Unsaturated Carboxylic Acids in Peptide Catalyzed Reactions

PRS Group Seminar

29th July 2011

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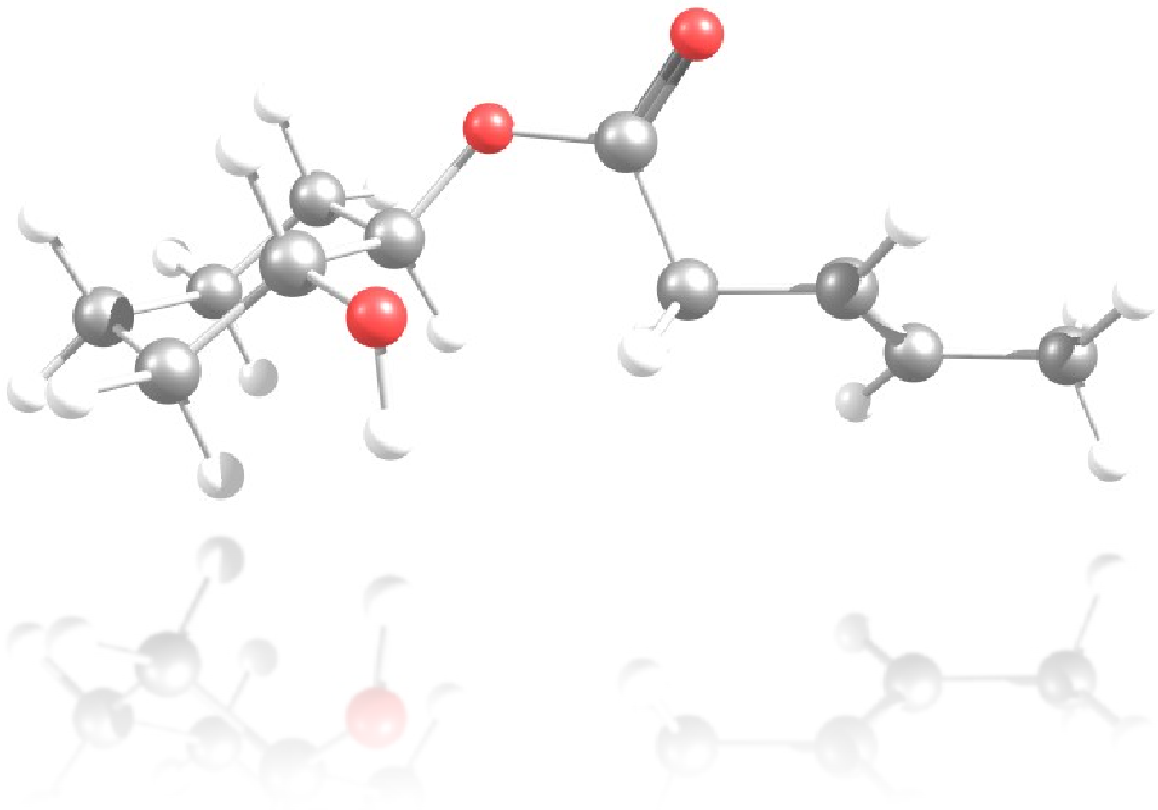
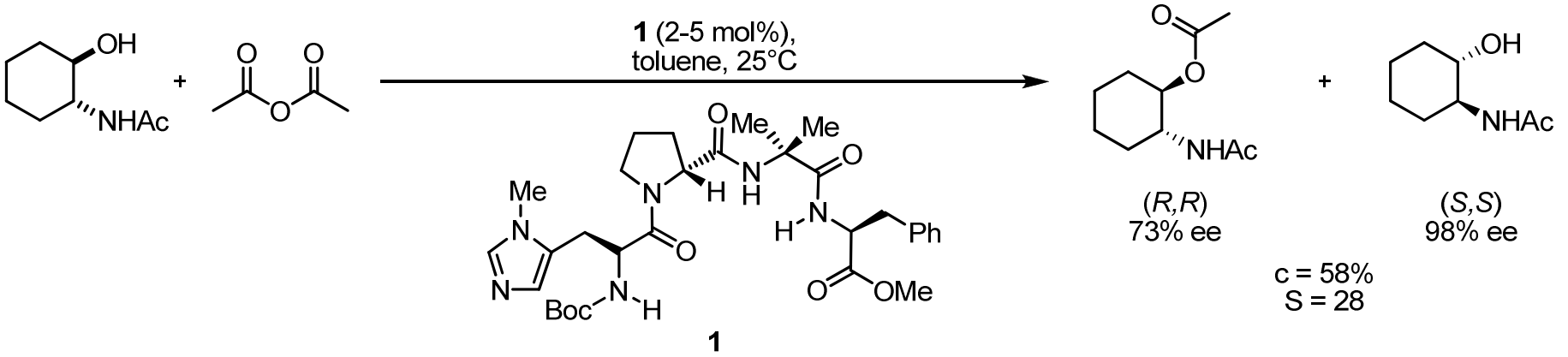
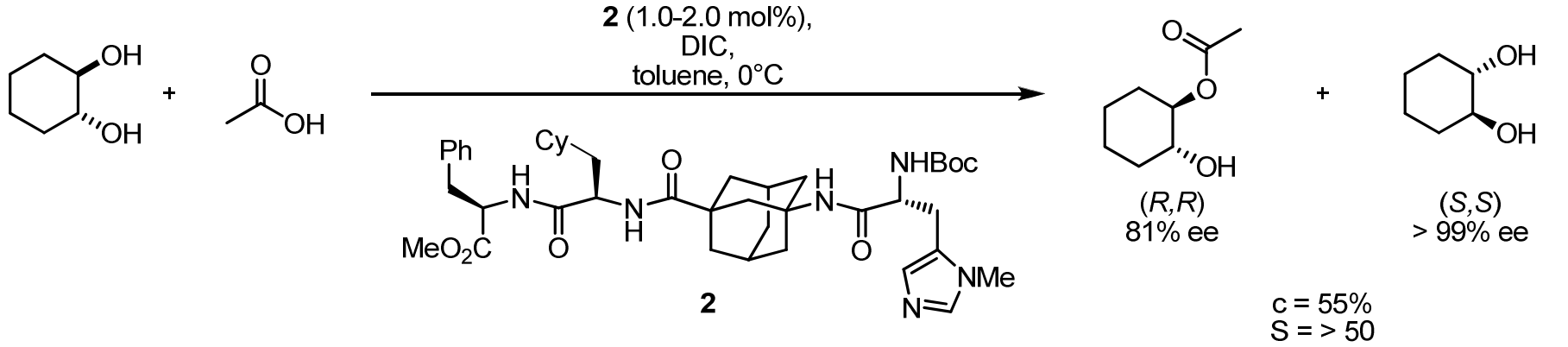


Outline

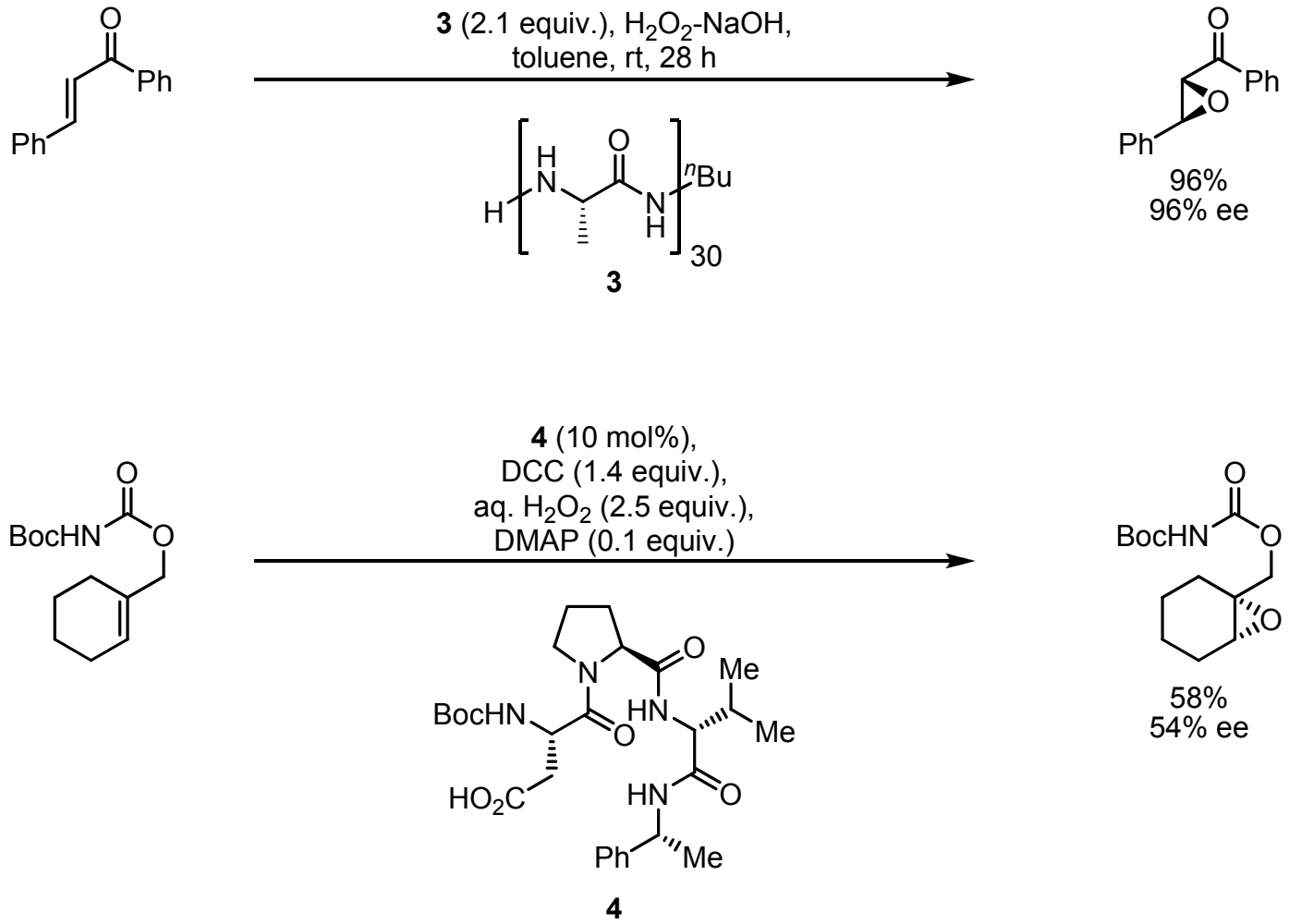
- Concept of peptide catalysis
- Epoxides in natural products and drugs
- Possible epoxidation conditions
- Long-term objective of multicatalysis
- Chemistry of two different unsaturated carboxylic acids
- Actual state of epoxidation reactions
- Outlook



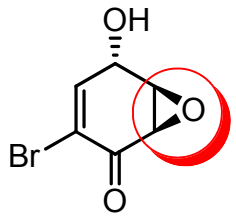


E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759.
G. T. Copeland, E. R. Jarvo, and S. J. Miller, *J. Org. Chem.* **1998**, *63*, 6784.
R. Hrdina, C. E. Müller, P. R. Schreiner, *Chem. Commun.* **2010**, *46*, 2689.

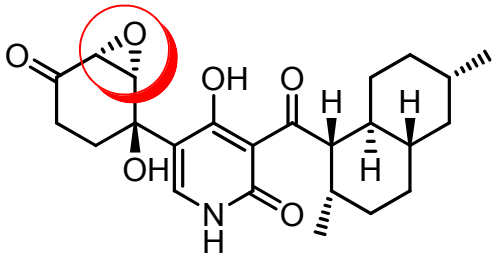
Concept of Peptide Catalysis - Epoxidation



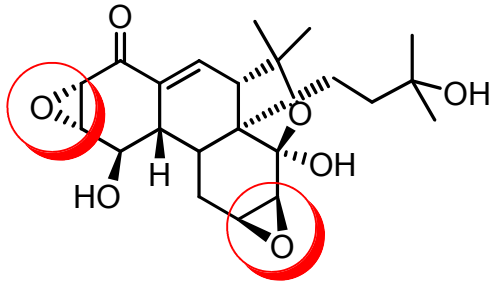
E. A. C. Davie, S. M. Mennen, Y. Xu, S. J. Miller, *Chem. Rev.* **2007**, *107*, 5759.
S. Juliá, J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annuziata, H. Molinari, *J. Chem. Soc. Perkin Trans. 1*, **1982**, 1317.
G. Peris, C. E. Jakobsche, S. J. Miller, *J. Am. Chem. Soc.* **2007**, 129, 8710.



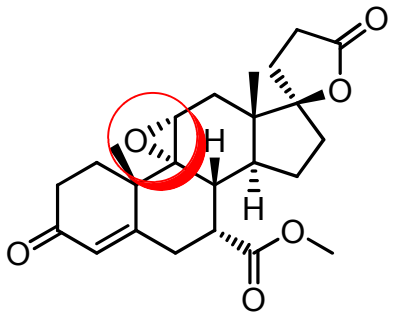
(+)-bromoxone



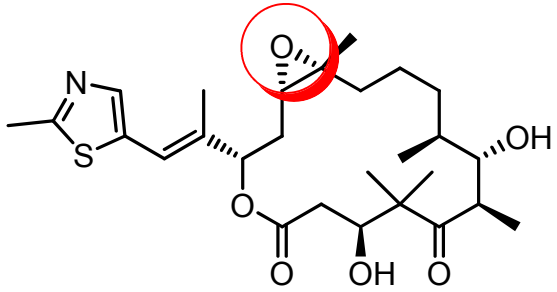
(+)-YM-215343



(+)-panepophenanthrin



Eplerenone



Epothilon B

A. R. Burns, R. J. K. Taylor, *Synthesis* **2011**, *5*, 681.
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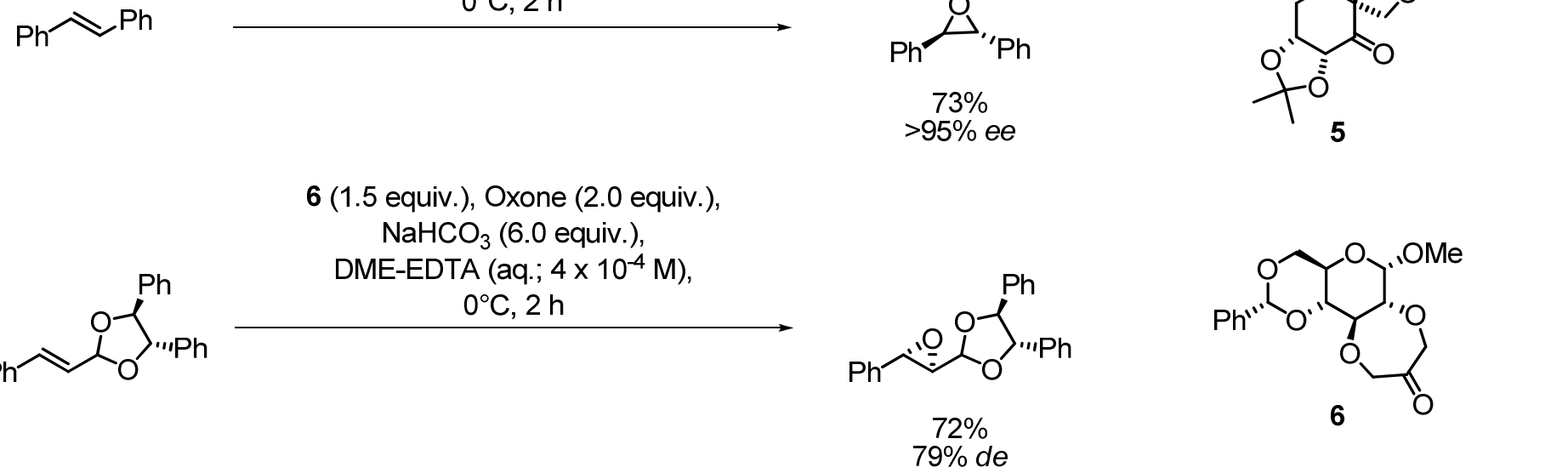
Possible Epoxidation Conditions - Oxone



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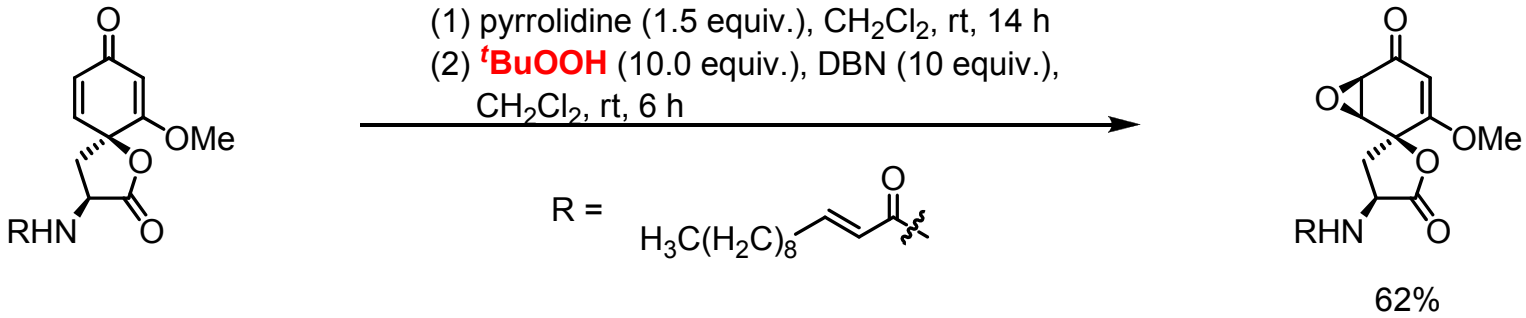
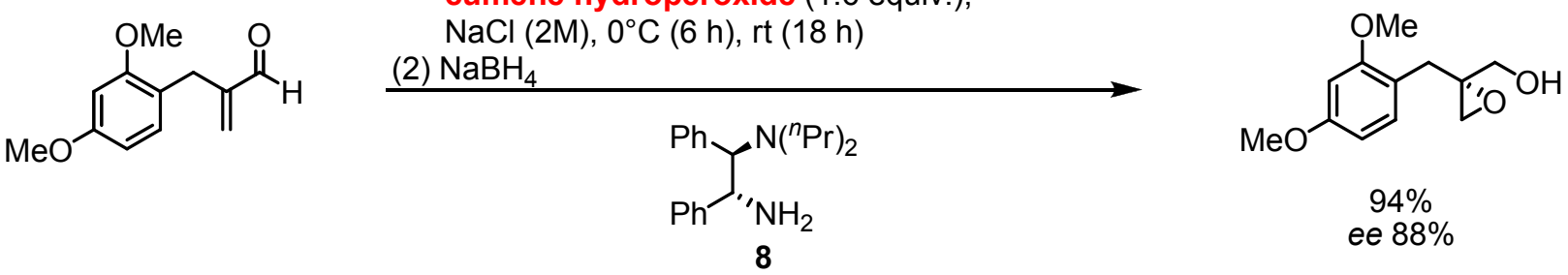
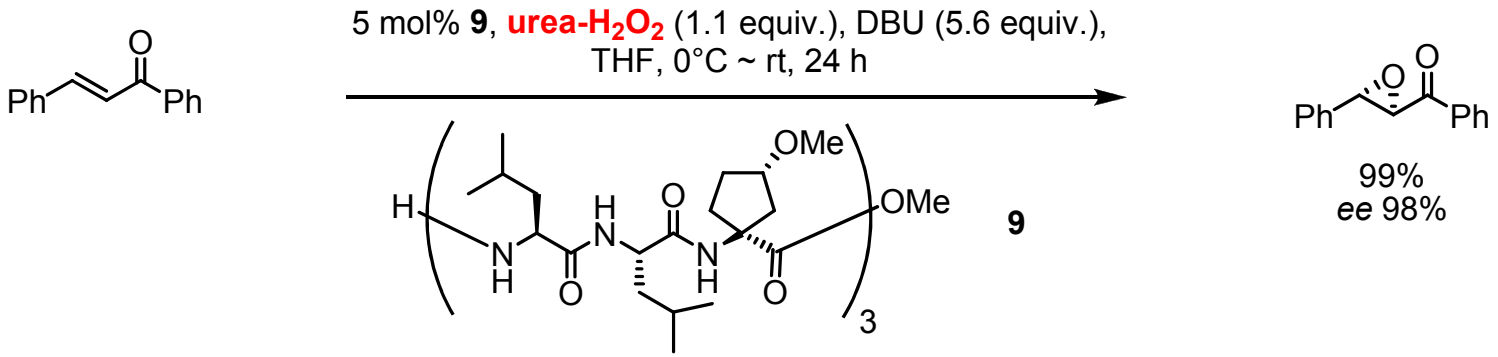
T. R. Boehlow, P. C. Buxton, E. L. Grocock, B. A. Marples, V. L. Waddington, *Tetrahedron Lett.* **1998**, *39*, 1839.

Possible Epoxidation Conditions - Hydroperoxides







J. Y. Cha, Y. Huang, T. R. R. Pettus, *Angew. Chem. Int. Ed.* **2009**,*48*, 9519.
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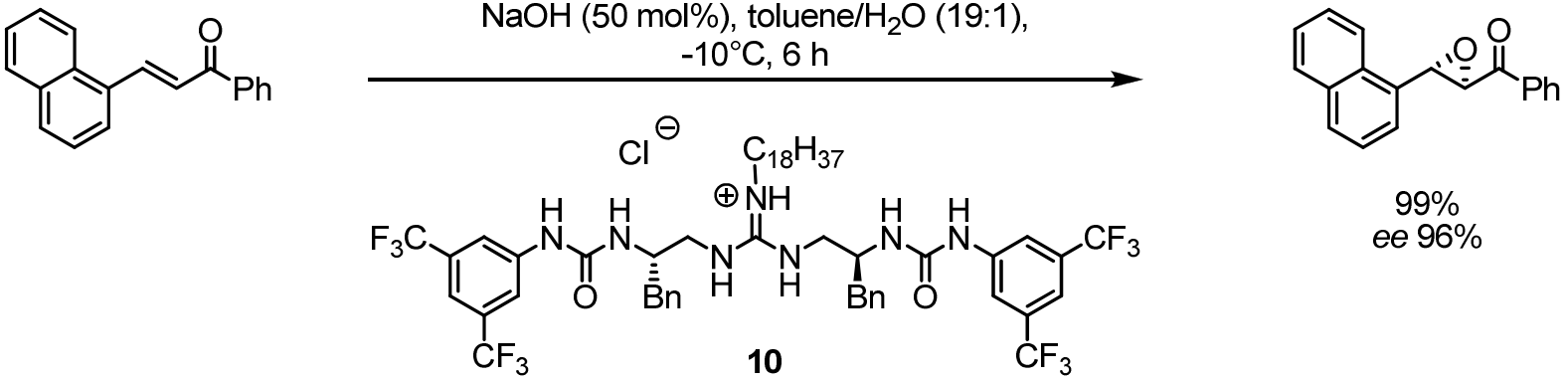
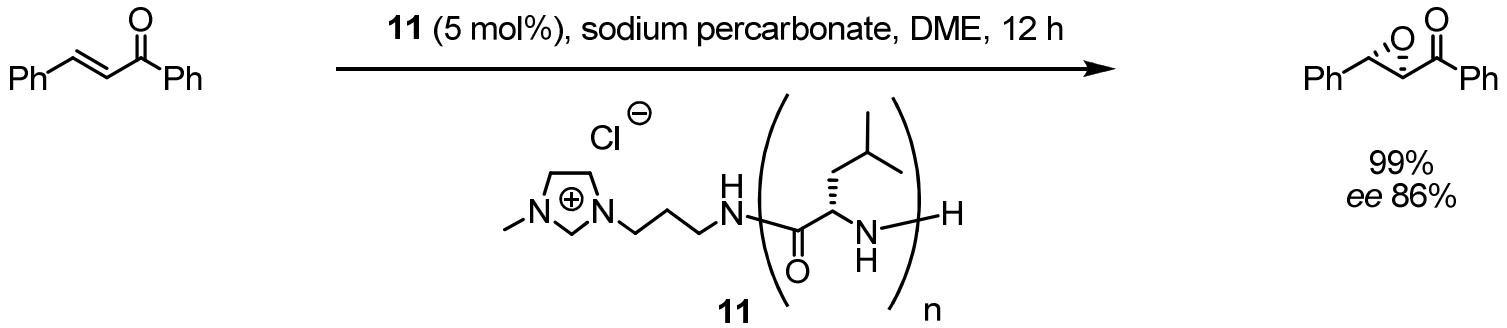
M. Nagano, M. Doi, M. Kurihara, H. Suemune, M. Tanaka, *Org. Lett.* **2010**, *12*, 3564.

Possible Epoxidation Conditions – Phase Transfer Catalyst

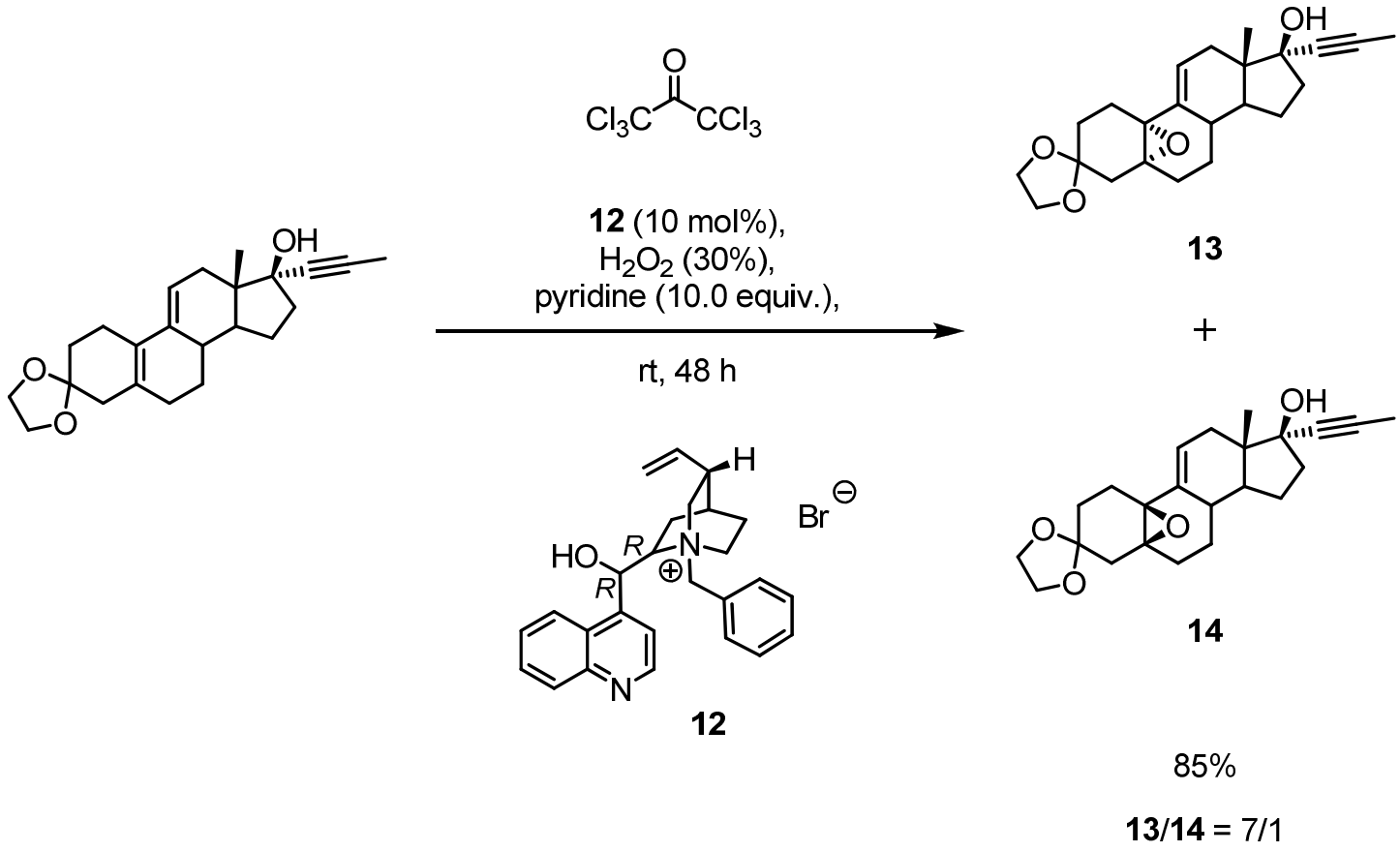




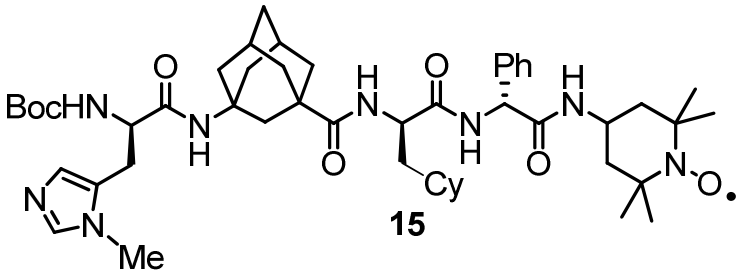
S. Tanaka, K. Nagasawa, *Synlett*. **2009**,*4*, 667.

W. Qui, L. He, Q. Chen, W. Luo, Z. Yu, F. Yang, J. Tang, *Tetrahedron Lett*. **2009**, *50*, 5225.

Possible Epoxidation Conditions – Phase Transfer Catalyst



Y.-X. Yang, Z. Li, G.-R. Chen, Y.-C. Li, *Lett. Org. Chem.* **2010**, *7*, 163.



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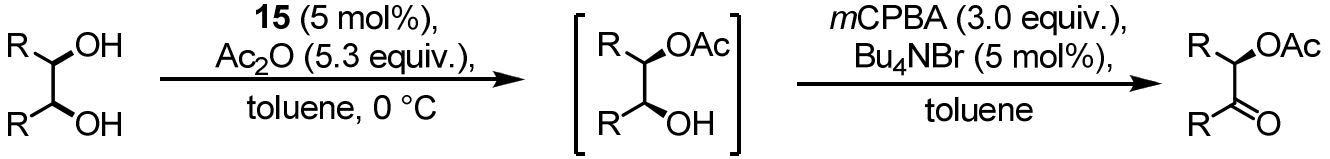
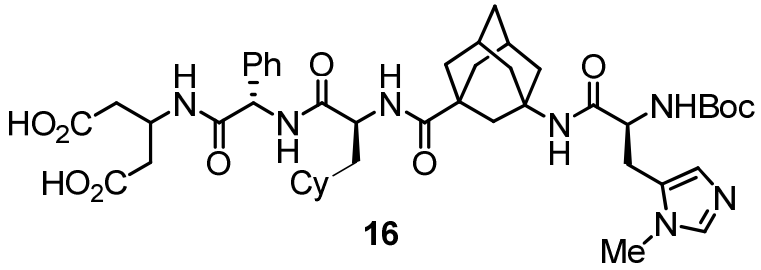


cyclooctene: 83%, e.r. 91:9
R = Me: 49%, e.r. 83:17



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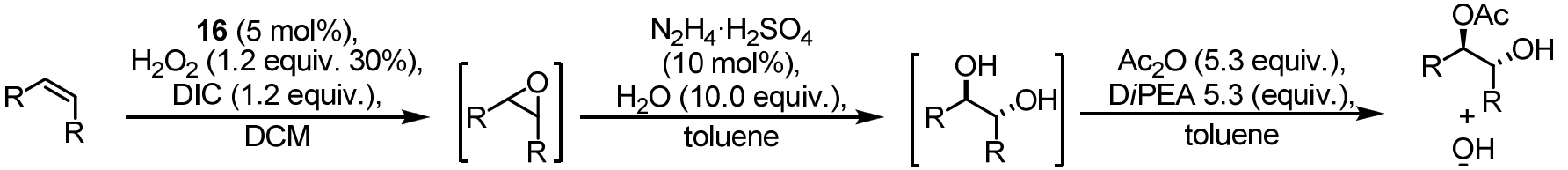
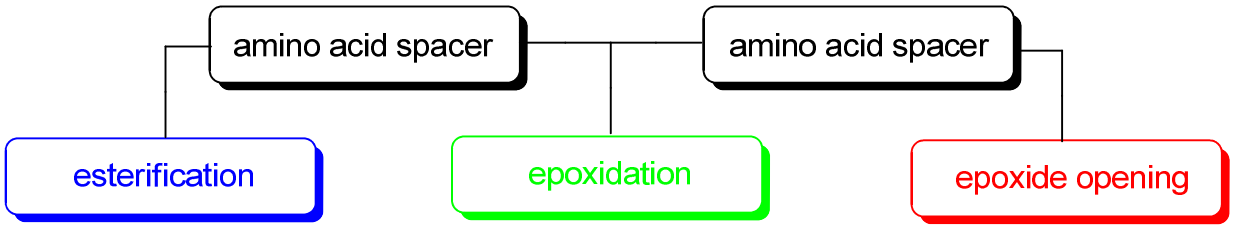
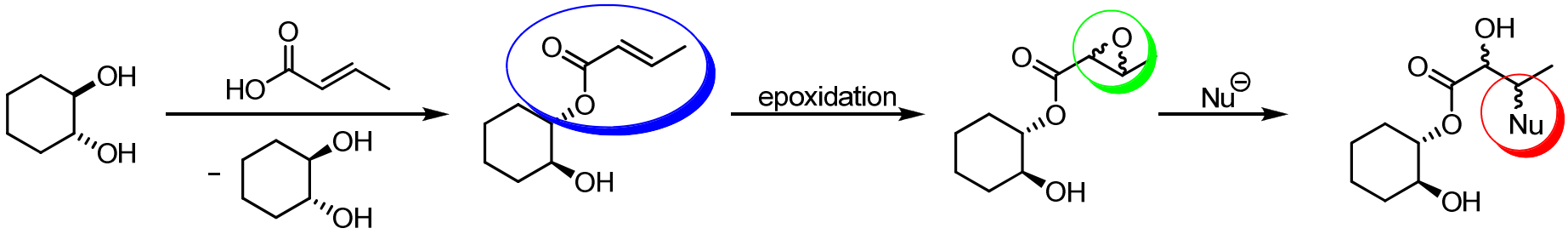


cyclohexene: S = 13
cycloheptene: S = 26

C. E. Müller, R. Hrdina, R. C. Wende, P. R. Schreiner *Chem. Eur. J.* **2011**, *17*, 6309 – 6314

R. Hrdina, C. E. Müller, R. C. Wende, L. Wanka, P. R. Schreiner, in preparation.


amino acid spacer
amino acid spacer
esterification
epoxidation
epoxide opening


OH
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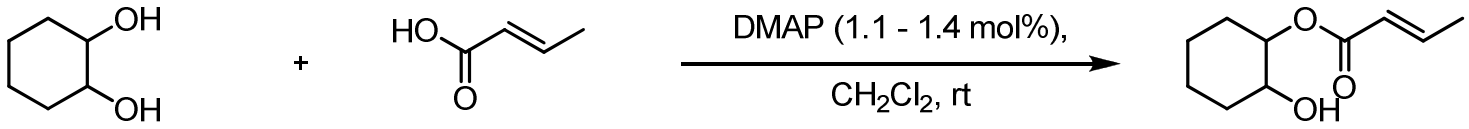
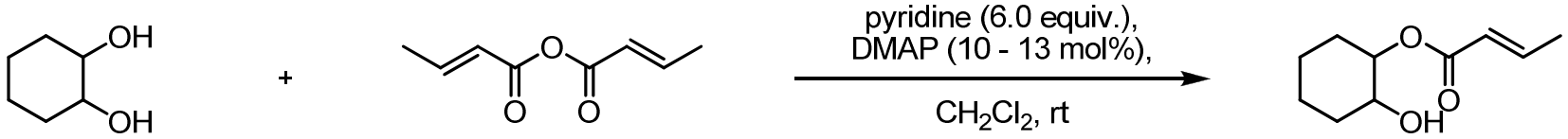
Crotonic Acid -Esterification



diol	carbodiimide	reaction time	yield
trans-diol	DIC (1.0 equiv.)	1 d	0%
trans-diol	EDAC + TEA (1.0 equiv.)	1 d	25%
cis-diol	EDAC + TEA (1.0 equiv.)	1 d	24%

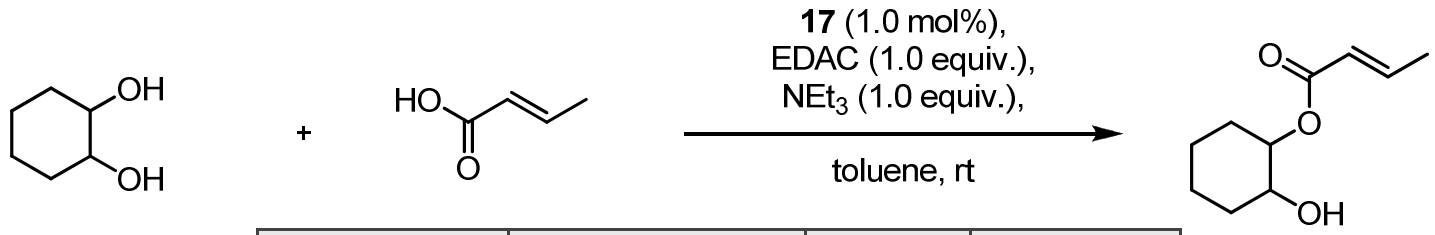


diol	reaction time	yield
trans-diol	16 h	59%
cis-diol	20 h	59%

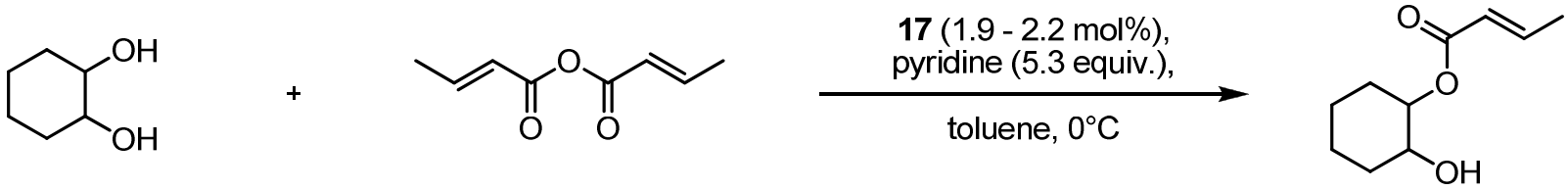
R. Hrdina, C. E. Müller, P. R. Schreiner, *Chem. Commun.* **2010**, *46*, 2689.

C. Fang, T. Tomoyuki, H. Suemune, K. Sakai, *Tetrahedron. Asym.* **1991**, *2*, 389.

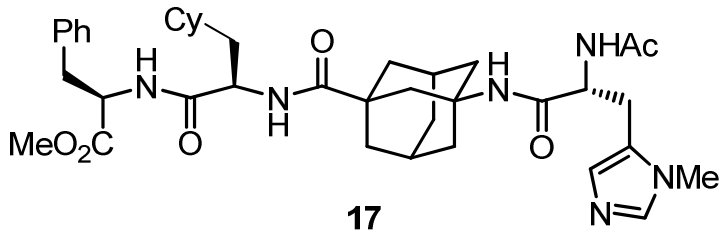
Crotonic Acid -Esterification



diol	reaction time	yield	e.r.
trans-diol	2 d	23%	-
cis-diol	1 d	16%	52:48



diol	reaction time	conversion	e.r.	concerning
trans-diol	1 d	minimal	53:47	*(S,S)*-diol:(*R,R)*-diol
cis-diol	1 d	minimal	67:33	(1*R*,2*S*):(1*S*,2*R*)



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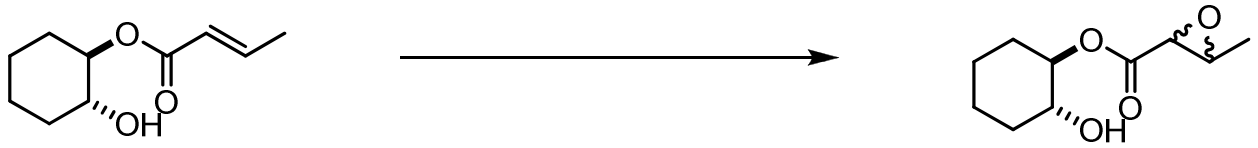
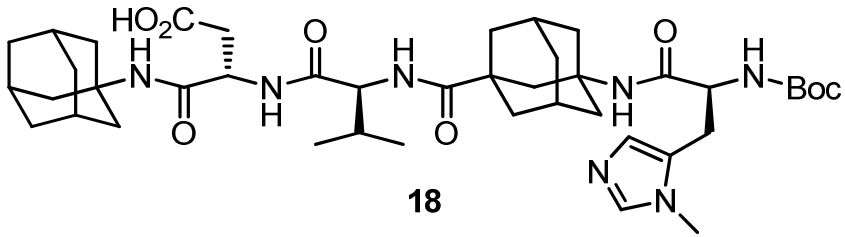
R. Hrdina, C. E. Müller, P. R. Schreiner, *Chem. Commun.* **2010**, *46*, 2689.

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

Crotonic Acid - Epoxidation



epoxidation condition	reaction time	yield	ee
H_2O_2(5.8 equiv., 30%), NaOH (0.07 equiv., 20%), H_2O-MeOH, 0°C	20 h	0%	-
*m*CPBA (1.1 equiv.), CH_2Cl_2, 0°C => rt	3 d	61%	-
H_2O_2(1.2 equiv., 30%), DIC (1.2 equiv.), **18** (1.3 mol%), CH_2Cl_2, rt	2 d	0%	0%
H_2O_2(1.2 equiv., 30%), DIC (1.2 equiv.), **19** (2.1 mol%), CH_2Cl_2, rt	4 d	0%	0%



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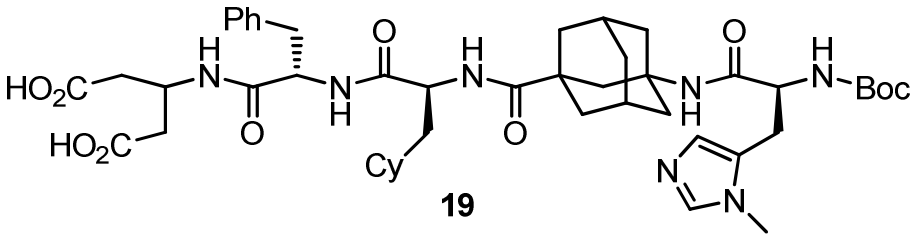

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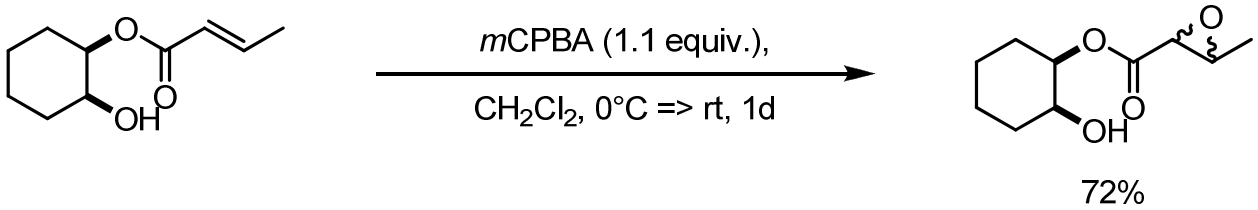
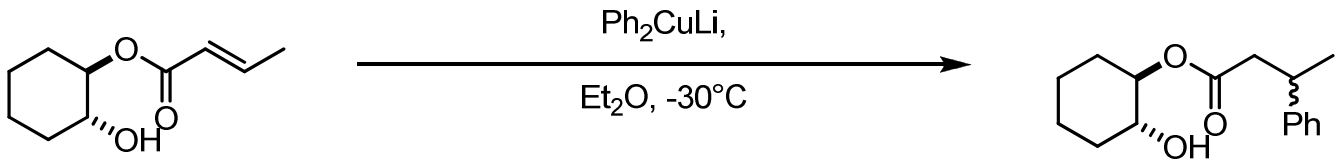


72%

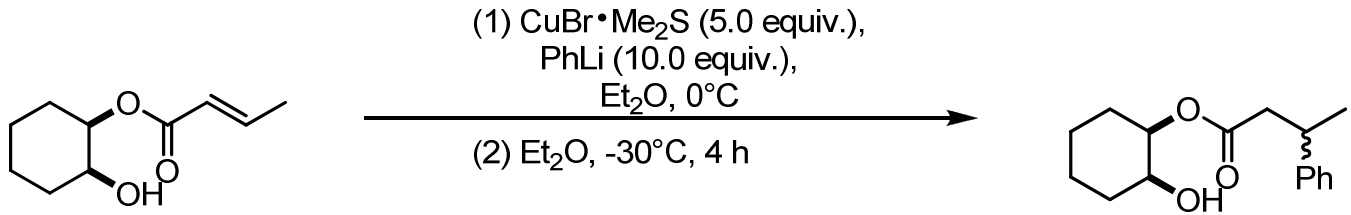
R. Nakajima, T. Ogino, S. Yokoshima, T. Fukuyama, *J. Am. Chem. Soc.* **2010**, *132*, 1236.
M. Welker, S. Woodward, A. Alexakis, *Org. Lett.*. **2010**, *12*, 576.
R. Hrdina, C. E. Müller, R. C. Wende, L. Wanka, P. R. Schreiner, in preparation.

20 (5.0 equiv.) + PhLi (10.0 equiv.)

Et_2O, 0°C



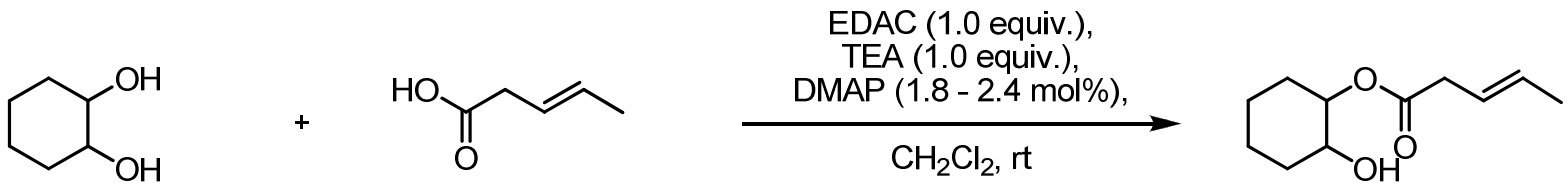
20	reaction time	yield	reisolated reactant
CuI	1 h	0%	77%
CuBr •Me_2S	4 h	39%	0%



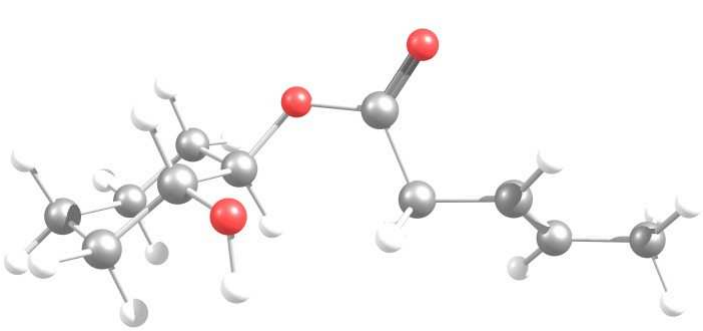
> 10%

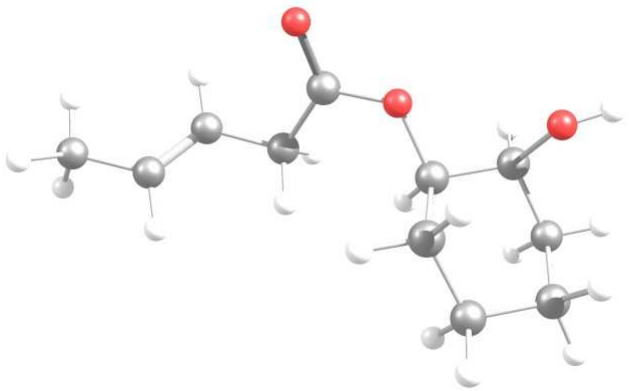
A. Becheanu, A. Baro, S. Laschat, W. Frey, *Eur. J. Org. Chem.* **2006**, 2215.
C. Fang, T. Ogawa, H. Suemune, K. Sakai, *Tetrahedron: Asym.* **1991**, *2*, 389.

Pentenoic Acid- Esterification



diol	reaction time	yield
trans-diol	1 d	70%
cis-diol	1 d	60%





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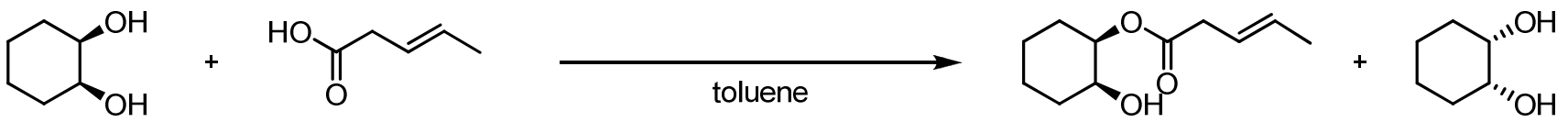
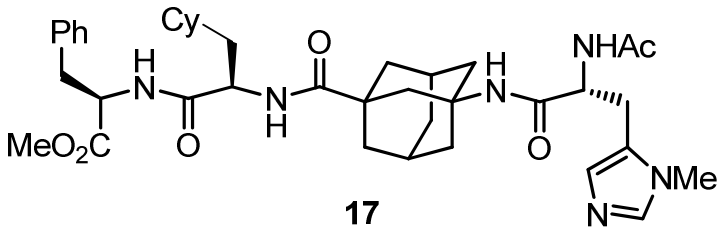
Pentenoic Acid- Esterification

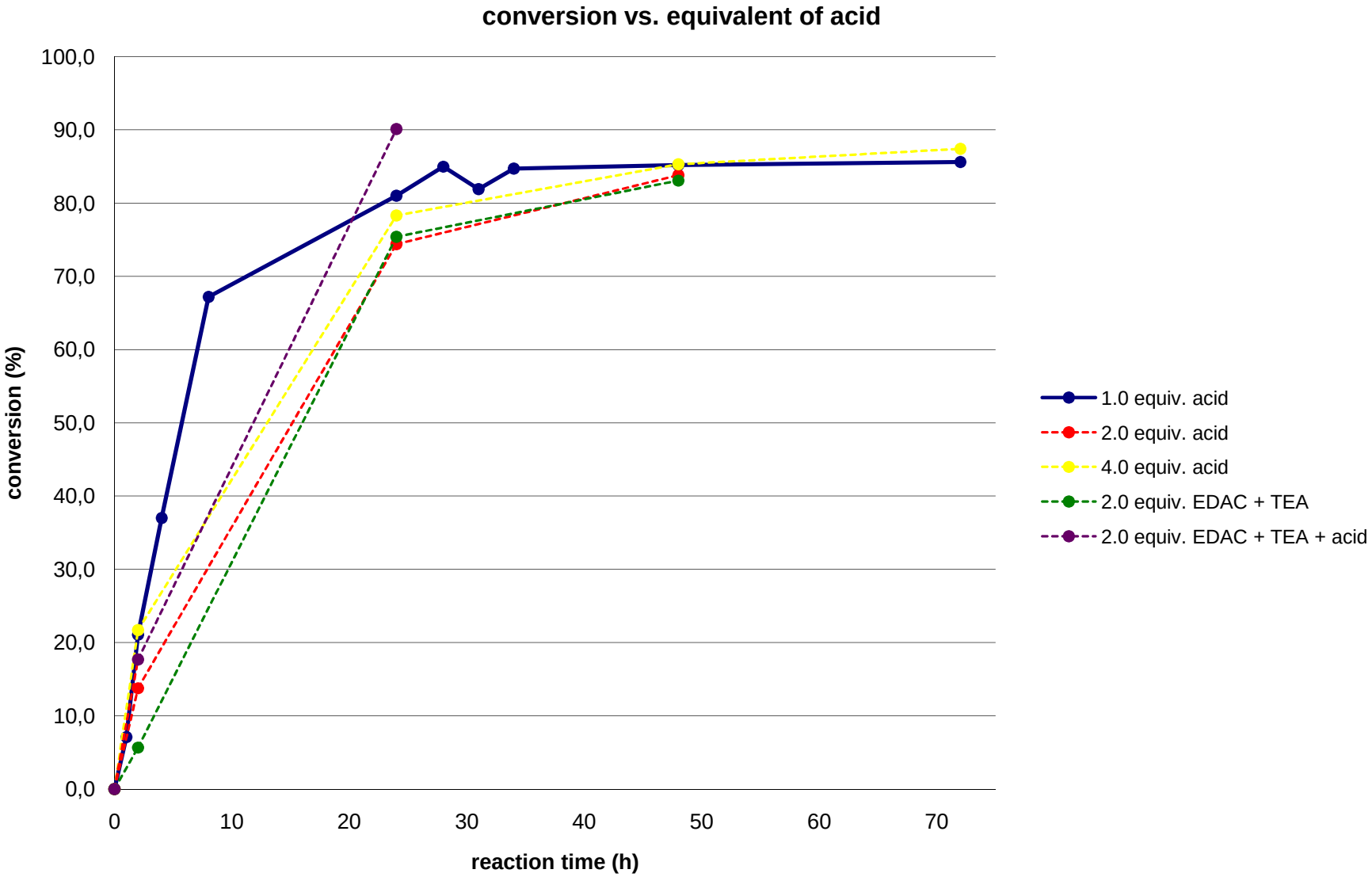


17	carbodiimide	acid	T	t	conversion	ee_{max} (t)
3.0 mol%	EDAC + TEA (1.0 equiv)	1.0 equiv.	rt	48 h	89%	67% (24 h)
2.4 mol%	EDAC + TEA (1.0 equiv)	1.0 equiv.	0°C	31 h	82%	82% (4 h)
2.1 mol%	EDAC + TEA (1.0 equiv)	1.0 equiv.	-15°C	71 h	82%	83% (24 h)
2.6 mol%	EDAC (1.0 equiv)	1.0 equiv.	0°C	48 h	62%	75%
2.2 mol%	EDAC + TEA (1.0 equiv)	2.0 equiv.	0°C	48 h	84%	83% (24 h)
2.7 mol%	EDAC + TEA (1.0 equiv)	4.0 equiv.	0°C	72 h	87%	81% (24 h)
2.2 mol%	EDAC + TEA (2.0 equiv)	1.0 equiv.	0°C	48 h	83%	78% (24 h)
2.2 mol%	EDAC + TEA (2.0 equiv)	2.0 equiv.	0°C	24 h	90%	79% (2 h)
1.8 mol%	DCC (1.0 equiv)	1.0 equiv.	0°C	48 h	67%	83% (24 h)

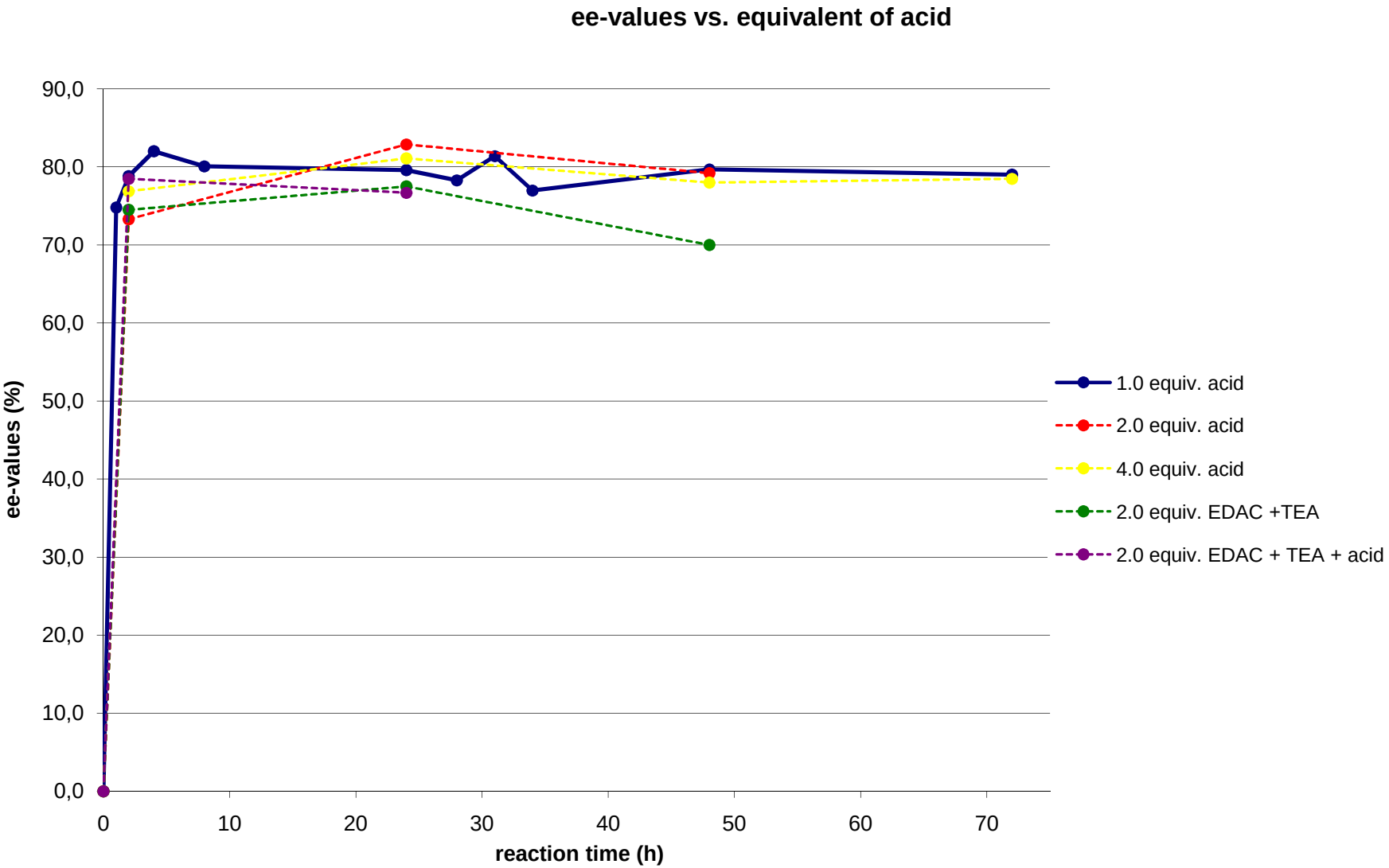


17

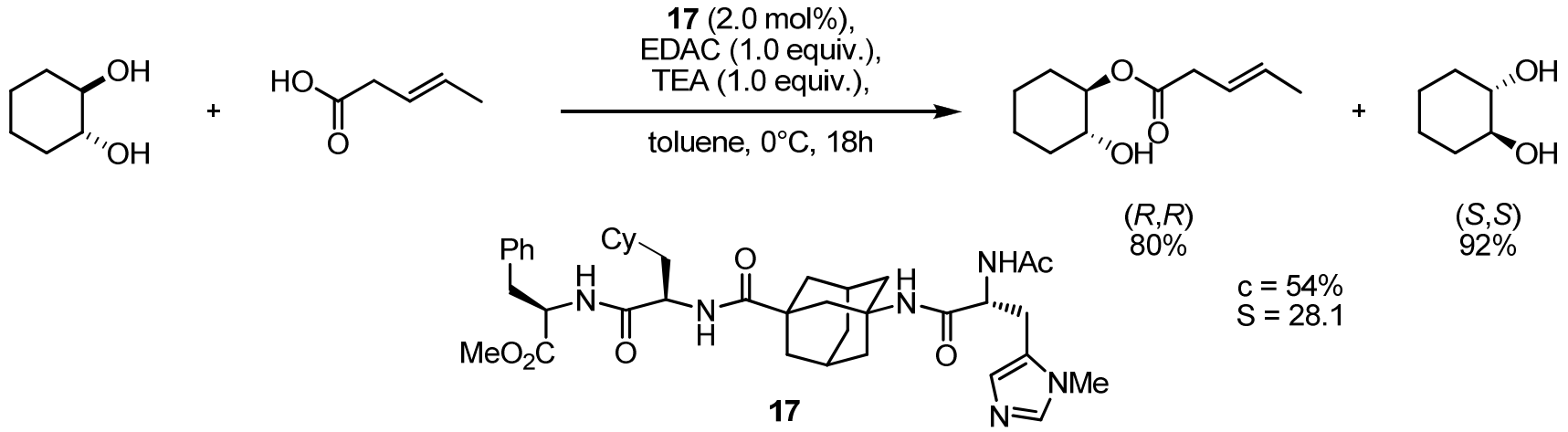
Pentenoic Acid- Esterification

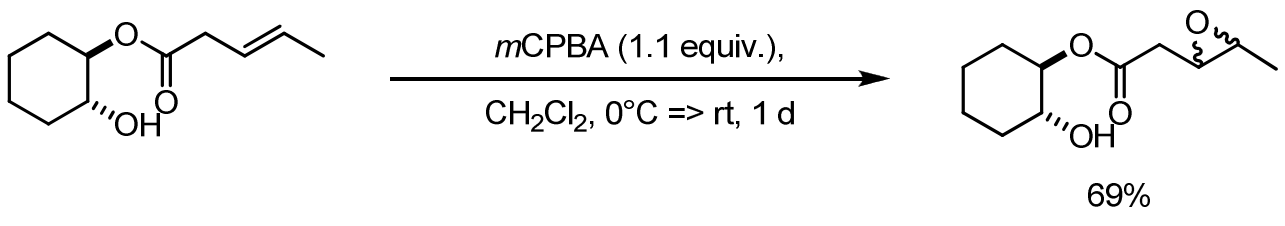


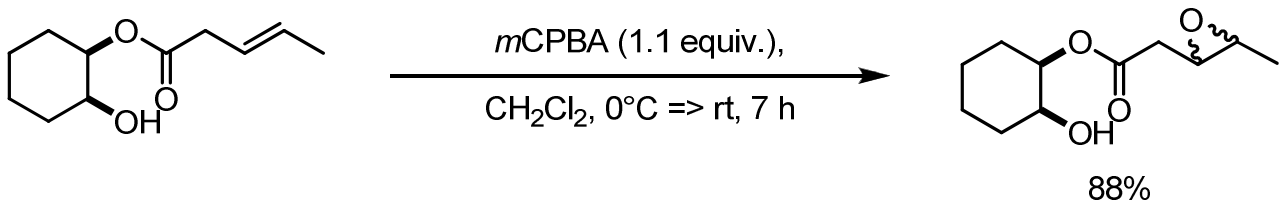
Pentenoic Acid- Esterification



Pentenoic Acid- Esterification & Epoxidation

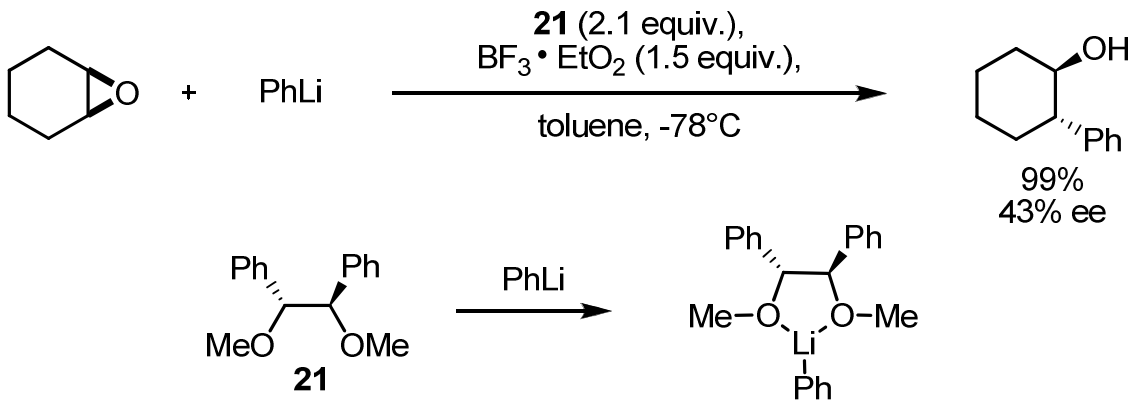


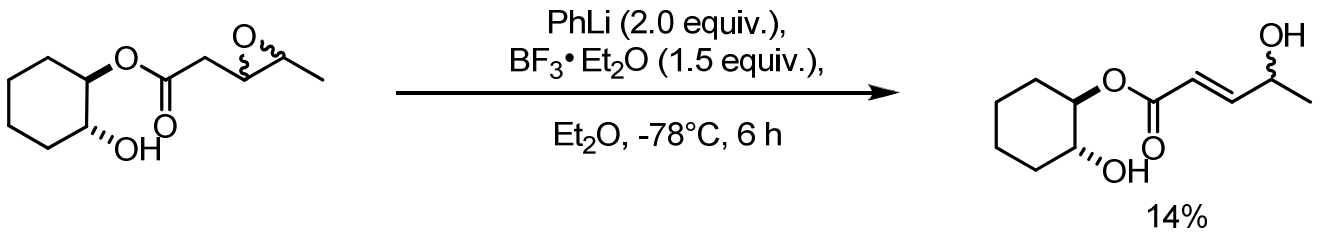


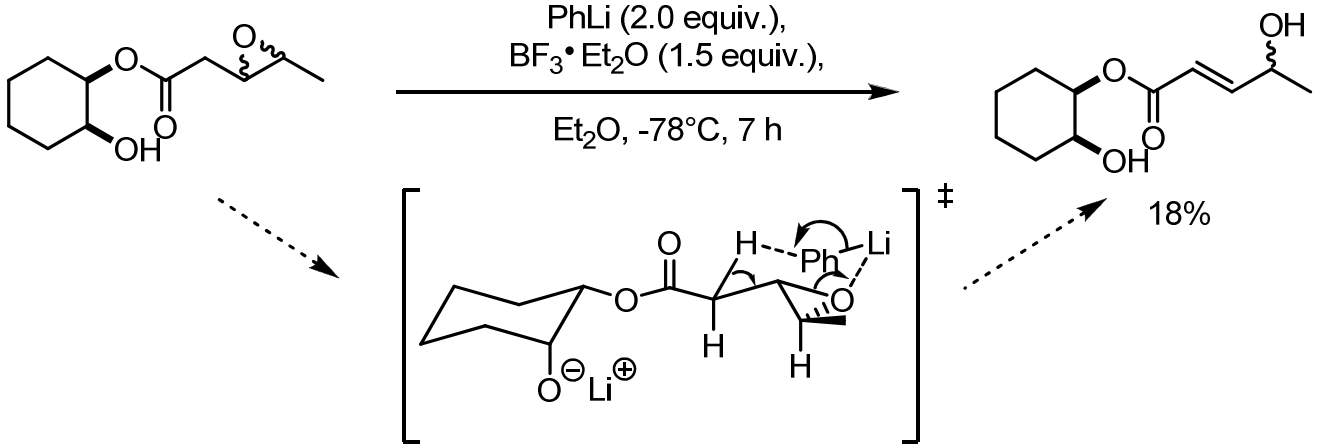


R. Hrdina, C. E. Müller, P. R. Schreiner, *Chem. Commun.* **2010**, *46*, 2689.
L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *Tetrahedron* **2010**, *66*, 3599.

Pentenoic Acid- Epoxide Opening Reaction

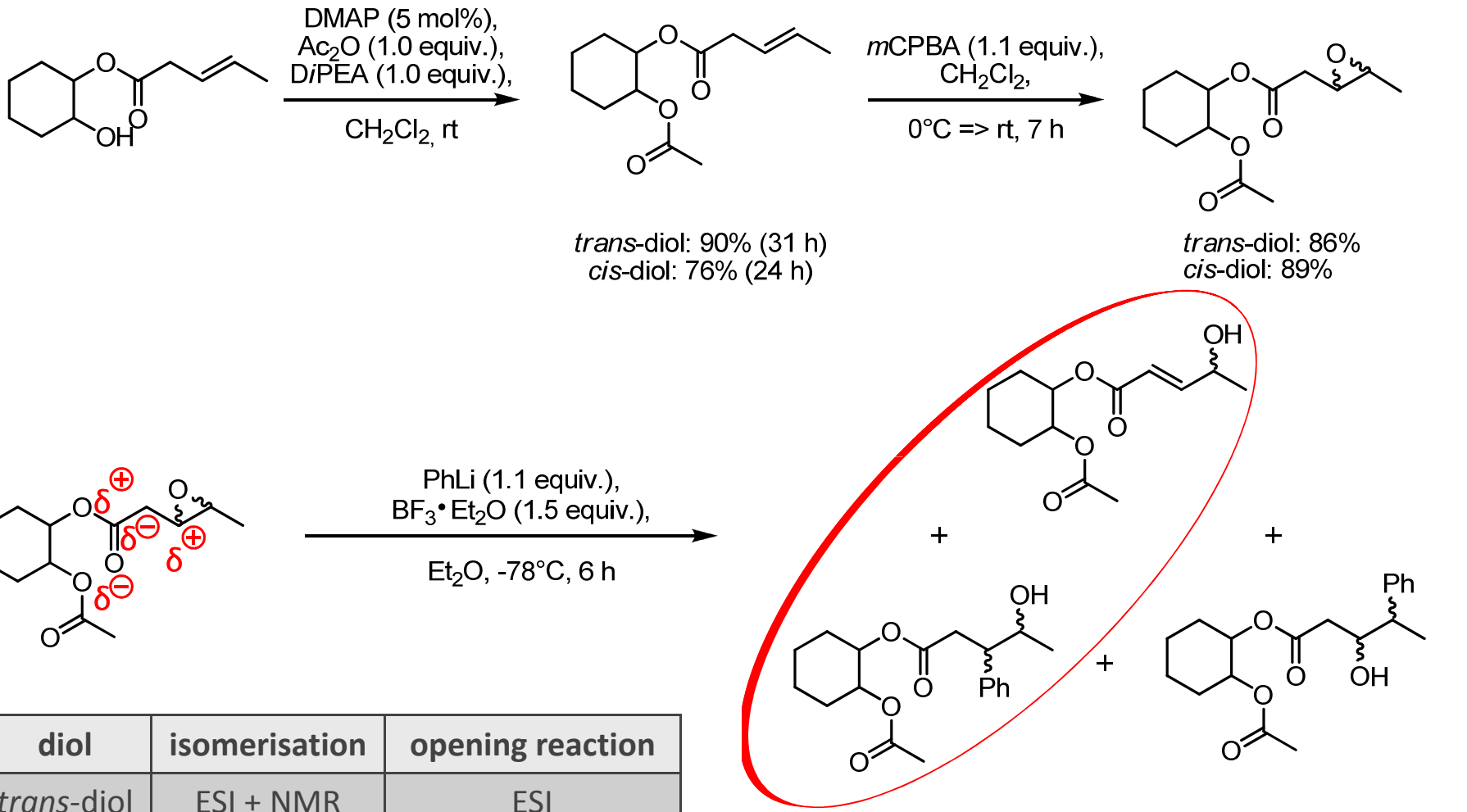






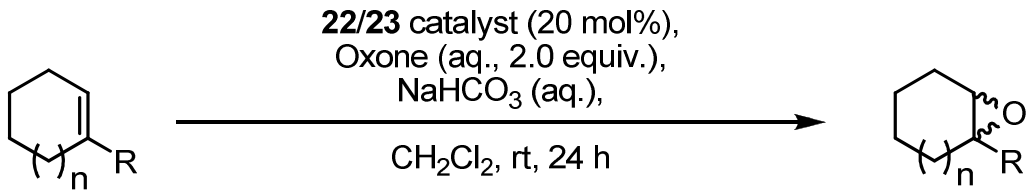
M. Mizuno, M. Kanai, A. Iida, K, Tomioka, *Tetrahedron* **1997**, *53*, 10699.

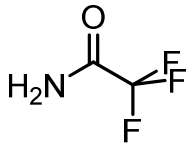
Pentenoic Acid- Epoxide Opening Reaction



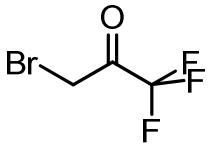
diol	isomerisation	opening reaction
trans-diol	ESI + NMR	ESI
cis-diol	ESI + NMR	ESI

J.-L. Cao, J. Qu, *J.Org. Chem.* **2010**, *75*, 3663.
L. Kiss, E. Forró, R. Sillanpää, F. Fülöp, *Tetrahedron* **2010**, *66*, 3599.
M. Mizuno, M. Kanai, A. Iida, K, Tomioka, *Tetrahedron* **1997**, *53*, 10699.





22



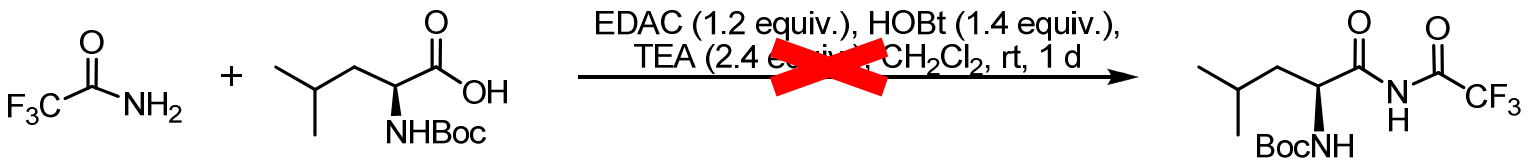
23

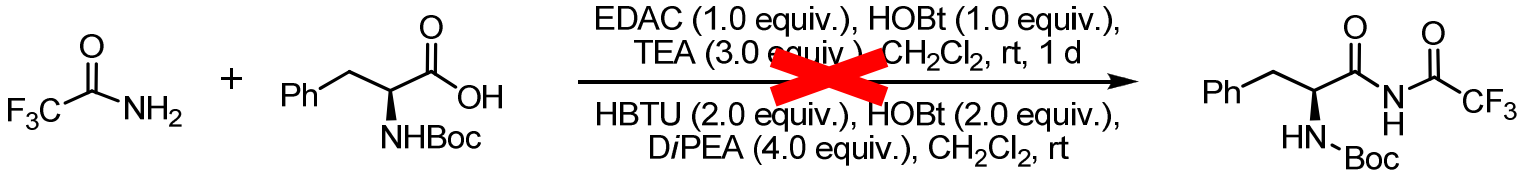
catalyst	n = 1 R = H	n = 1 R = Me	n = 1 R = Ph	n = 3 R = H
22	GC-MS	GC-MS	0%	0%
23	0%	0%	0%	0%

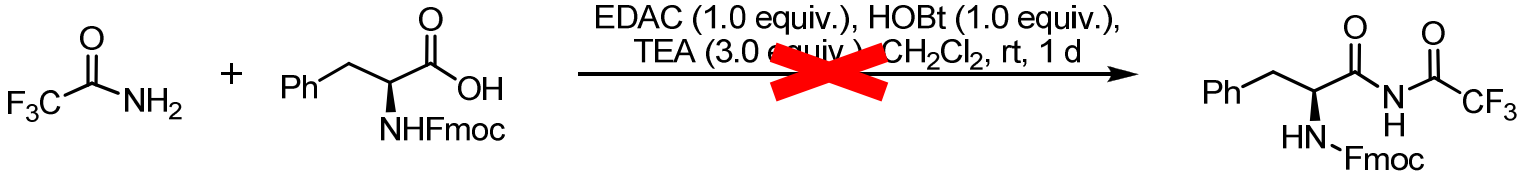
conversion is very low in all cases

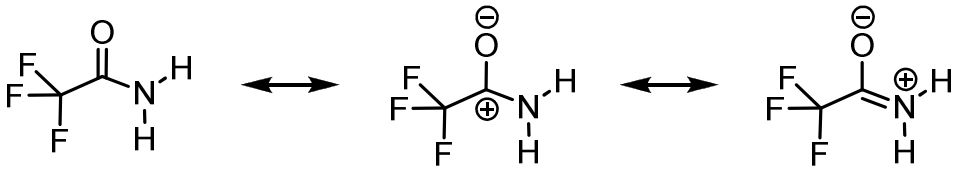
J. Cubillos, I. Montilla, C. Montes de Correa, *Applied Catalysis A: General* **2009**, *366*, 348.
T. R. Boehlow, P. C. Buxton, E. L. Grocock, B. A. Marples, V. L. Waddington, *Tetrahedron Lett.* **1998**, *39*, 1839.

Actual State of Epoxidation Reactions





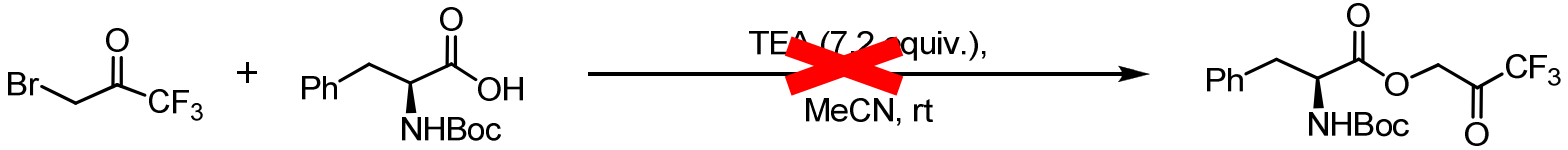


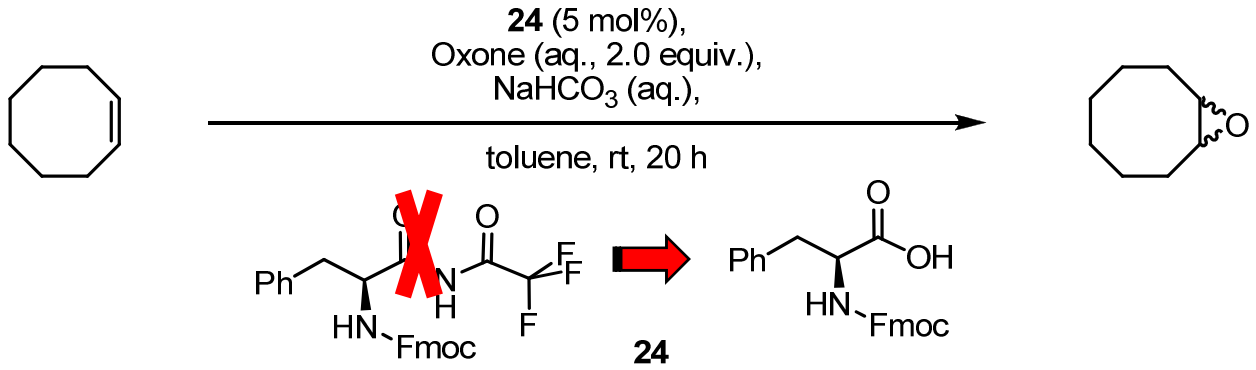


unsuitable for the synthesis of a peptide bonds

N. Koyama, S. Kojima, T. Fukuda, T. Nagamitsu, T. Yasuhara, S. Omura, H. Tomoda, *Org. Lett.* **2010**, *12*, 432.
M. Porcelloni, P. D´Andrea, C. Rossi, A. Sisto, A. Ettorre, A. Madami, M. Altamura, S. Giuliani, S. Meini, D. Fattori, *Chem. Med. Chem.* **2008**, *3*, 1048.

Actual State of Epoxidation Reactions



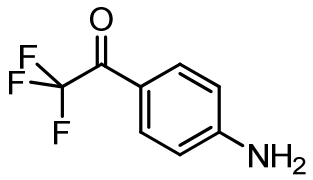


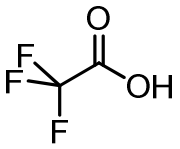
free amino acids could catalyse epoxidation reactions with oxone as oxidant

concept with a selective carbonyl group possible

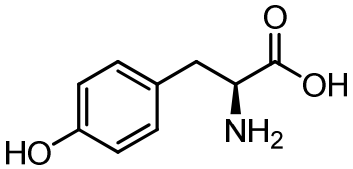
Md. J. Uddin, P. N. P. Roa, E. E. Knaus, *J. Heterocyclic. Chem.* **2003**, *40*, 861.
J. Cubillos, I. Montilla, C. Montes de Correa, *Applied Catalysis A: General* **2009**, *366*, 348.
T. R. Boehlow, P. C. Buxton, E. L. Grocock, B. A. Marples, V. L. Waddington, *Tetrahedron Lett.* **1998**, *39*, 1839.

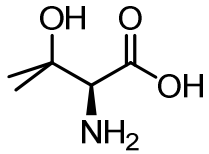
- Catalytic unit
  - Phase transfer conditions
  - Different fluorinated carbonyl compounds
  - Different oxidable alcohols
  - Ammonium salts



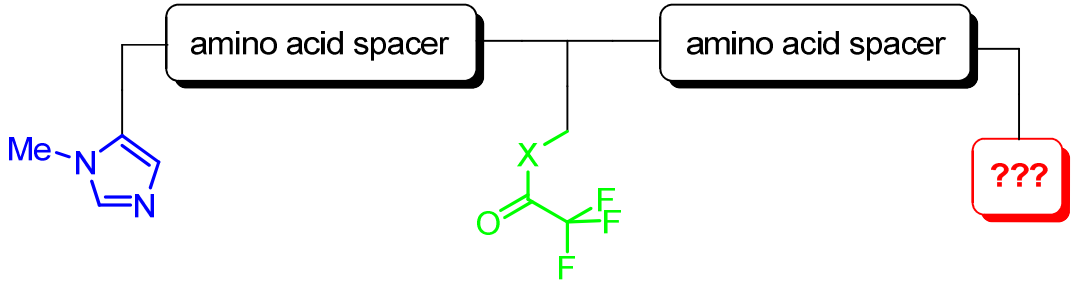


- Synthesis of the peptide backbone
  - Screening via “Otto”
  - Substrate correlated structures

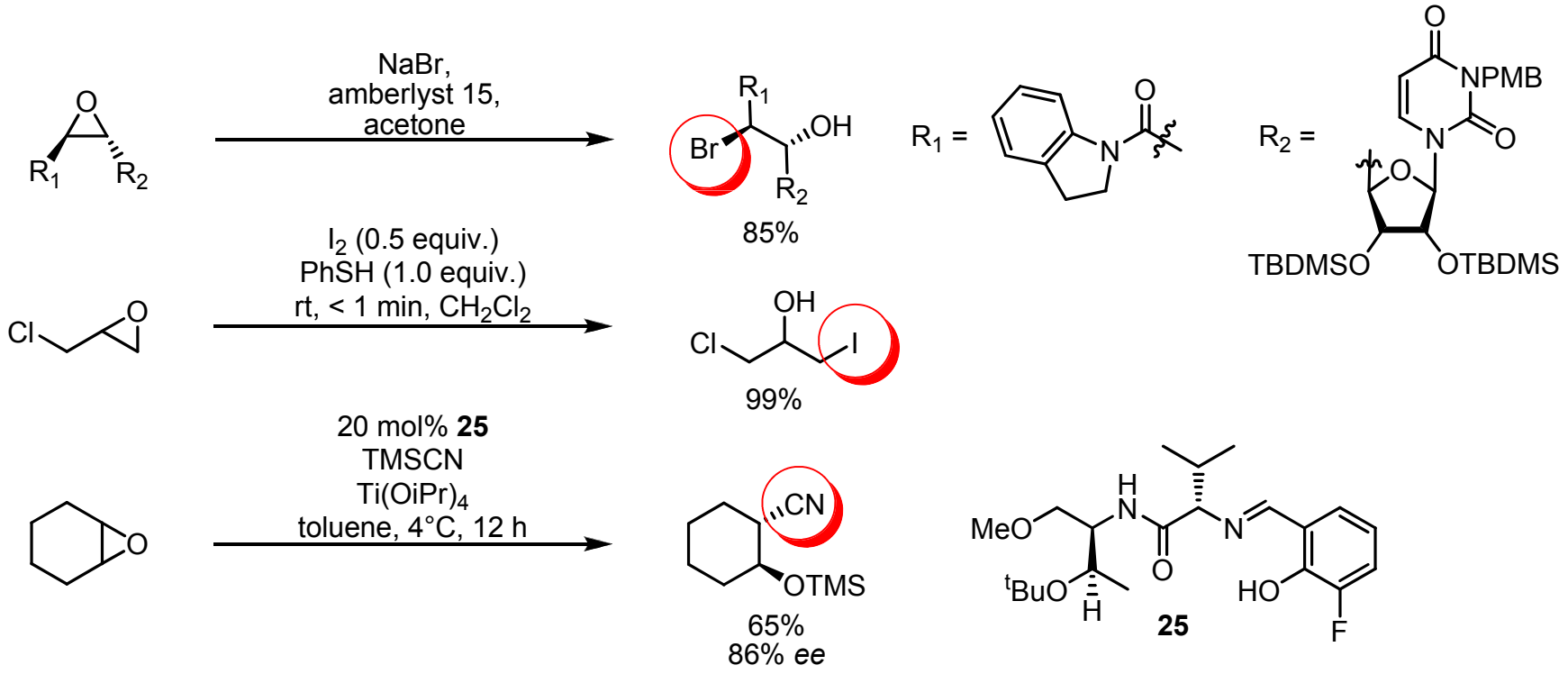




- Combination of the esterification and epoxidation subunit



- Further experiments with Li-organyls
- Other interesting epoxide opening reactions
  - Generation of flexible and useful chiral compounds
  - Important substrates for further reactions



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J. Wu, X. Sun, W. Sun, S. Ye, *Synlett.* **2006**, *15*, 2489.
M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979.

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… Christian Müller, Radim Hrdina, Daniela Zell and Raffael Wende

… Mareike Machuy, Katharina Lippert, Dennis Gerbig and David Ley

… the whole PRS group

... Dr. Erwin Röcker

… “Otto”

Thank you for your attention!