreiner *Chem. Commun.* **2006**, 4315–4317; highlight: *Green Chem.* **2006**, 8, 1018.

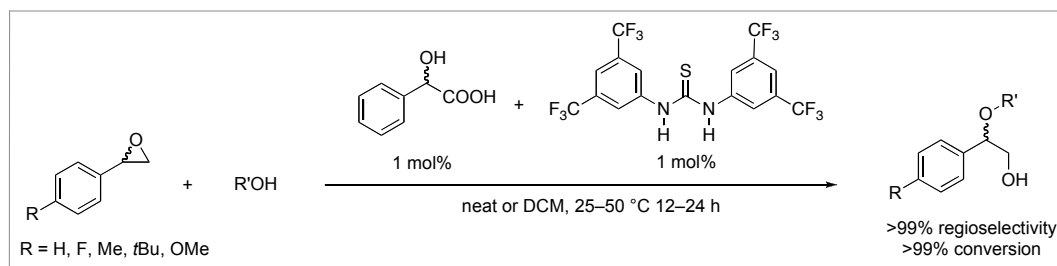
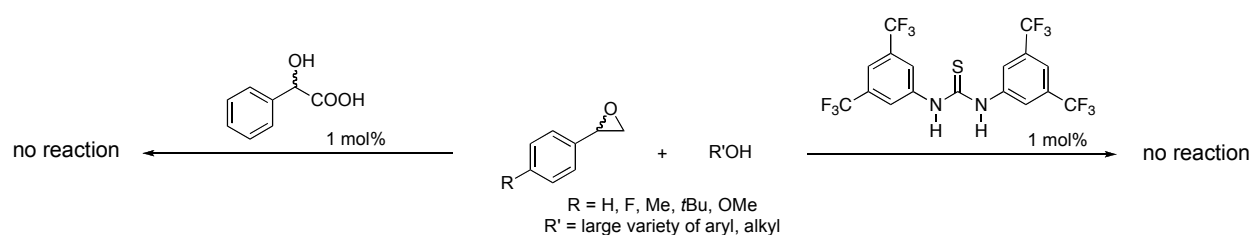


#	Nucleophile	Yield (%) CH ₂ Cl ₂ /uncat.	Yield (%) H ₂ O/cat.	ratio 5:6 H ₂ O/cat.
1	<i>n</i> -BuNH ₂	26	96	3:17
2	<i>n</i> -Bu ₂ NH	6	80	1:1
3	morpholine	16	85	1:1
4	(C ₃ H ₅) ₂ NH	8	92	1:19
5	PhSH	19	76	1:4
6	PhOH	11	74	1:1
7	C ₃ H ₅ OH	0	60	1:2



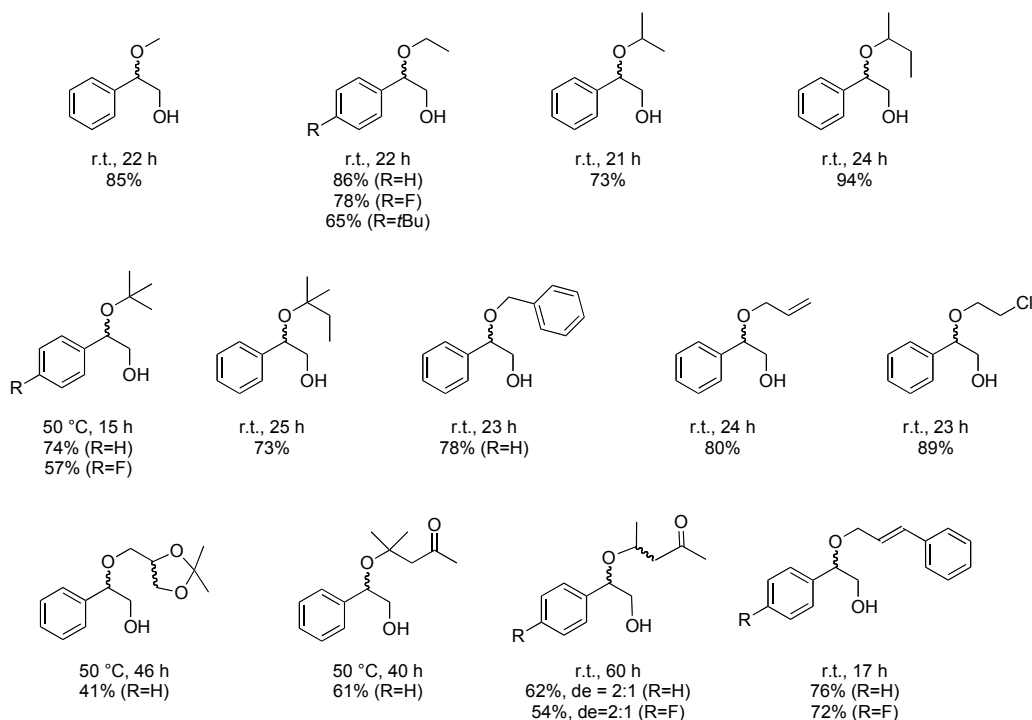
C. Kleiner and P. R. Schreiner *Chem. Commun.* **2006**, 4315–4317; highlight: *Green Chem.* **2006**, 8, 1018.
 Level of theory: B3LYP/6-311++G(d,p)//B3LYP/6-31G(d); barriers in kcal mol⁻¹

Epoxide Opening with weak nucleophiles – ROH



T. Weil, M. Kotke, C. M. Kleiner, and P. R. Schreiner *Org. Lett.* **2008**, 10, 1513–1516.

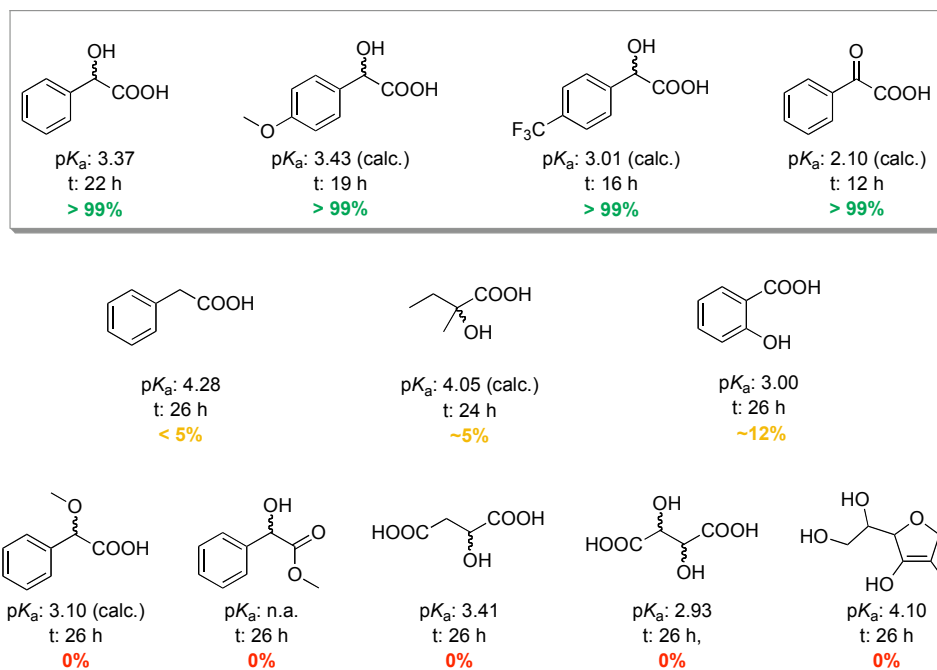
Organocatalytic Epoxide Opening: Dual Brønsted-type Catalysis



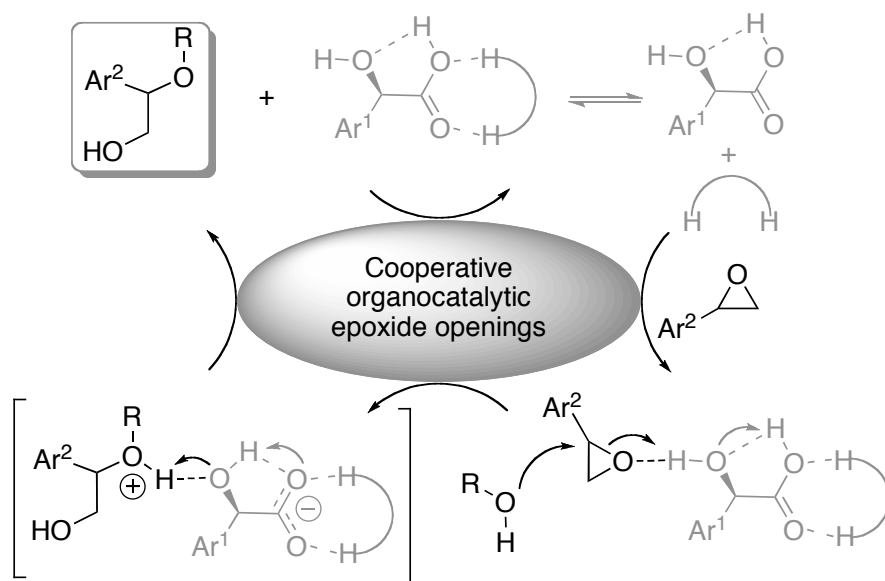
(Yields of isolated CHN-pure products)

T. Weil, M. Kotke, C. M. Kleiner, and P. R. Schreiner *Org. Lett.* **2008**, *10*, 1513–1516.

Dual H-Bonding Catalysis: Mechanistic Considerations

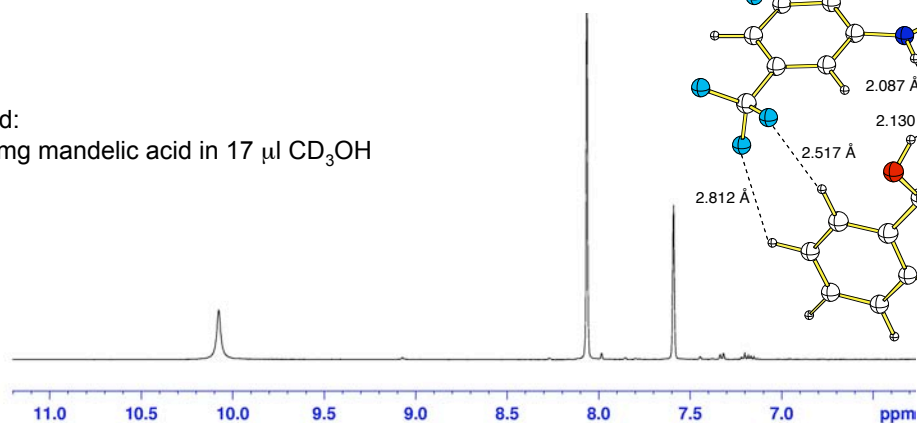


T. Weil, M. Kotke, C. M. Kleiner, and P. R. Schreiner *Org. Lett.* **2008**, *10*, 1513–1516.



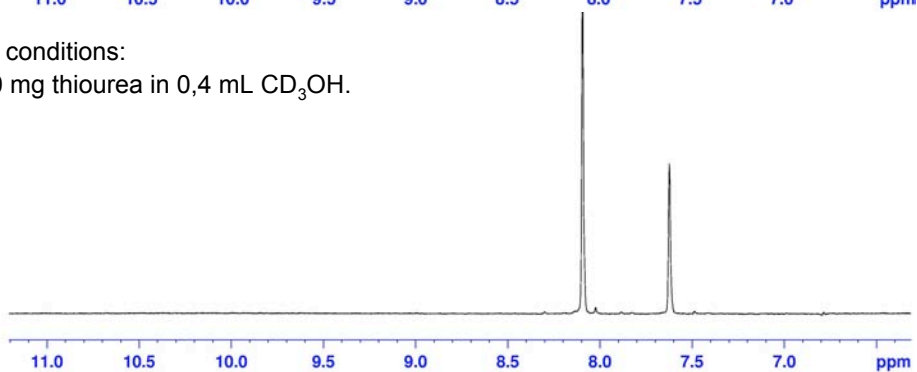
T. Weil, M. Kotke, C. M. Kleiner, and P. R. Schreiner *Org. Lett.* **2008**, *10*, 1513–1516.

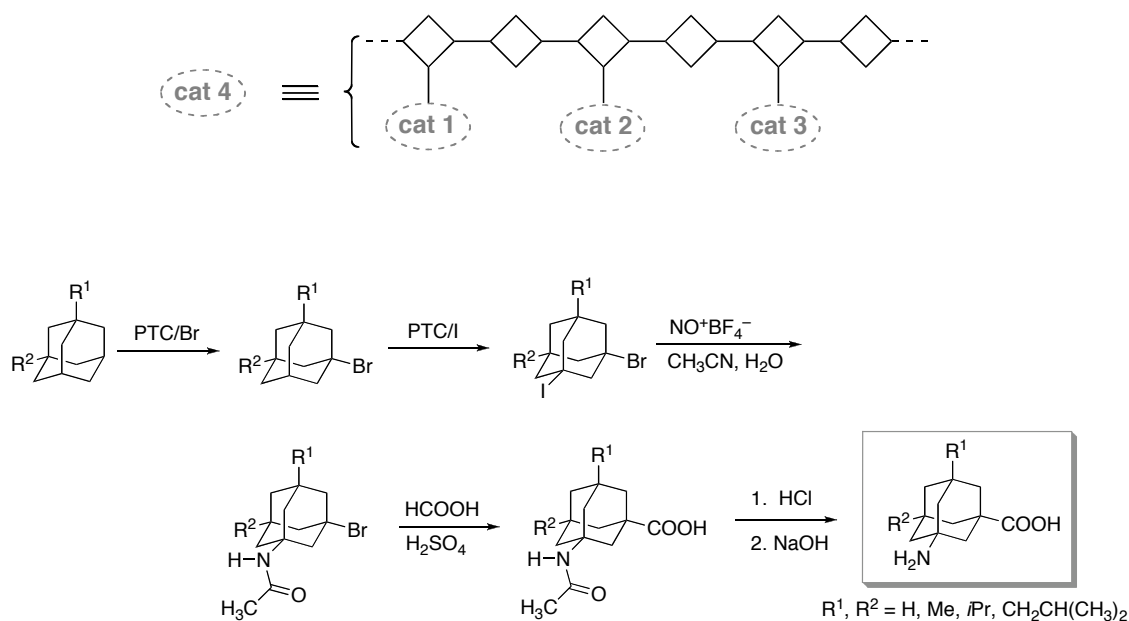
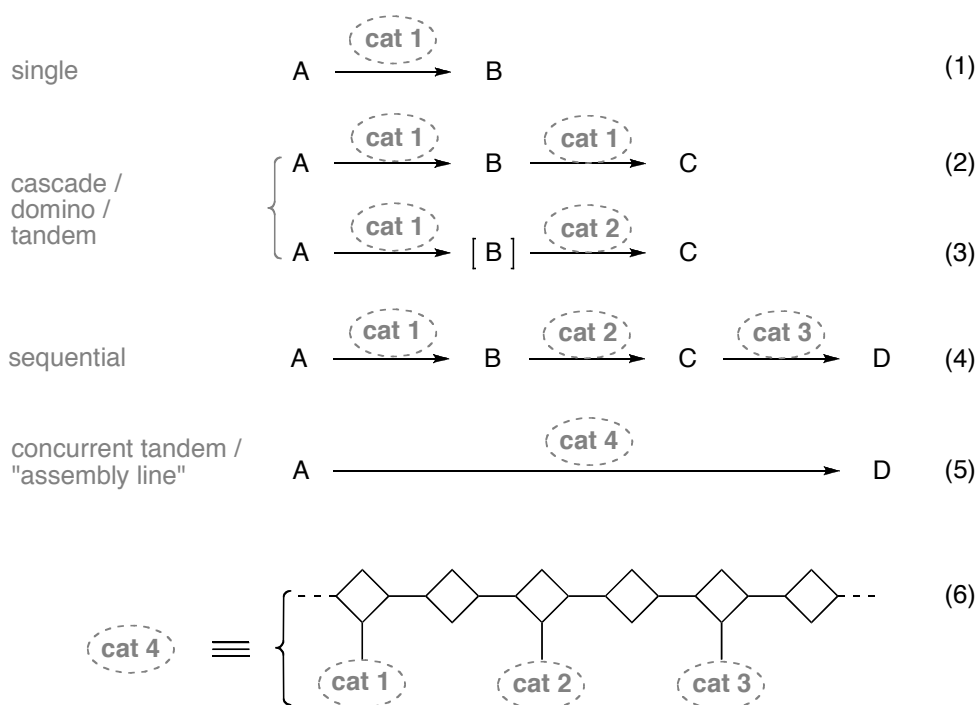
Added:
0.69 mg mandelic acid in 17 μL CD_3OH

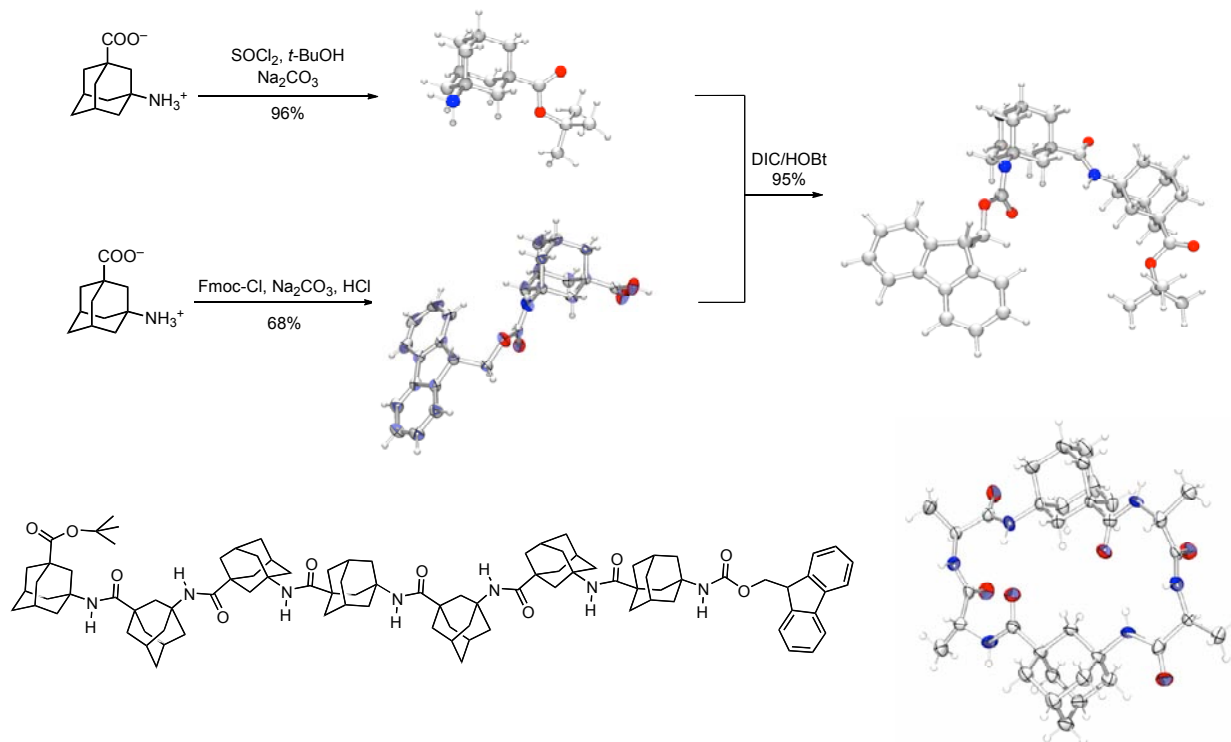


$\Delta H_0 = -13.0 \text{ kcal mol}^{-1}$
(B3LYP/6-31+G(d,p))

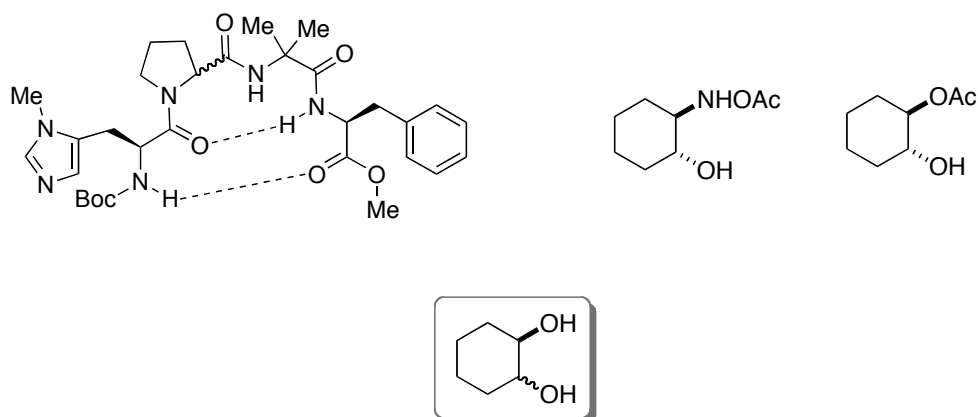
Initial conditions:
15.00 mg thiourea in 0.4 mL CD_3OH .



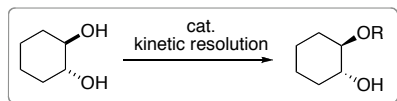




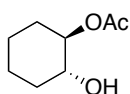
L. Wanka, C. Cabrele, M. Vanejews, P. R. Schreiner *Eur. J. Org. Chem.* **2007**, 1474–1490



- E. A. C. Davie, S. M. Mennen, Y. J. Xu, S. J. Miller, *Chem. Rev.* **2007**, 107, 5759-5812.
- E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, 58, 2481-2495.
- J. T. Blank, S. J. Miller, *Biopolymers* **2006**, 84, 38-47.
- E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, S. J. Miller, *J. Am. Chem. Soc.* **1999**, 121, 11638-11643.



With various lipases from *Pseudomonas* sp.:

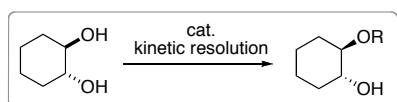


r.t., 10 d, 16%, 66% *ee*

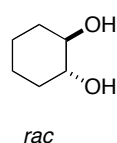
R. Seemayer, M. P. Schneider *J. Chem. Soc., Chem. Commun.* **1991**, 49–50.

30 °C, 3 h, 12–40%, 52–98% *ee*, ***s* = 5**

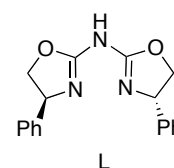
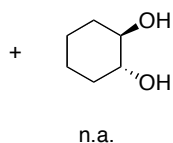
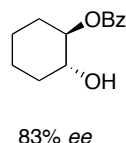
K. Naemura, M. Murata, R. Tanaka, M. Yano, K. Hirose, Y. Tobe *Tet. Asymm.* **1996**, 7, 3285–3294.



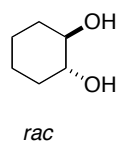
See, for instance: Y. Matsumura, T. Maki, S. Murakami, O. Onomura *J. Am. Chem. Soc.* **2003**, 25, 2052–2053.



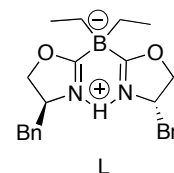
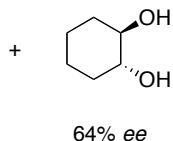
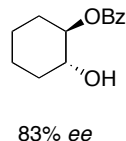
5 mol% CuCl₂, 5 mol% L
0.51 eq. PhCOCl, 1 eq. DIPEA
CH₂Cl₂, 0 °C, 3 h
46% conversion; ***s* = 22**



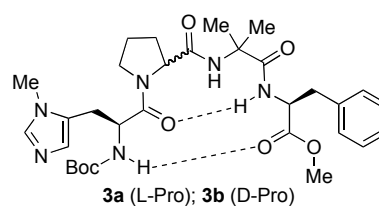
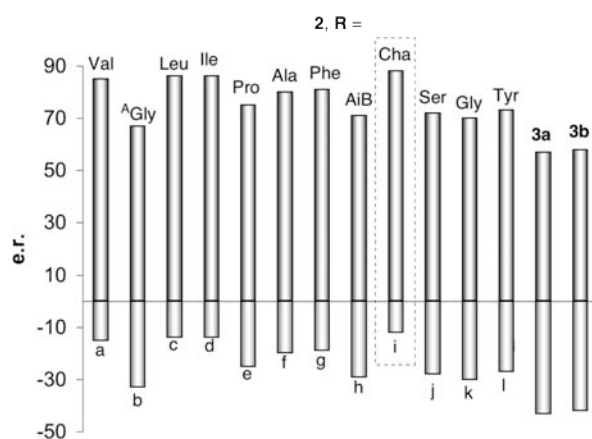
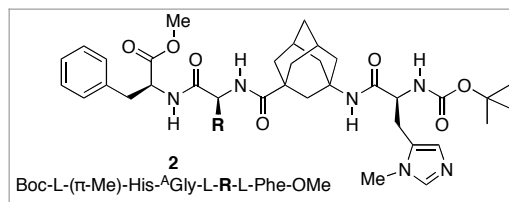
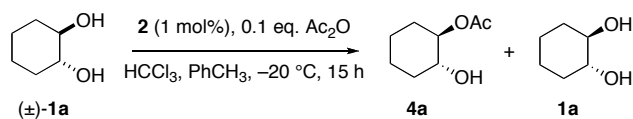
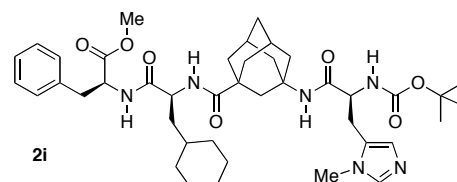
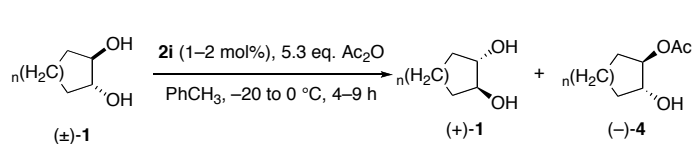
A. Gissibl, M. G. Finn, O. Reiser *Org. Lett.* **2005**, 7, 2325–2328.



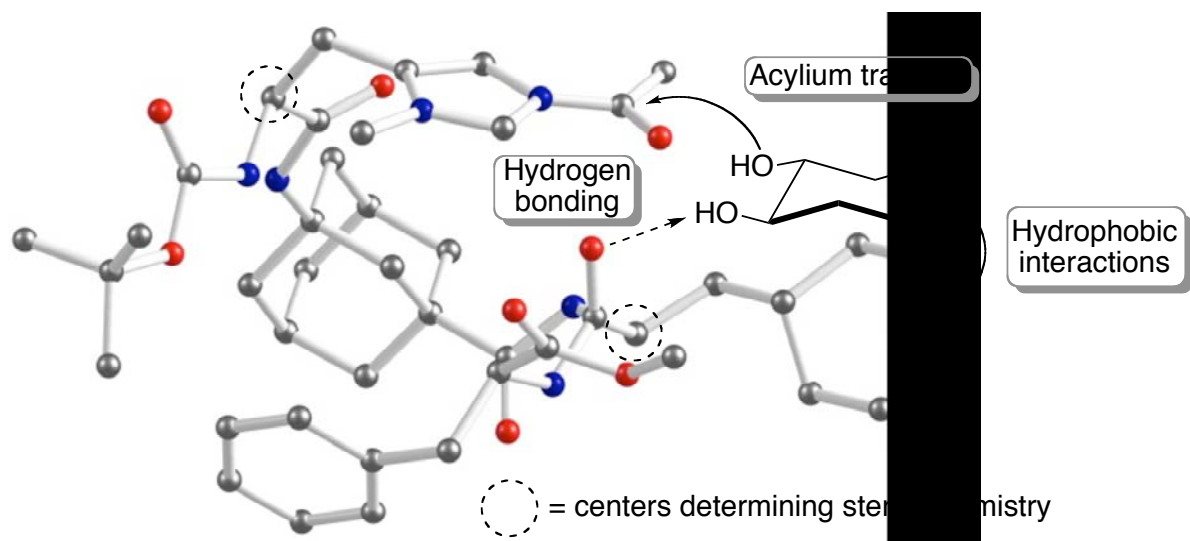
1 mol% CuCl₂, 1 mol% L
0.51 eq. PhCOCl, 1 eq. DIPEA
CH₂Cl₂, 0 °C, 2 h
44% conversion; ***s* = 21**



C. Mazet, S. Roseblade, V. Köhler, A. Pfaltz *Org. Lett.* **2006**, 8, 1879–1882.


 Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6180-6183.


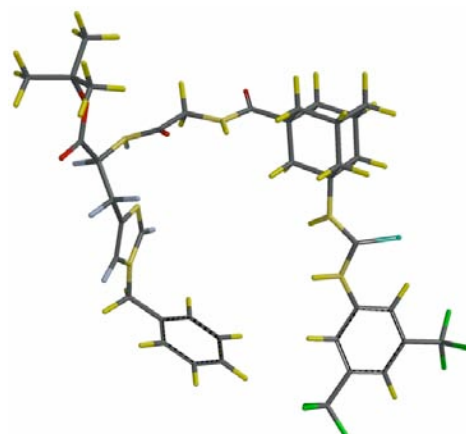
Substrate	mol% cat	T / °C	t / h	Conv. / %	ee / % (+)-1	ee / % (-)-4	s
	2	-20	4	57	>99	75	>50
(±)-1a (1.0 mmol)	1	0	4	37 (yield)	>99	78	>50
	2	-20	9	63	85	49	8
	2	-20	5	57	>99	77	>50
(±)-1c (1.0 mmol)	1	0	5	41 (yield)	>99	79	>50
	2	-20	6	55	>99	83	>50
(±)-1d (1.0 mmol)	1	0	5	44 (yield)	>99	85	>50



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- H-Bonding organocatalysis fits in the niche between Brønsted acid and metal catalysis
- *Complementarity* to metal- and acid-catalyzed reactions
- Many *reactions* are feasible: general acid catalysis for H-bonding catalysts
- Learn from Nature for catalyst design
- Computational analyses point way to catalyst optimization
- Novel concepts of concurrent tandem catalysis with peptide backbones combined with unnatural amino acid spacers





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