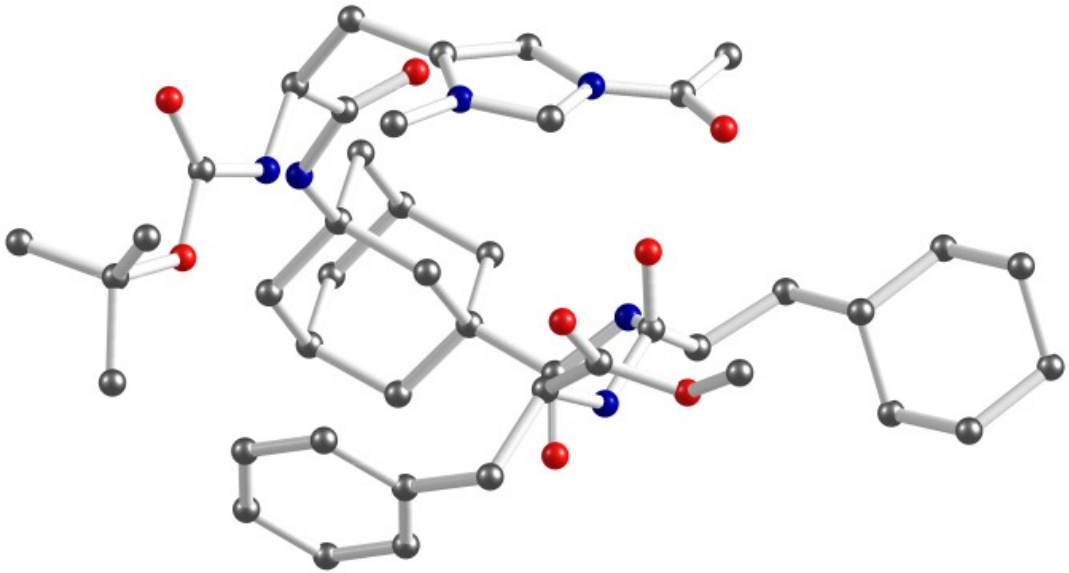
Nucleophilic Biomimetic Organocatalysis: Enantioselective Transfer of Acyl Groups



Christian E. Müller

Justus-Liebig-University Giessen

22.01.2010

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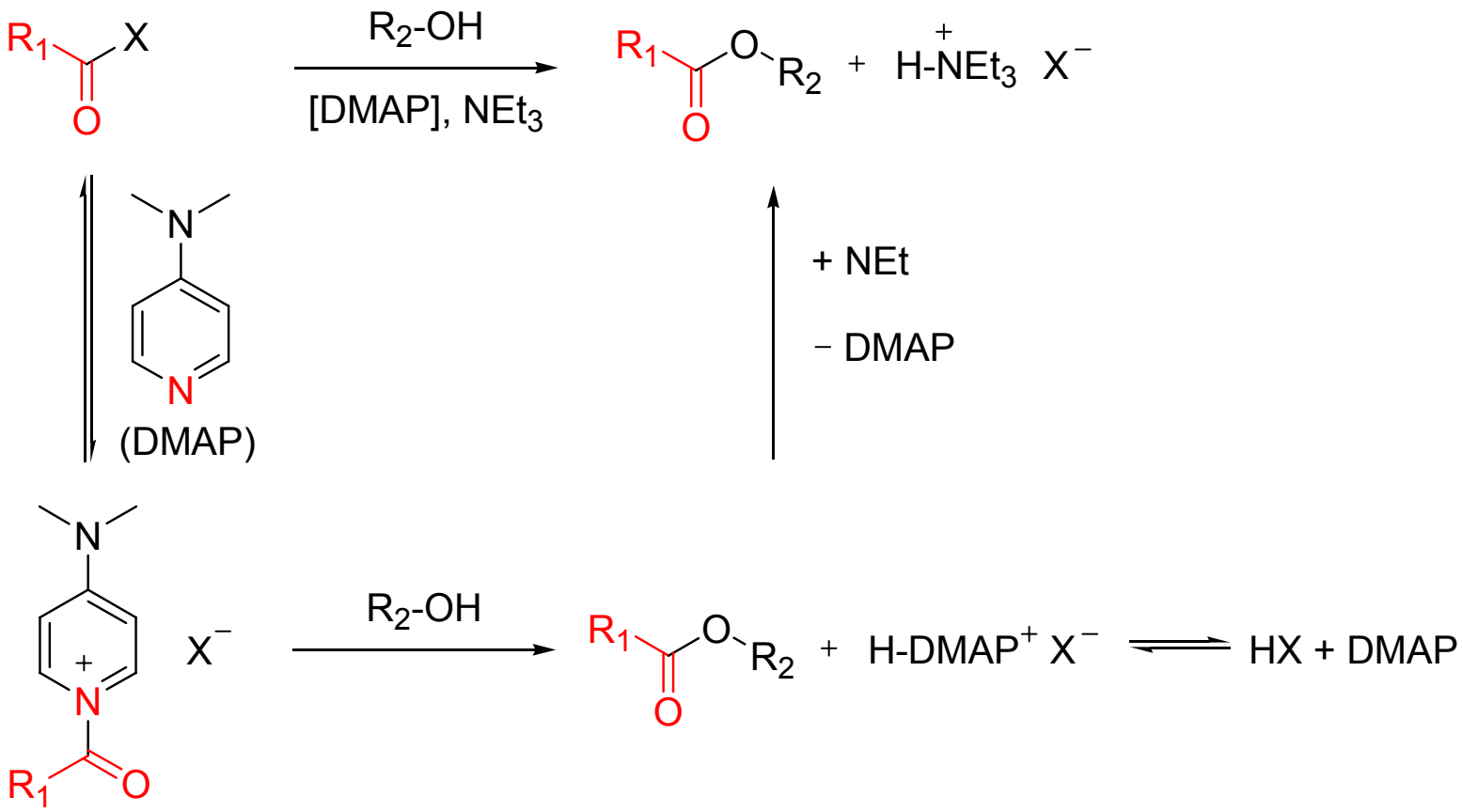
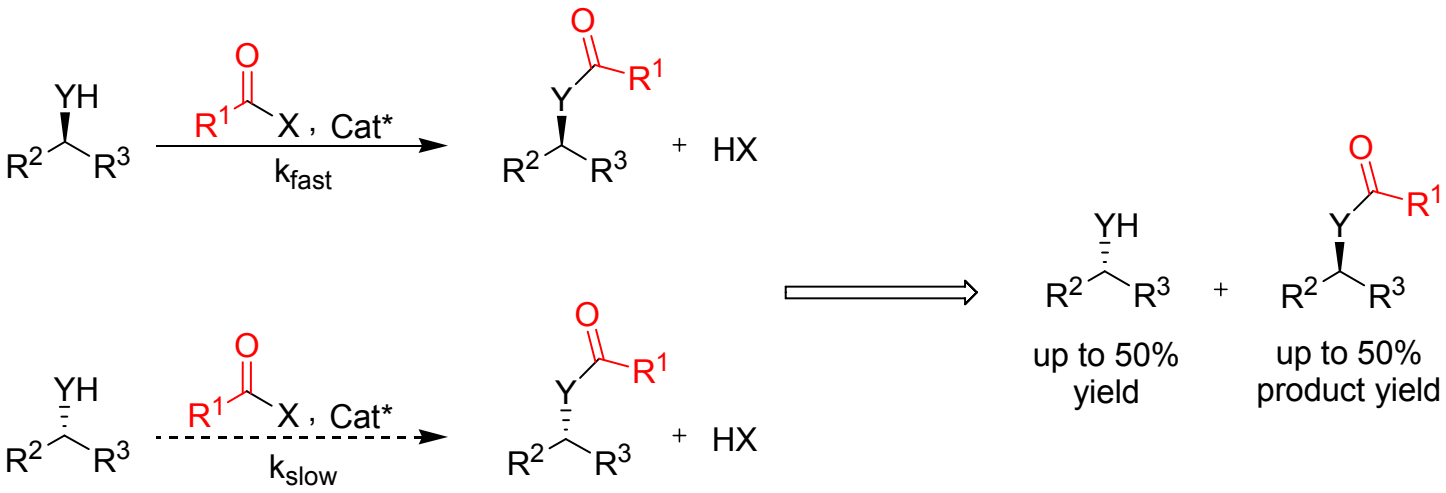
Nucleophilic Catalysis: Acylation Mechanism



S. Xu, I. Held, B. Kempf, H. Mayr, W. Steglich, H. Zipse, *Chem-Eur. J.* **2005**, *11*, 4751.
A. C. Spivey, S. Arseniyadis, *Angew. Chem. Int. Ed.* **2004**, *43*, 5436.
V. Lutz, J. Glatthaar, C. Würtele, M. Serafin, H. Hausmann, P. R. Schreiner, *Chem. Eur. J.* **2009**, *15*, 8548.

Kinetic Resolution and Kagan´s S-value

Kinetic Resolution: R^2 unequal R^3



$s = k_{fast}/k_{slow}$

C = conversion

ee = enantiomeric excess starting material

ee´= enantiomeric excess product

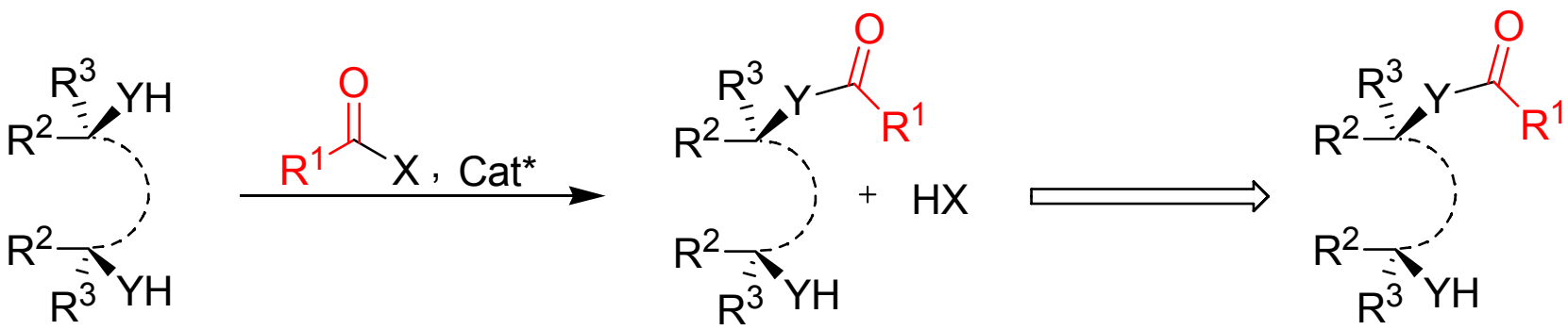
$$s = \frac{\ln\ [1 - C(1 + ee')]}{\ln\ [1 - C(1 - ee')]} \qquad s = \frac{\ln\ [(1 - C)(1 - ee)]}{\ln\ [(1 - C)(1 + ee)]}$$

$$C = \frac{ee}{ee + ee'} \cdot 100$$

Kagan, H. B.; Fiaud, J. C., *J. C. Top. Stereochem.* **1988,** 18, 249.

Desymmetrization

Desymmetrization of *meso* compounds: R^2 unequal R^3

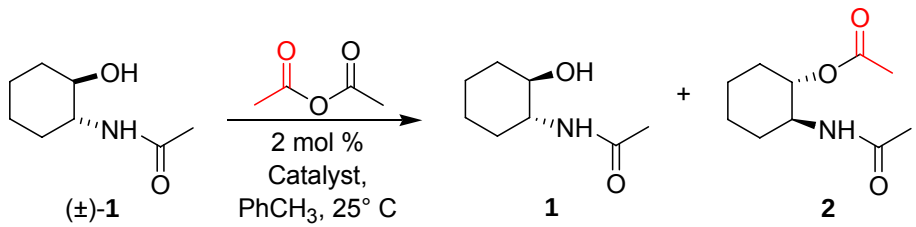


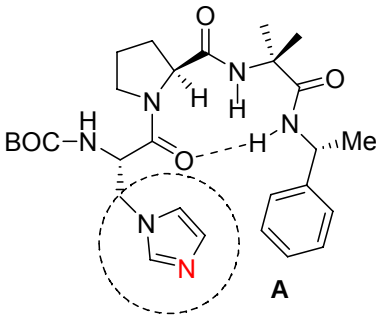
meso compound

up to 100% product yield

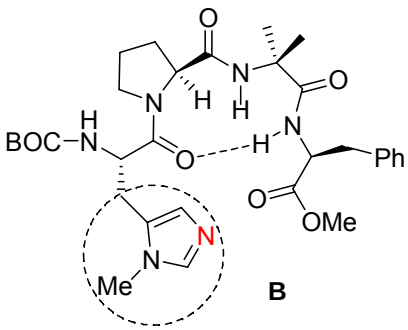
Miller´s Peptide Organocatalysis

Kinetic resolution of *trans*-1-acetamidocyclohexan-2-ol

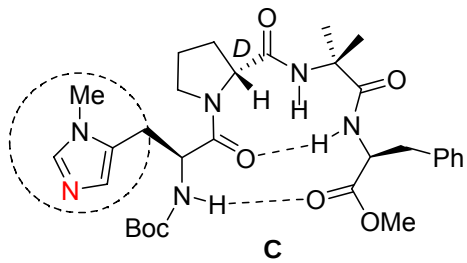




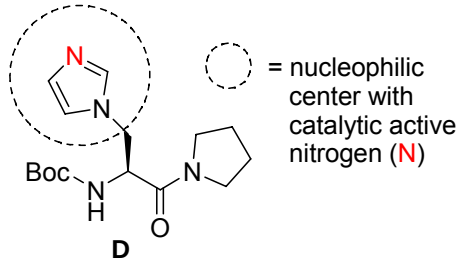
$k_{(S,S)}/k_{(R,R)}$ = **s-value = 17**



$k_{(S,S)}/k_{(R,R)}$ = **s-value = 3**
ee of recovered **1** = 44%
ee of **2** = 34%, c = 56%



$k_{(R,R)}/k_{(S,S)}$ = **s-value = 28**
ee of recovered **1** = 98%
ee of **2** = 73%, c = 58%

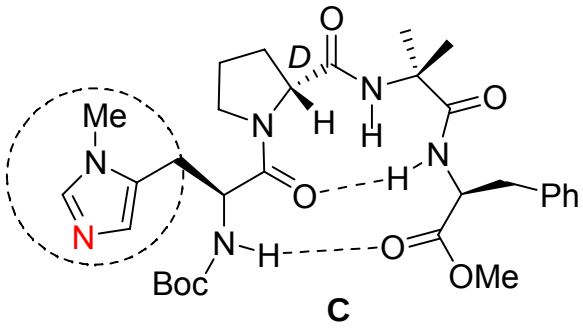


$k_{(S,S)}/k_{(R,R)}$ = **s-value = 1**

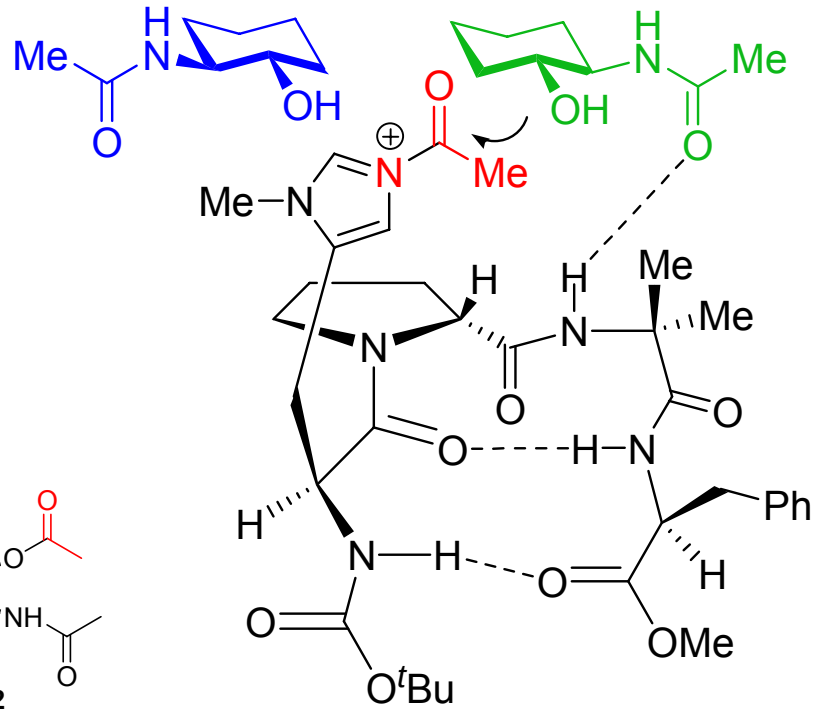
S. J. Miller, G. T. Copeland, N. Papaioannou, T. E. Horstmann, E. M. Ruel, *J. Am. Chem. Soc.* **1998,** 120, 1629.
G. T. Copeland, E. R. Jarvo, S. J. Miller, *J. Org. Chem.* **1998**, *63*, 6784.
E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, S. J. Miller, *J. Am. Chem. Soc.* **1999,** 121, 11638.

Miller´s Peptide Organocatalysis

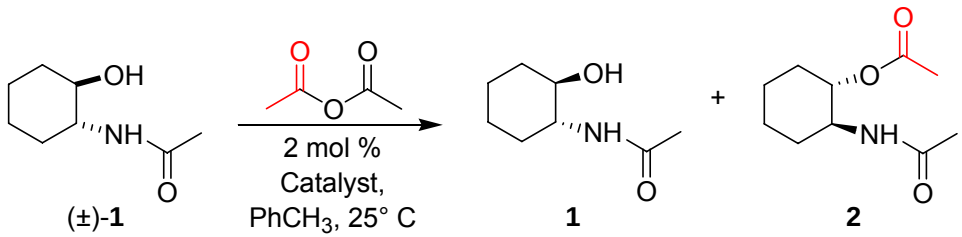
Proposed Transition State:



C



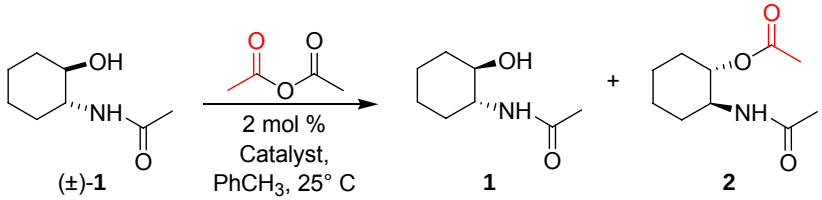
$k_{(R,R)}/k_{(S,S)}$ **= s-value = 28**
ee of recovered **1** = 98%
ee of **2** = 73%, c = 58%



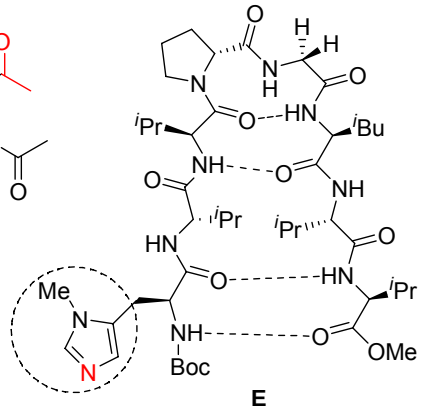
M. M. Vasbinder, E. R. Jarvo, S. J. Miller, *Angew. Chem. Int. Ed.* **2001**, *40*, 2824.
E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, S. J. Miller, *J. Am. Chem. Soc.* **1999,** 121, 11638.

Miller´s Peptide Organocatalysis

Structural Investigations:

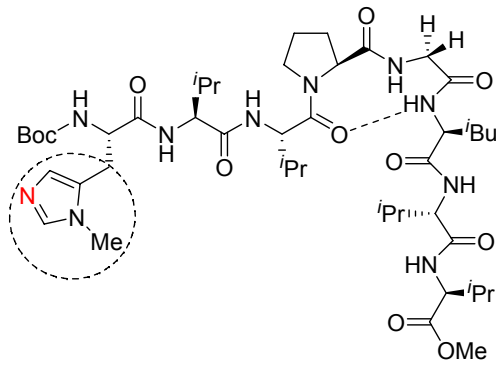


= nucleophilic center with catalytic active nitrogen (N)



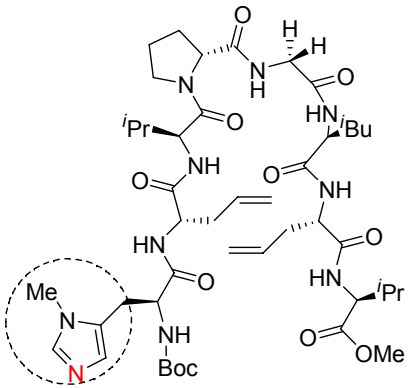
E

s = 51



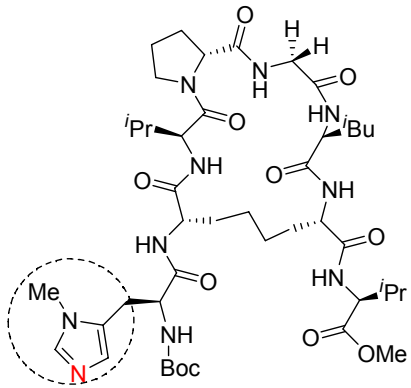
F

s = 7



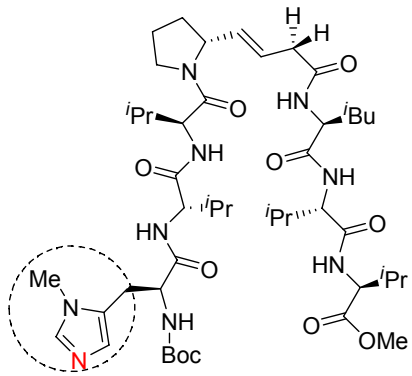
G

s = 20



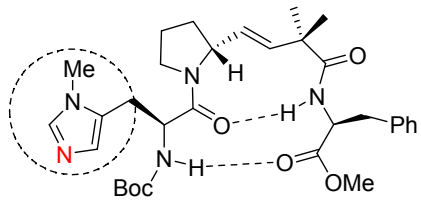
H

s = 12



I

s = 50

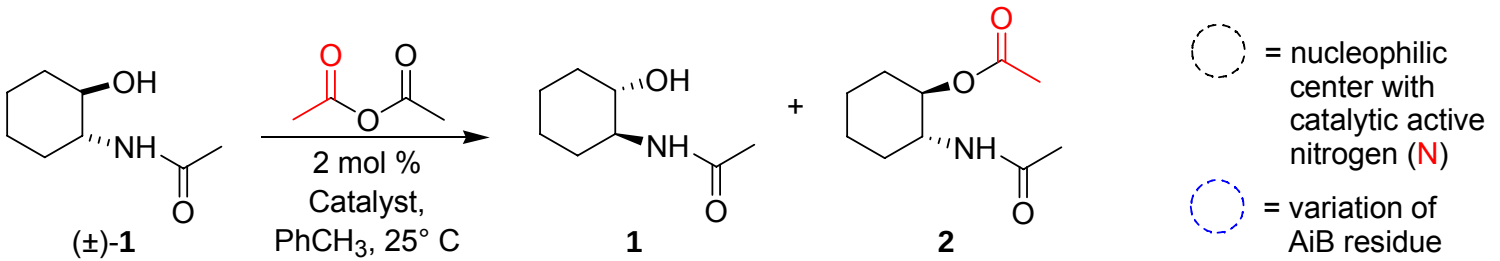


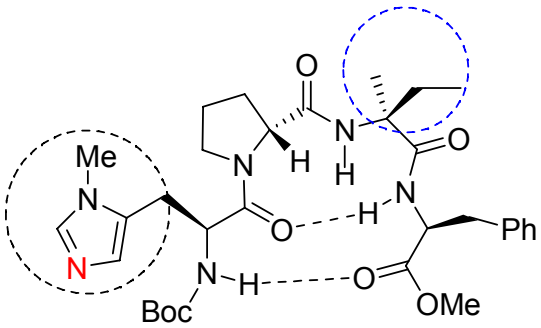
J

s < 1.5

E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, S. J. Miller, *J. Am. Chem. Soc.* **1999,** 121, 11638.
E. R. Jarvo, M. M. Vasbinder, S. J. Miller, *Tetrahedron* **2000**, *56*, 9773.
M. M. Vasbinder, E. R. Jarvo, S. J. Miller, *Angew. Chem. Int. Ed.* **2001**, *40*, 2824.

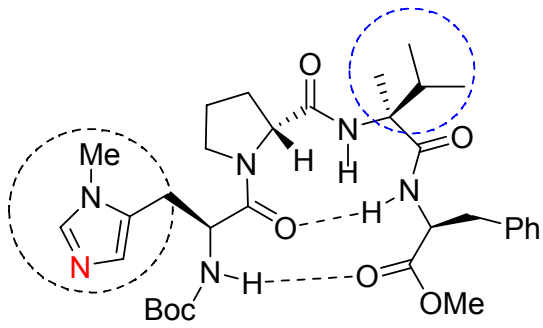
Toniolo´s Variation of Miller´s Peptide C





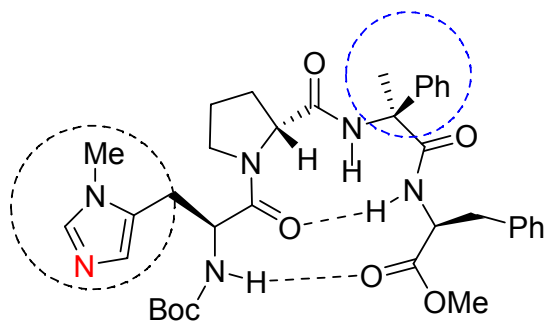
K

$k_{(R,R)}/k_{(S,S)}$ = **s-value = 23**



L

$k_{(R,R)}/k_{(S,S)}$ = **s-value = 33**

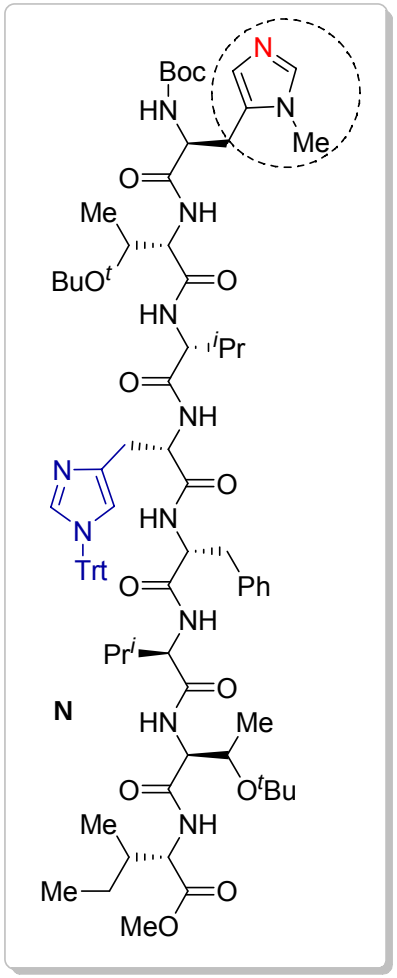


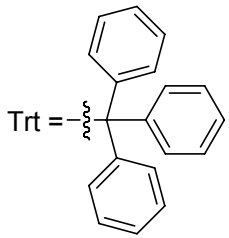
M

$k_{(R,R)}/k_{(S,S)}$ = **s-value = 10**

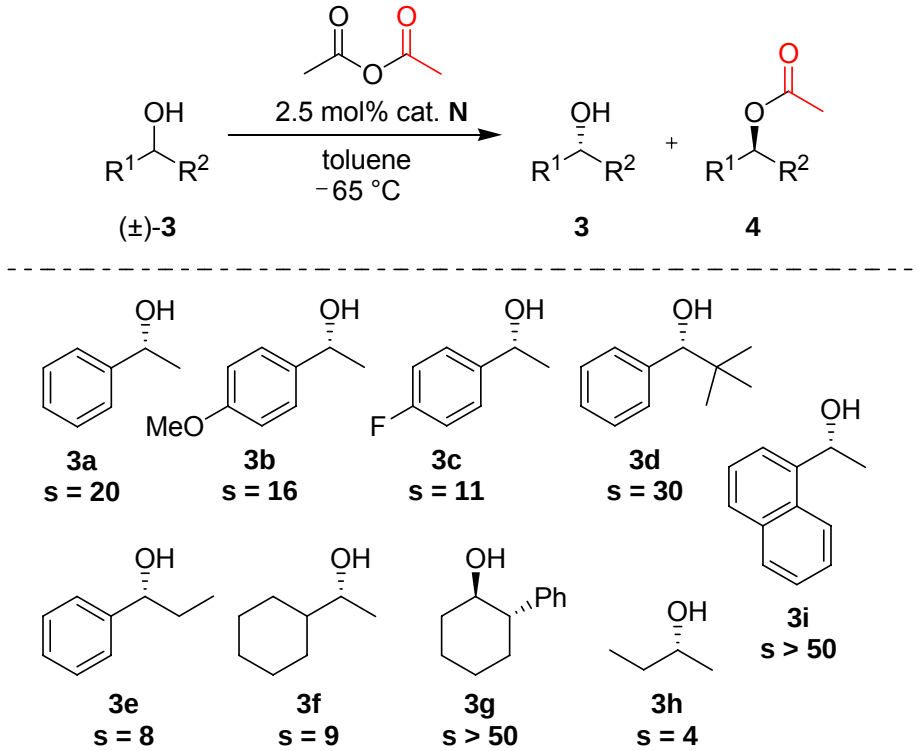
F. Formaggio, A. Barazza, A. Bertocco, C. Toniolo, Q. B. Broxterman, B. Kaptein, E. Brasola, P. Pengo, L. Pasquato, P. Scrimin, *J. Org. Chem.* **2004**, *69*, 3849.

Kinetic Resolution of Secondary Alcohols



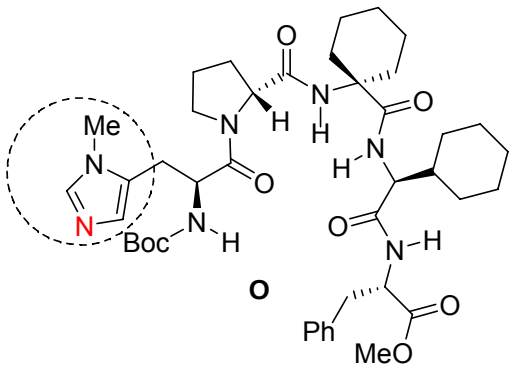


= nucleophilic center with catalytic active nitrogen (N)



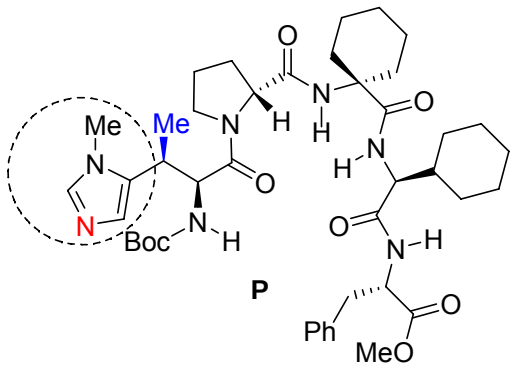
G. T. Copeland, S. J. Miller, *J. Am. Chem. Soc.* **2001**, *123*, 6496.

Introduction of an Additional Stereocenter

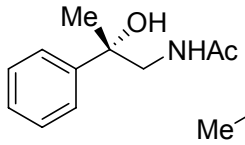


O

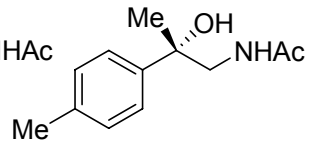
= nucleophilic center with catalytic active nitrogen (N)



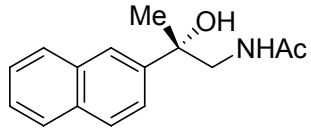
P



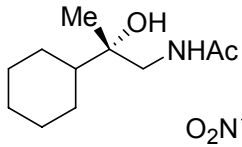
5a
s = 40 (−23 °C)
s = 14 (25 °C)



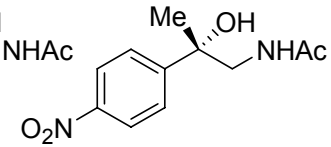
5b
s > 50 (−23 °C)



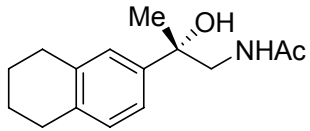
5c
s = 40 (−23 °C)



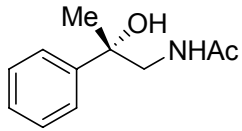
5d
s = 19 (−23 °C)
s = 9 (4 °C)



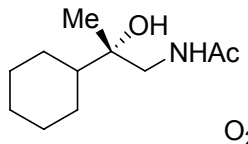
5e
s = 32 (−23 °C)
s = 10 (25 °C)



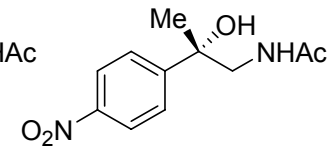
5f
s = 39 (−23 °C)



5a
s > 50 (25 °C)



5d
s > 50 (4 °C)

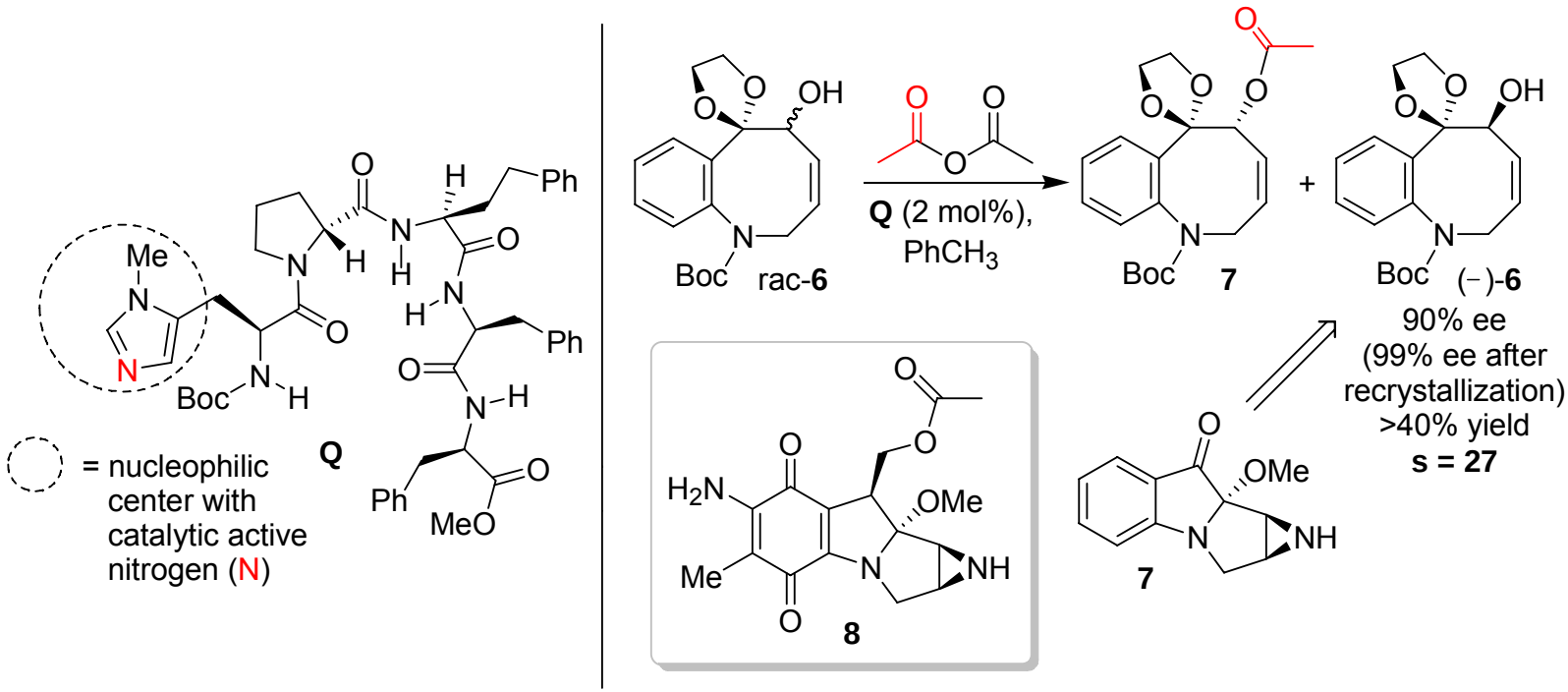


5e
s = 24 (25 °C)

E. R. Jarvo, C. A. Evans, G. T. Copeland, S. J. Miller, *J. Org. Chem.* **2001**, *66*, 5522.
M. C. Angione, S. J. Miller, *Tetrahedron* **2006**, *62*, 5254.

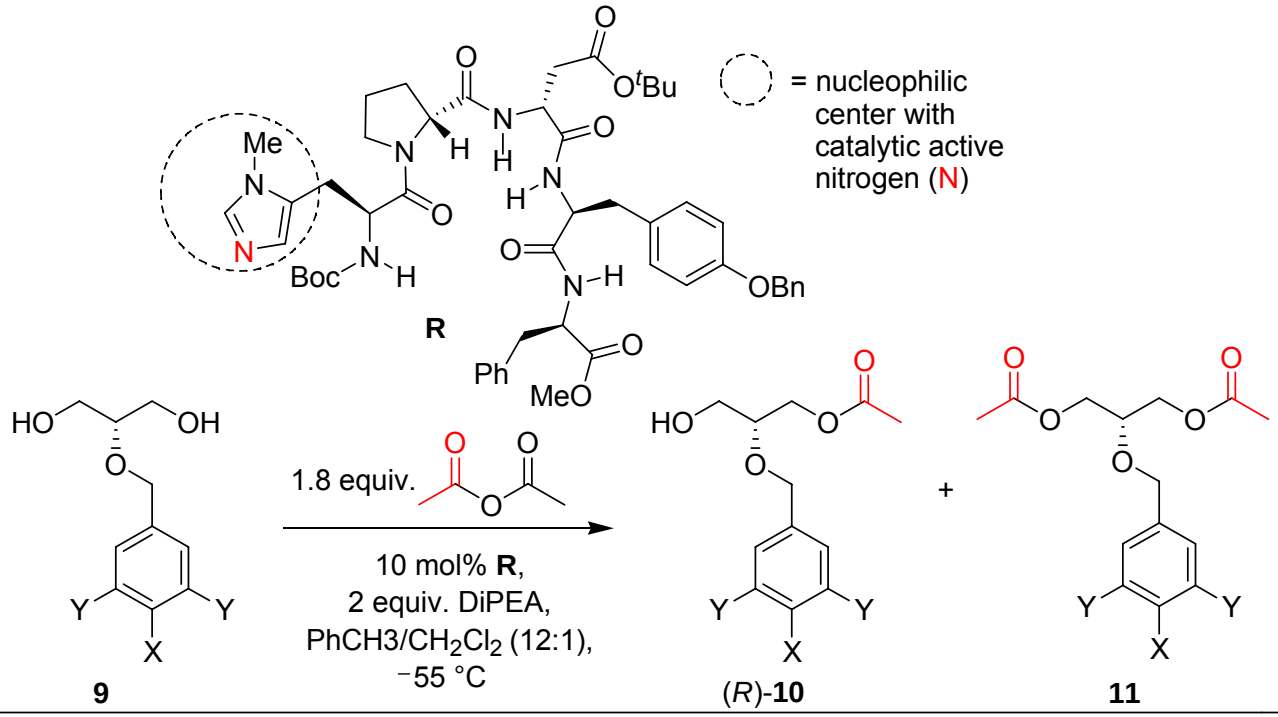
Application as Part of the Total Synthesis of Mitomycin C (O4)

Acylative Enantioseparation of Key Intermediate (–)-**6** in the Total Synthesis of Mitosane **7** which is the Core Structure of Mitomycin C **8**



N. Papaioannou, C. A. Evans, J. T. Blank, S. J. Miller, *Org. Lett.* **2001**, *3*, 2879.
N. Papaioannou, J. T. Blank, S. J. Miller, *J. Org. Chem.* **2003**, *68*.

Desymmetrization of meso-Compounds

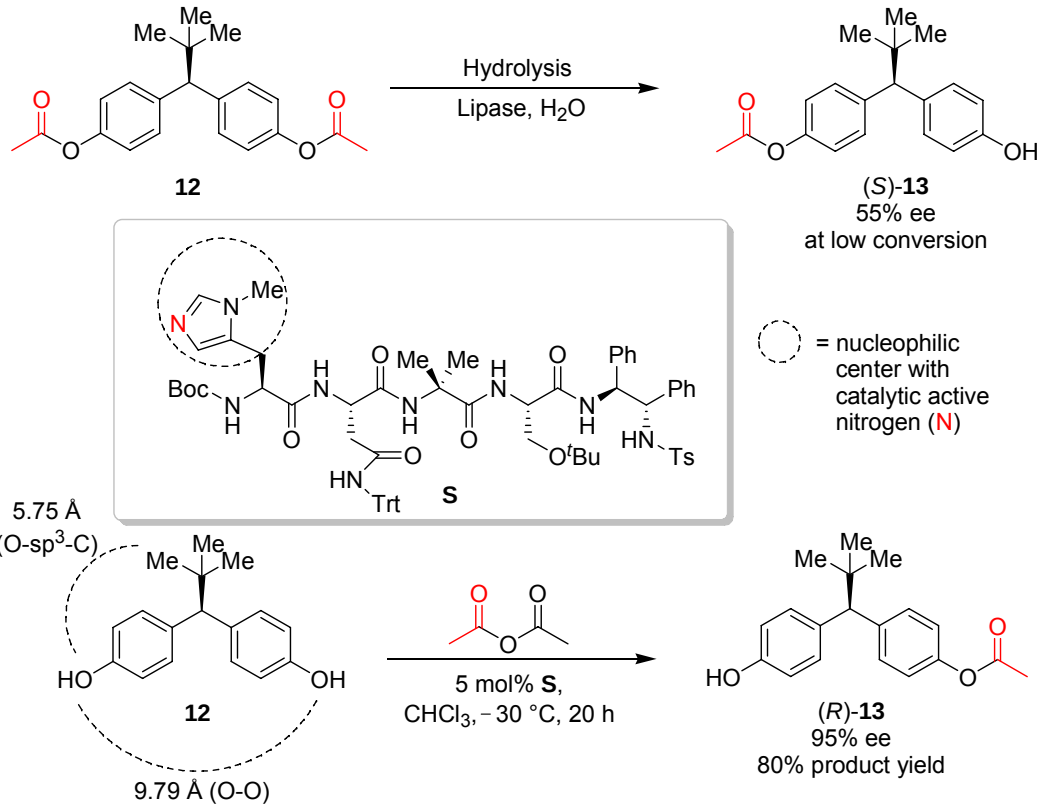


#	X	Y	ee (%) 10	isolated yield (*R*)-10 (%)	10:11 ratio
1	H	H	91	37	39:61
2	F	H	68	40	50:50
3	CF_3	H	73	37	43:57
4	OMe	H	88	48	51:49
5	H	OMe	95	34	37:63

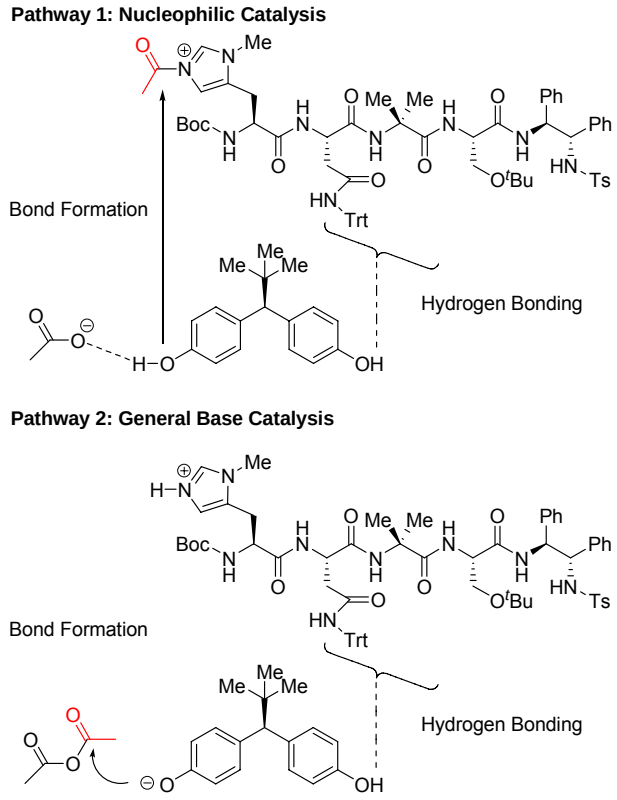
C. A. Lewis, B. R. Sculimbrene, Y. Xu, S. J. Miller, *Org. Lett.* **2005**, *7*, 3021.

Desymmetrization of meso-Compounds

Protocol: Enzymatic as well as Biomimetic



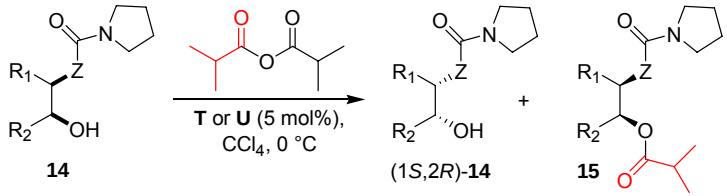
Proposed Mechanism:

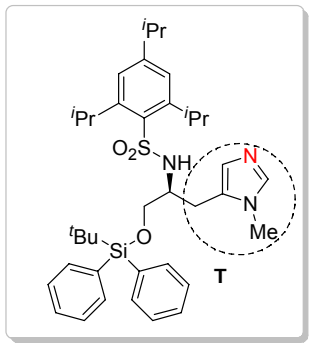


C. A. Lewis, A. Chiu, M. Kubryk, J. Balsells, D. Pollard, C. K. Esser, J. Murry, R. A. Reamer, K. B. Hansen, S. J. Miller, *J. Am. Chem. Soc.* **2006**, *128*, 16454; Also: *"Research Highlights" Nature* **2006**, *444*, 974.

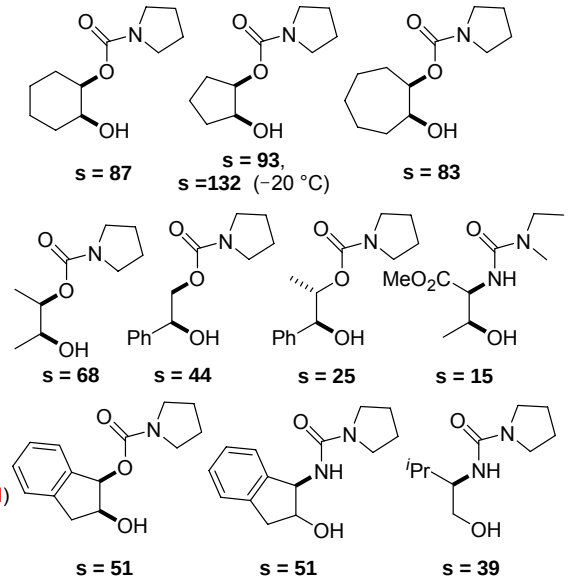
C. A. Lewis, J. L. Gustafson, A. Chiu, J. Balsells, D. Pollard, J. Murry, R. A. Reamer, K. B. Hansen, S. J. Miller, *J. Am. Chem. Soc.* **2008**, *130*, 16358.

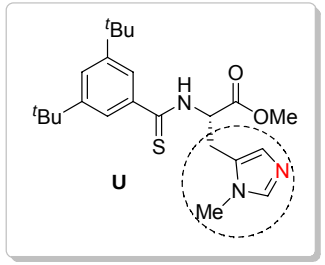
Other Imidazole Based Catalysts



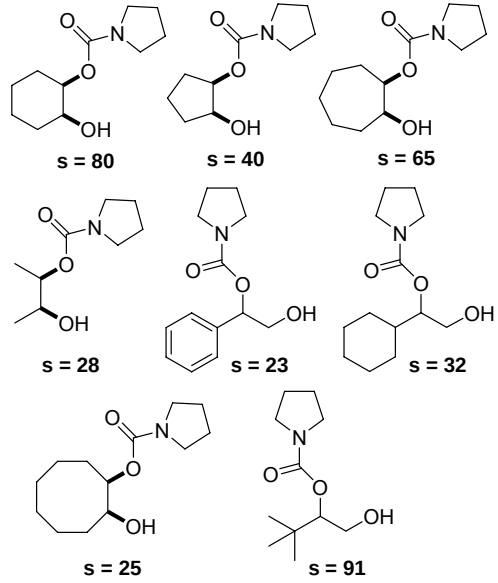


= nucleophilic center with catalytic active nitrogen (N)



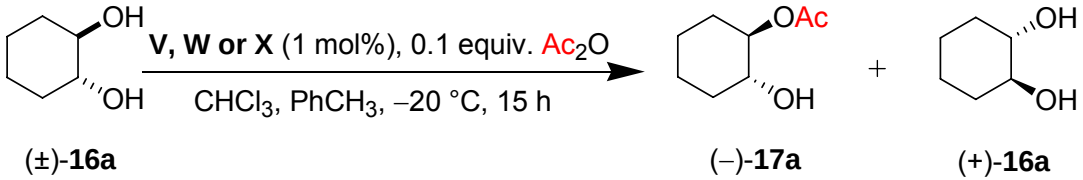


= nucleophilic center with catalytic active nitrogen (N)

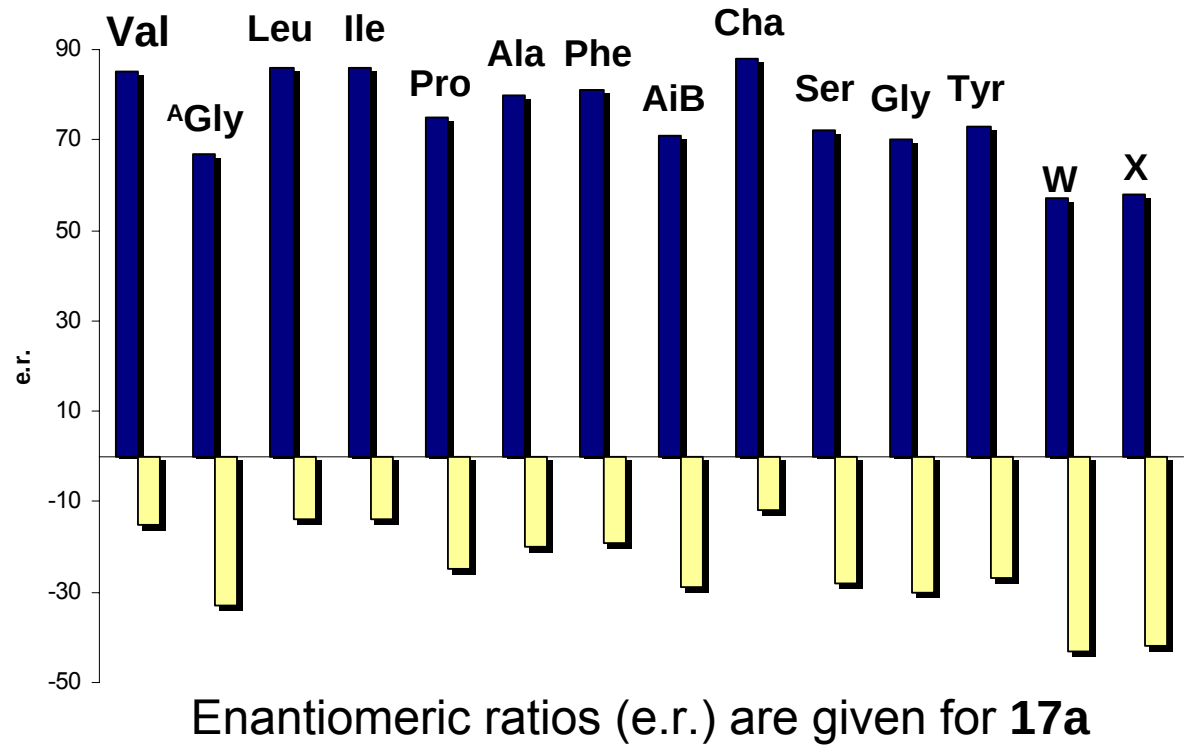


K. Ishihara, Y. Kosugi, M. Akakura, *J. Am. Chem. Soc.* **2004**, *126*, 12212.
Y. Kosugi, M. Akakura, K. Ishihara, *Tetrahedron* **2007**, *63*, 6191.
X.-L. Geng, J. Wang, G.-X. Li, P. Chen, S.-F. Tian, J. Qu, *J. Org. Chem.* **2008**, *73*, 8558.

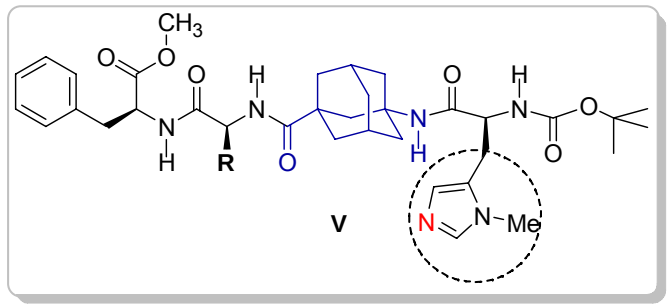
Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols

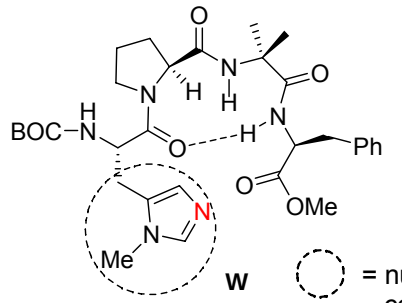


(±)-**16a** (–)-**17a** (+)-**16a**

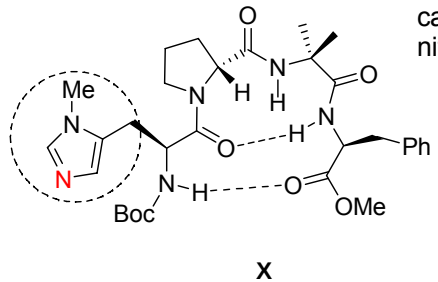


Enantiomeric ratios (e.r.) are given for **17a**



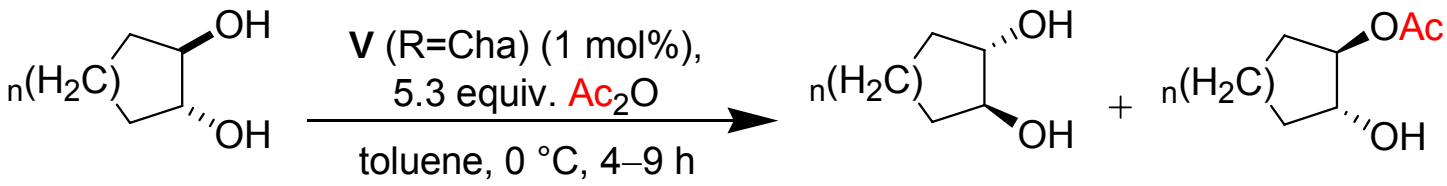


= nucleophilic center with catalytic active nitrogen (N)

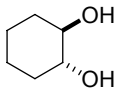
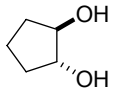
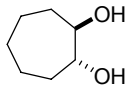
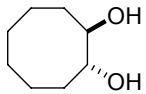


C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 6180.

Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols



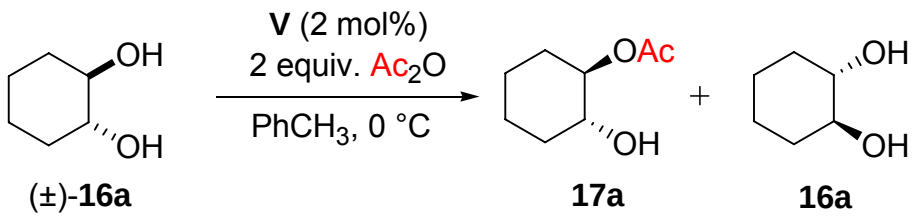
(±)-**16** (+)-**16** (–)-**17**

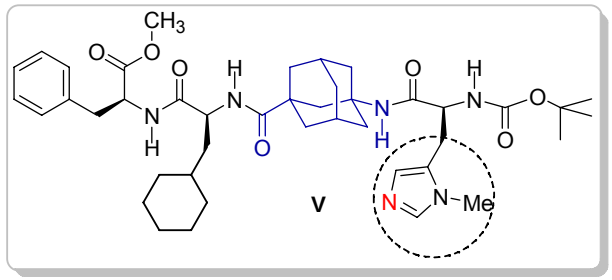
Substrate	*t*/h	Conv./%[a] *(Isolated Yield 16/%)*	*ee* /% (+)-16	*ee* /% (–)-17	*s*-value[a]
 (±)-**16a**	4	56 *(37)*	>99	78	>50
 (±)-**16b**	9	63 *(30)*	85	49	8
 (±)-**17c**	5	56 *(41)*	>99	79	>50
 (±)-**16d**	5	54 *(44)*	>99	85	>50

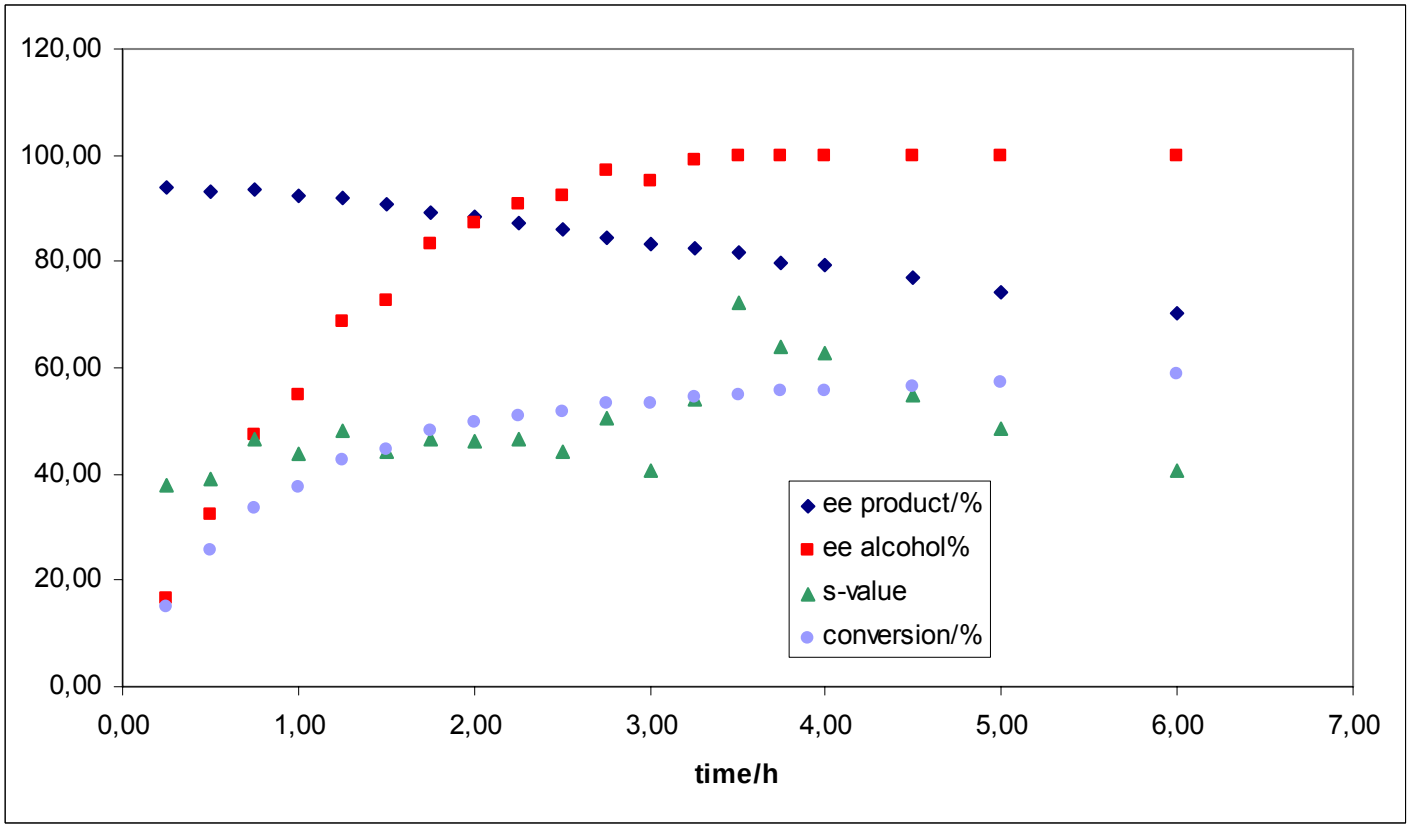
[a]Conversions and *s*-factors determined following the procedure of Kagan and Fiaud.

C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 6180.
H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.

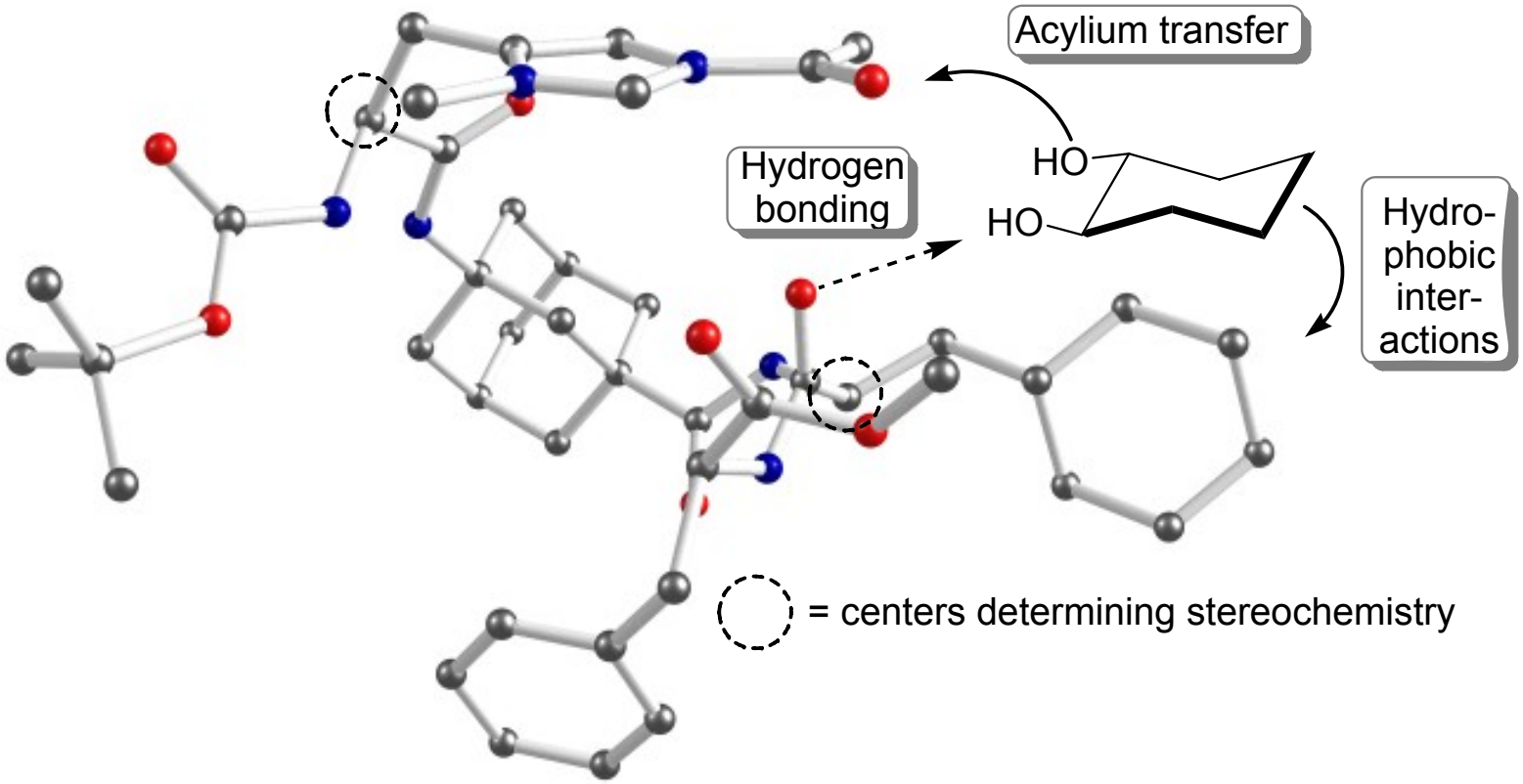
Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols







Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols

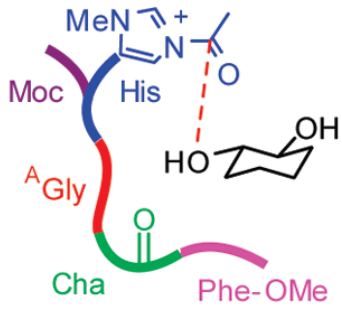


Merck Molecular Force Field (MMFF) conformer distribution;
the low lying conformers were optimized at B3LYP/6-31+G(d,p).

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

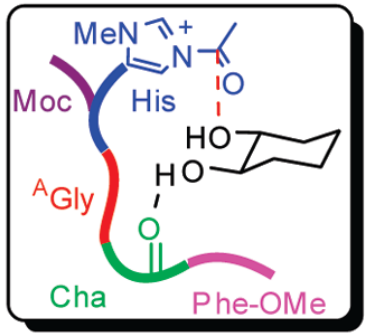
Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols

Peptide Acylium Ion Diol Complexes:



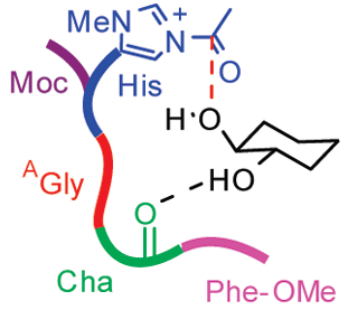
$(1S,2S)_{e,e}$-α

Boc	16.7
Moc	16.8



$(1R,2R)_{e,e}$-α

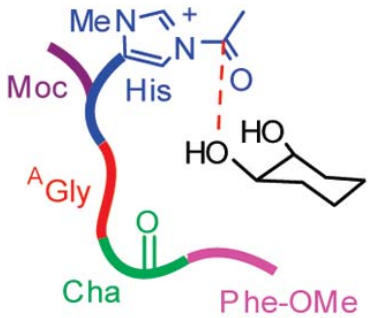
0.0	
0.0	



$(1S,2S)_{e,e}$-β

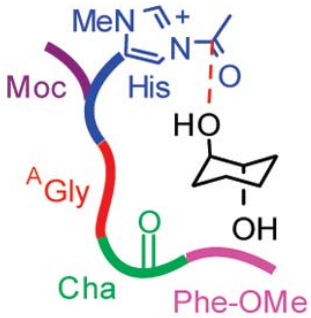
7.5	
4.3	

Relative energies ΔE of the peptide acylium ion-diol complex in kcal/mol



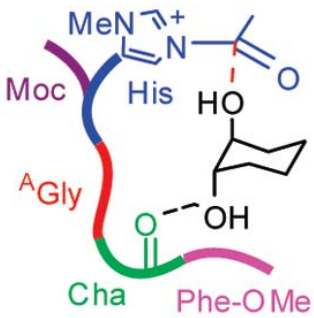
$(1R,2R)_{e,e}$-β

16.7	
16.8	



$(1R,2R)_{a,a}$-β

8.2	
12.4	



$(1S,2S)_{a,a}$-β

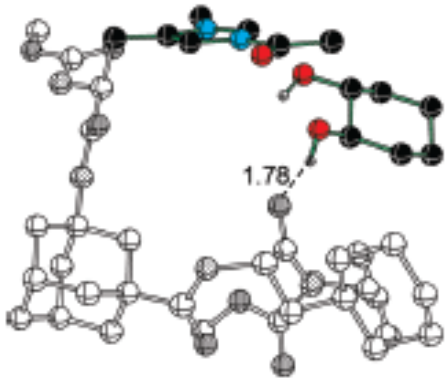
12.4	
12.7	

B3LYP/6-31G*//ONIOM2 (B3LYP/6-31G*:PM3)

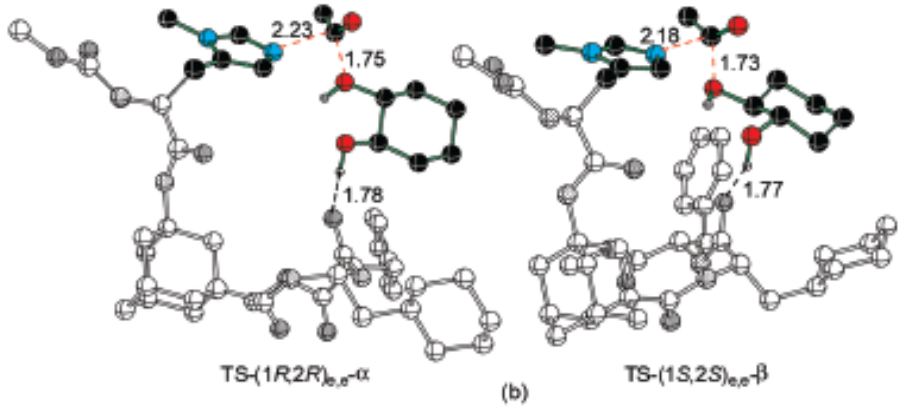
C. B. Shinisha, R. B. Sunoj, *Org. Lett.* **2009**, *11*, 3242.

Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols

Peptide Acylium Ion Diol Complex:



Transition States:

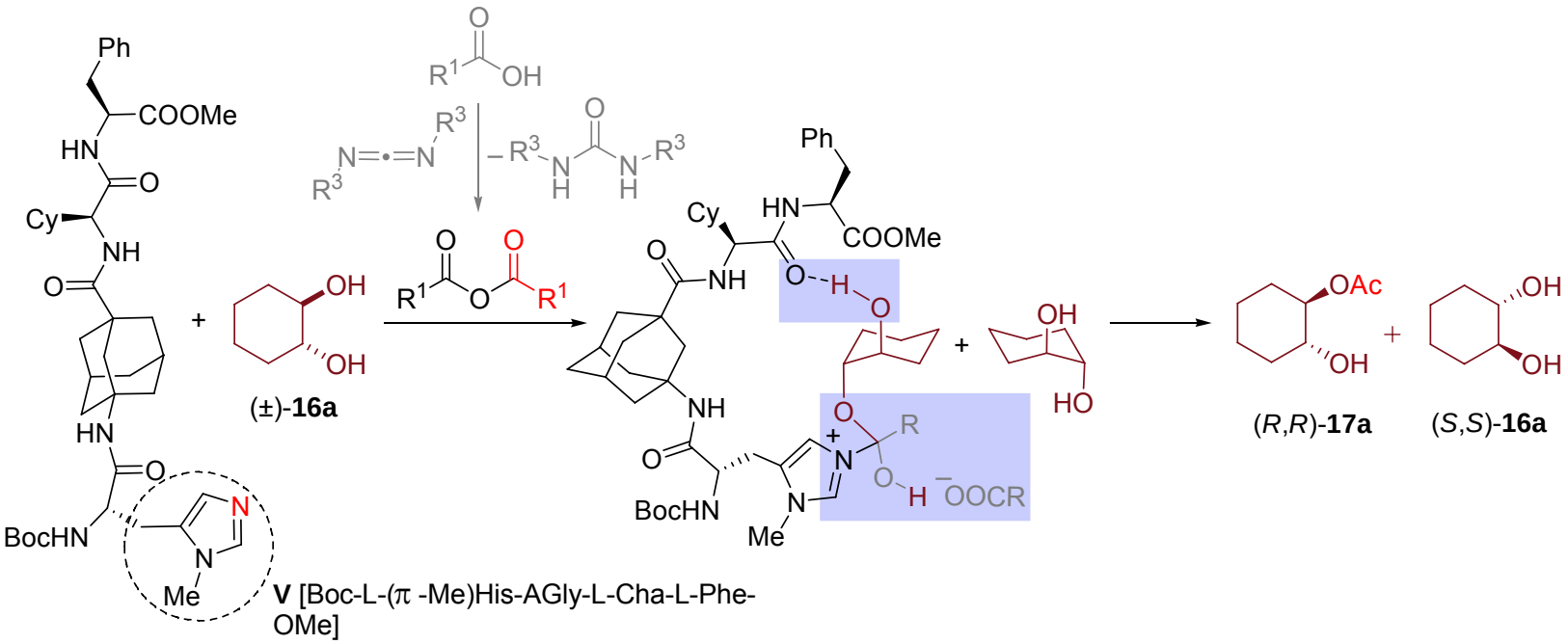


B3LYP/6-31G*//ONIOM2(B3LYP/6-31G*:PM3)

diol	transition states	relative $\Delta E^{\ddagger}$ (in kcal/mol) Boc (**2**)	Moc (**3**)
	$(1S,2S)_{e,e}$-$\alpha^{\ddagger}$ [b]	13.5	13.4
	$(1S,2S)_{e,e}$-$\beta^{\ddagger}$	4.6	4.5
	$(1S,2S)_{a,a}$-$\beta^{\ddagger}$	7.6	7.7
	$(1R,2R)_{e,e}$-$\alpha^{\ddagger}$	**0.0**	**0.0**
	$(1R,2R)_{e,e}$-$\beta^{\ddagger}$	11.5	11.6
trans-diol	$(1R,2R)_{a,a}$-$\beta^{\ddagger}$	9.7	11.6

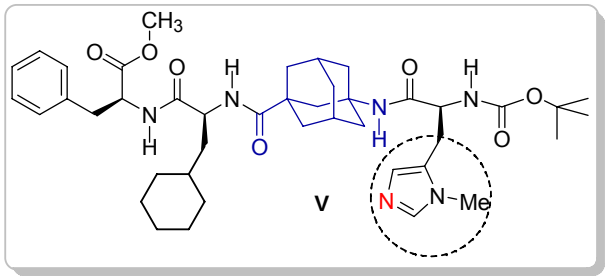
C. B. Shinisha, R. B. Sunoj, *Org. Lett.* **2009**, *11*, 3242.

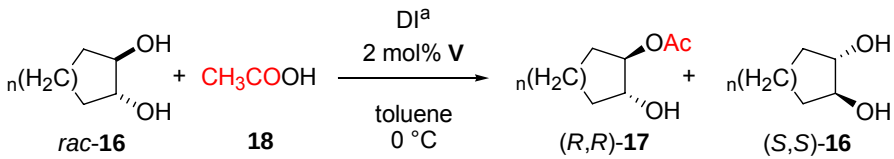
Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols *via* Steglich Esterification



R. Hrdina, C. E. Müller, P. R. Schreiner, *Chem. Comm.*, submitted for publication.

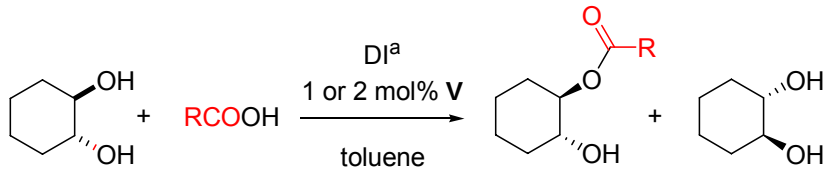
Kinetic Resolution of *trans*-Cycloalkane-1,2-Diols *via* Steglich Esterification

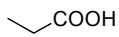
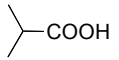
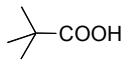
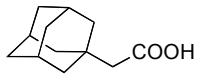




n	*t* (h)	C (%)	*ee* (%)	*ee* (%)	*S*
1	10	76	**17b**, 32	**16b** >99	11
2	10	55	**17a**, 81	**16a** >99	>50
3	16	55	**17c**, 82	**16c** >99	>50
4	18	55	**17d**, 81	**17c** >99	>50

a) DI = Diimide

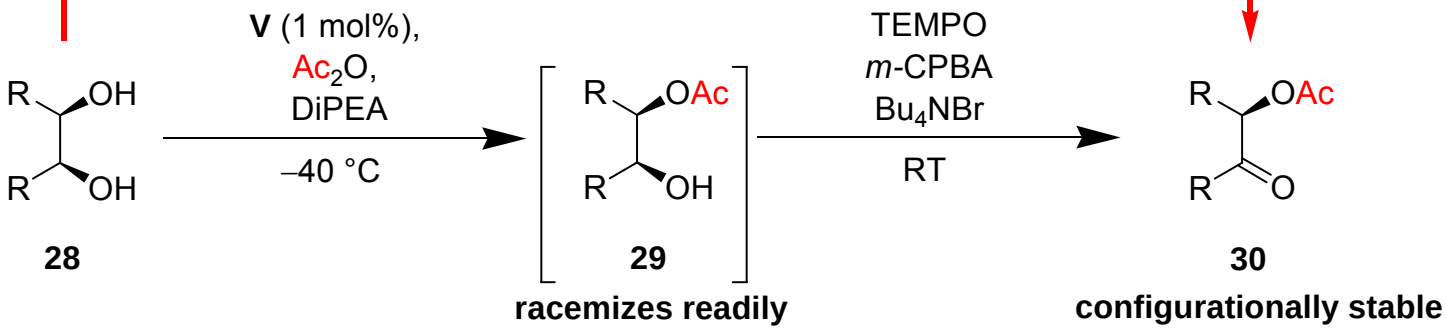


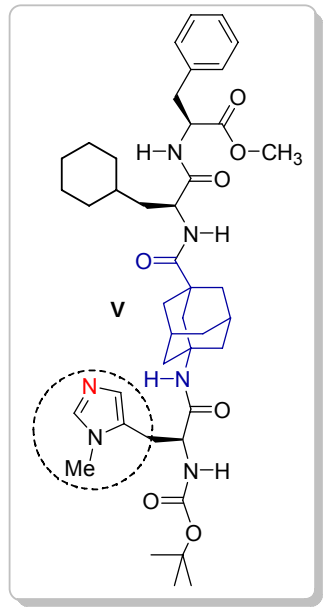
	Carboxylic acid	*t* (h)	C (%)	ee (%)	ee (%) 2	*S*
19	HCOOH	7	67	41	83	6
20		15	55	83	>99	>50
		41	(48, 43)	90	98	>50
21		24	54	85	>99	>50
		45	(55, 41)	90	98	>50
22		48	4	86	4	14
23		48	60	57	85	9
24	$PhCH_2COOH$	2	57	75	>99	>50
		2	(54, 41)	82	>99	>50
25	$PhCO\text{-}_2H$	48	38	60	36	6
26	*p*-Cl-$PhCO_2H$	48	58	60	84	10
27	*p*-MeO-$PhCO_2H$	48	–	–	3	–

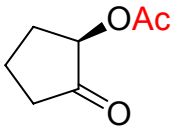
R. Hrdina, C. E. Müller, P. R. Schreiner, *Chem. Comm.*, submitted for publication.
H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249.

Desymmetrization of *meso*-Hydrocarbon-1,2-Diols

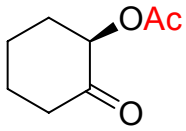
Desymmetrization and direct one-pot Oxidation!



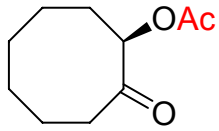




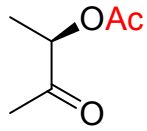
64% ee
(80% ee after desymmetrization)
69% isolated yield



88% ee
(88% ee after desymmetrization)
70% isolated yield



94% ee
(84% ee after desymmetrization)
97% isolated yield

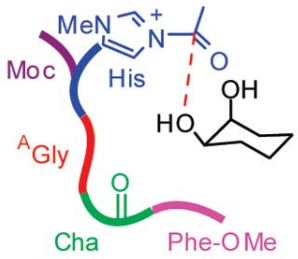


81% ee
(84% ee after desymmetrization)
42% isolated yield

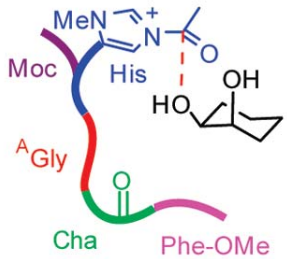
C. E. Müller, D. Zell, P. R. Schreiner, *Chem. Eur. J.* **2009**, *15*, 9647.

Desymmetrization of *meso*-Hydrocarbon-1,2-Diols

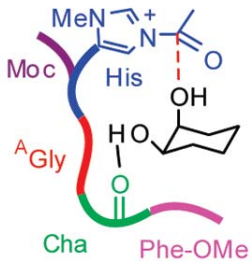
Peptide Acylium Ion Diol Complexes:



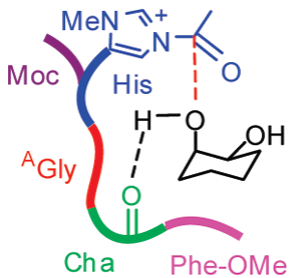
$(1R,2S)_{e,a}$-β
Boc 8.7
Moc 22.0



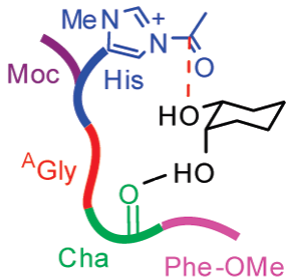
$(1S,2R)_{e,a}$-β
15.3
15.4



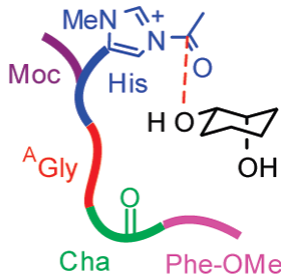
$(1S,2R)_{a,e}$-β
6.3
6.7



$(1R,2S)_{a,e}$-β
10.6
12.1



$(1R,2S)_{e,a}$-α
0.0
0.0



$(1S,2R)_{e,a}$-α
18.4
18.5

Relative energies ΔE of the peptide acylium ion-diol complex in kcal/mol

B3LYP/6-31G*//ONIOM2 (B3LYP/6-31G*:PM3)

Transition States for Acyl Transfer:

diol	transition states	relative $\Delta E^{\ddagger}$ (in kcal/mol) Boc (**2**)	Moc (**3**)
	$(1R,2S)_{e,a}$-α‡	**0.0**	**0.0**
	$(1R,2S)_{e,a}$-$\beta^{\ddagger}$	16.1	16.3
	$(1R,2S)_{a,e}$-$\beta^{\ddagger}$	12.5	12.6
	$(1S,2R)_{e,a}$-α‡	12.7	12.7
	$(1S,2R)_{e,a}$-$\beta^{\ddagger}$	14.9	15.0
cis-diol	$(1S,2R)_{a,e}$-$\beta^{\ddagger}$	4.3	4.4

C. B. Shinisha, R. B. Sunoj, *Org. Lett.* **2009**, *11*, 3242.

Conlusions

Biomimetic organocatalysts

- show a good performance in enantioselective acylation reactions
- are highly tunable
- often have a high molecular mass
- often only work under highly diluted conditions
- often show a high substrate specificity

Acknowledgement

Many Thanks

- to *Prof. Dr. Peter R. Schreiner* for support, ideas, inspiration, comments and discussions,
- to Dr. Hausmann, Dr. Reisenauer, Dr. Röcker
- to the analytic
- to my colleagues for the good cooperation and interesting discussions.
- DFG (SPP 1179)