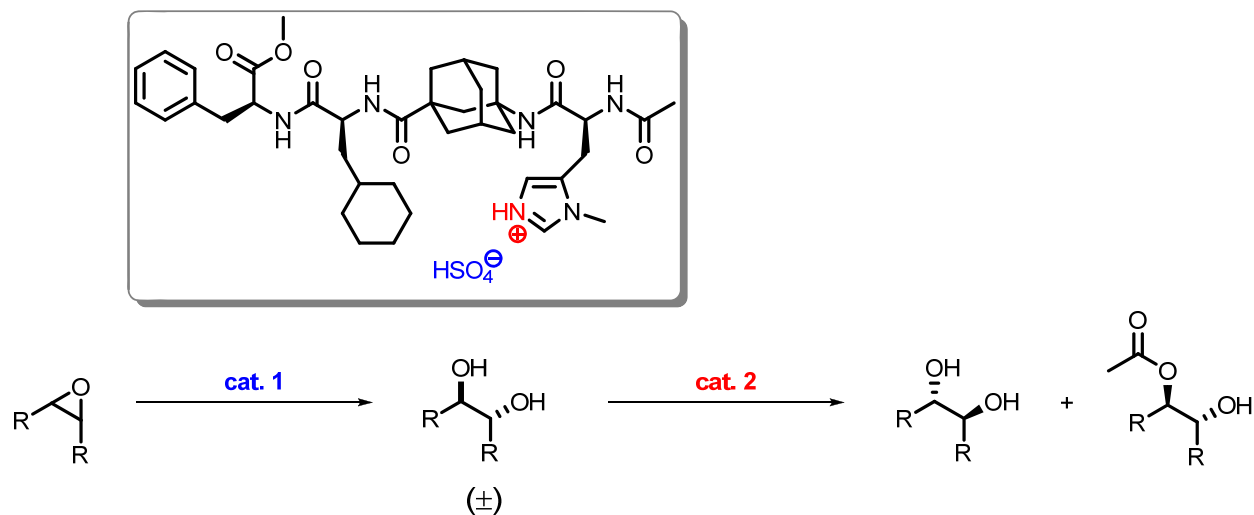


Multifunctional catalysts –

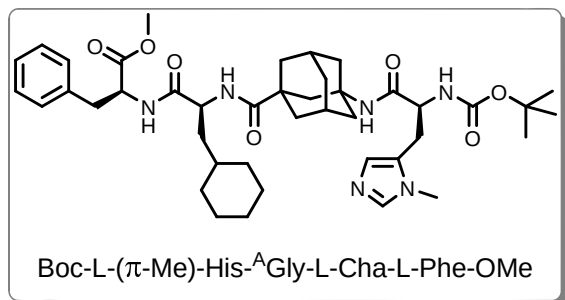
Peptide salts as organocatalysts in tandem reactions



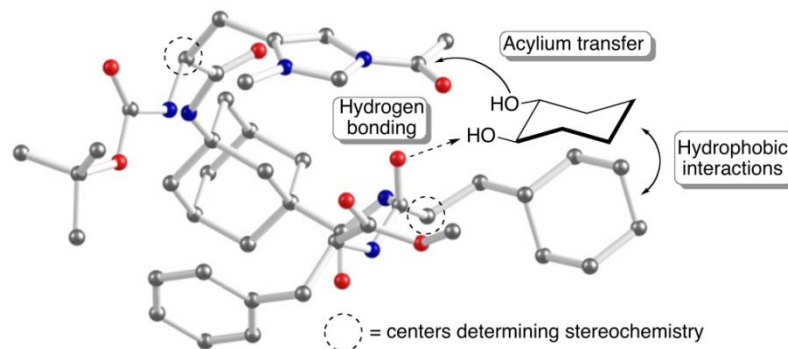
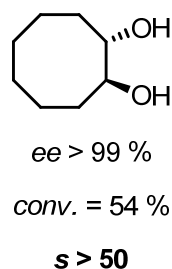
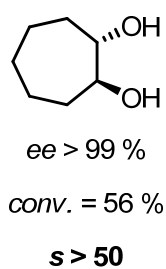
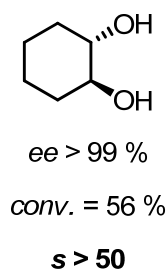
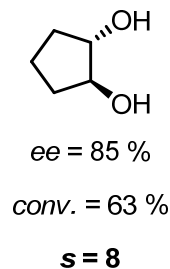
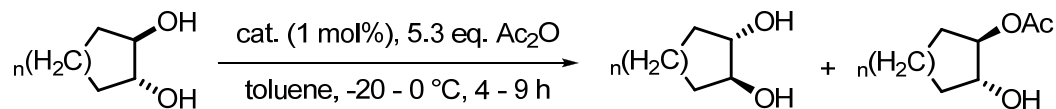
Raffael Wende

*Institute of Organic Chemistry
Justus-Liebig-University Giessen*

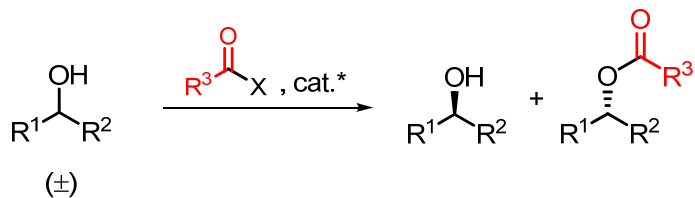
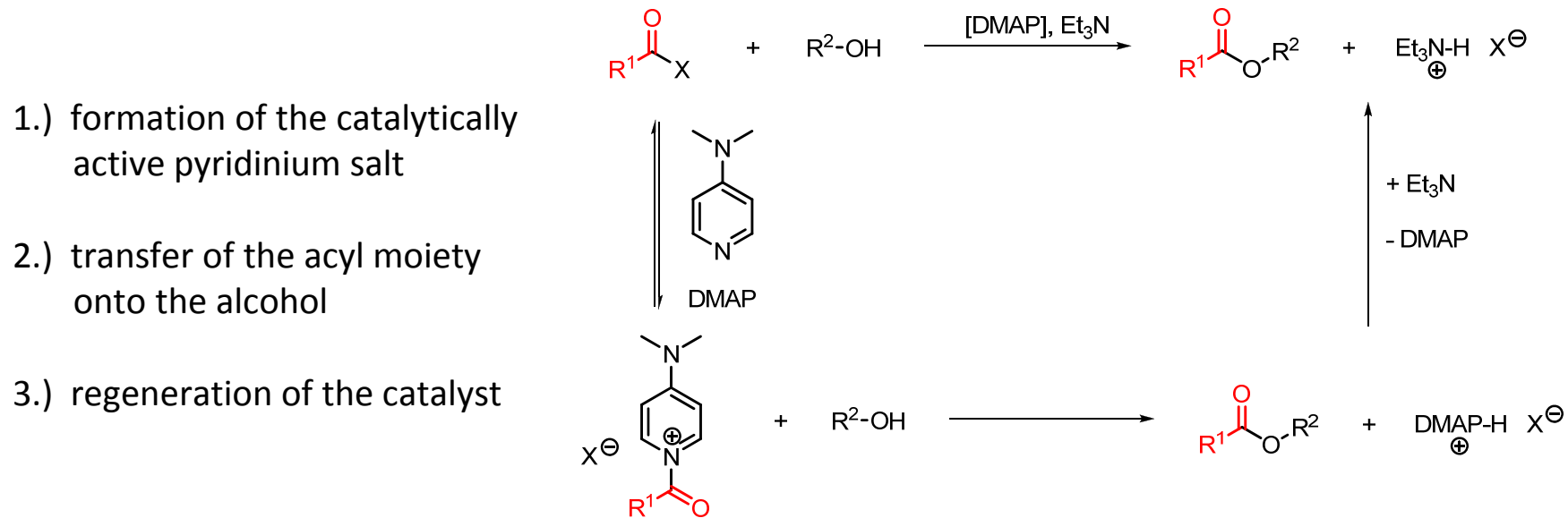
26.11.2010



MODIFICATION OF THIS CATALYST FOR THE USE IN TANDEM REACTIONS



Merck Molecular Force Field (MMFF) model for the enantioselective acylation of *trans*-cyclohexane-1,2-diol in the 'molecular-pocket' of the peptide catalyst. The low lying conformers were optimized at B3LYP/6-31+G(d,p). Hydrogen atoms are omitted for clarity.



$\text{R}^1 \neq \text{R}^2$

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

C = conversion

ee = enantiomeric excess starting material

ee' = enantiomeric excess product

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

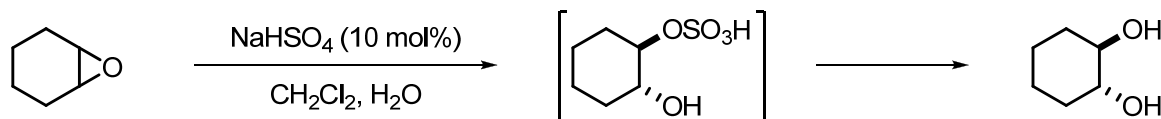
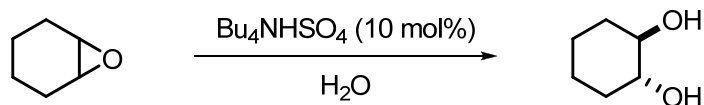
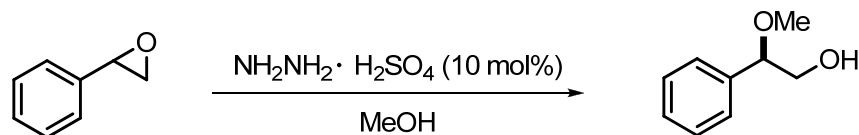
comparison of kinetic resolutions

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



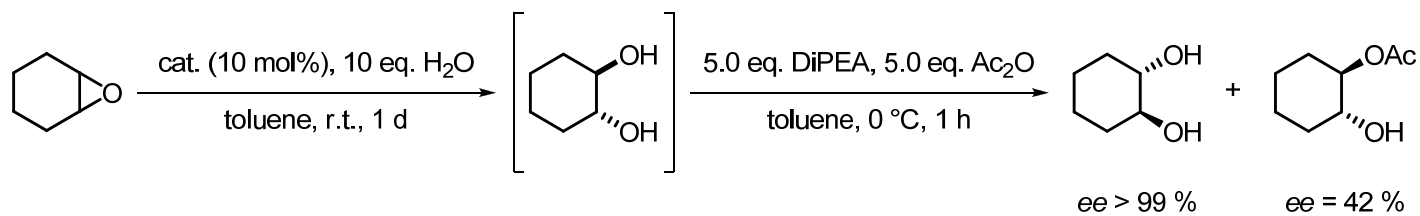
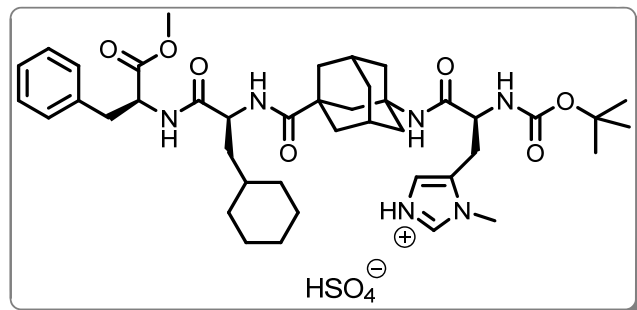
currently used methods are either catalyzed by **metals** or **enzymes** or involve harsh conditions such as **high temperature**, **high acidity** or **basicity**, the use of **oxidizing agents** or **water as solvent** itself

Which approach could be used for this purpose? The use of bisulfate or sulfate salts!





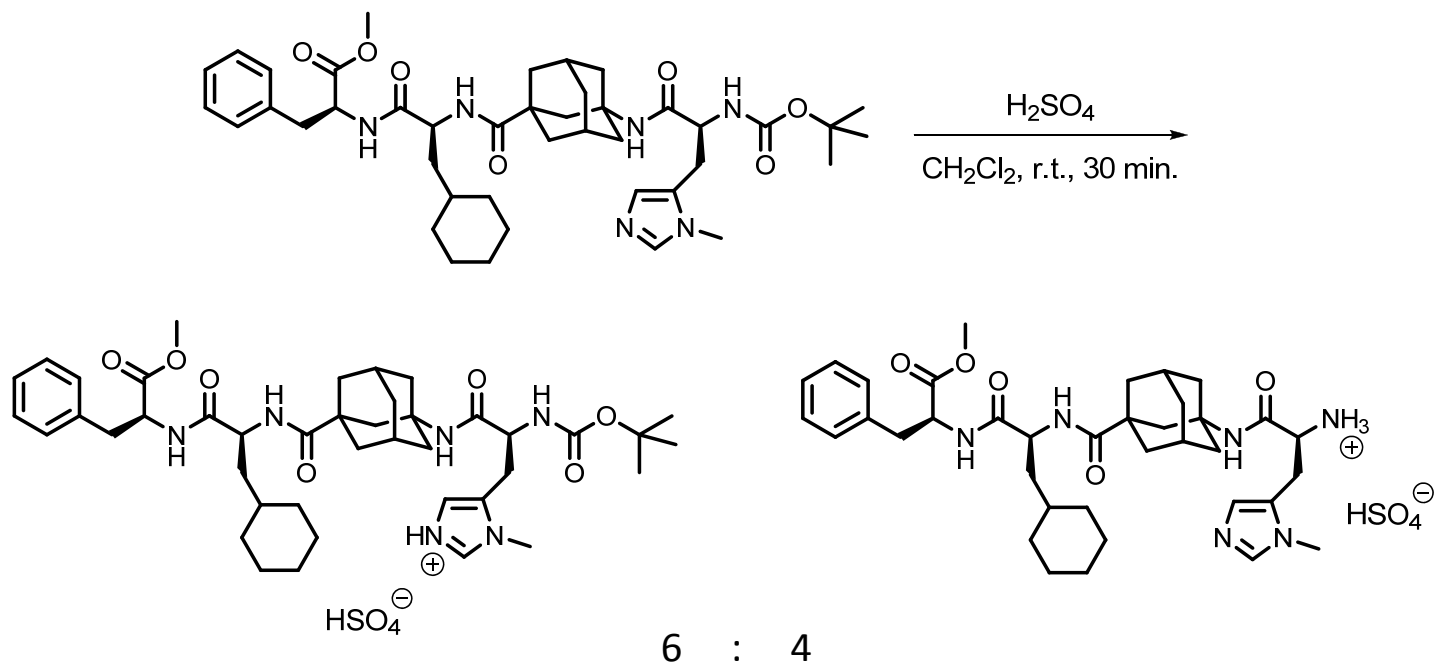
First try – first success!



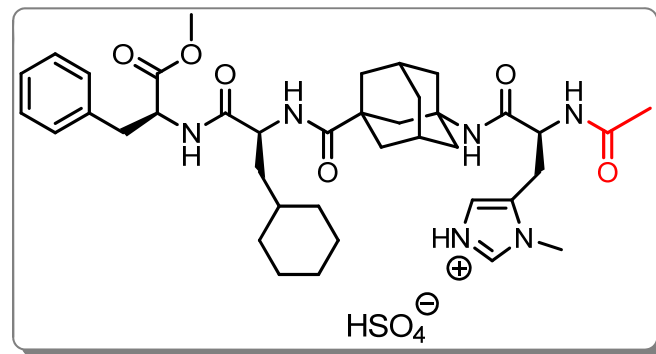
*epoxide is opened by the bisulfate to the racemic diol
which can be subsequently resolved by the peptide*

conv. = 70 %

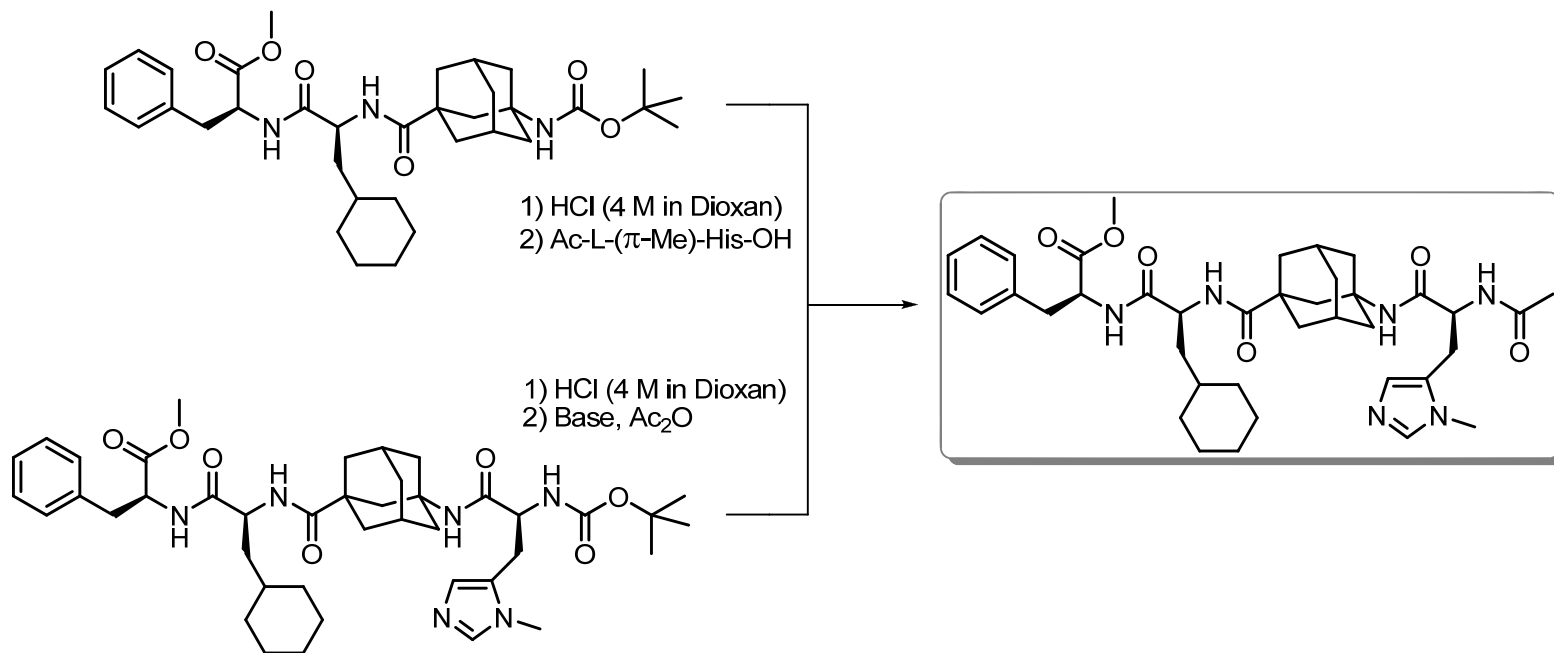
s = 16

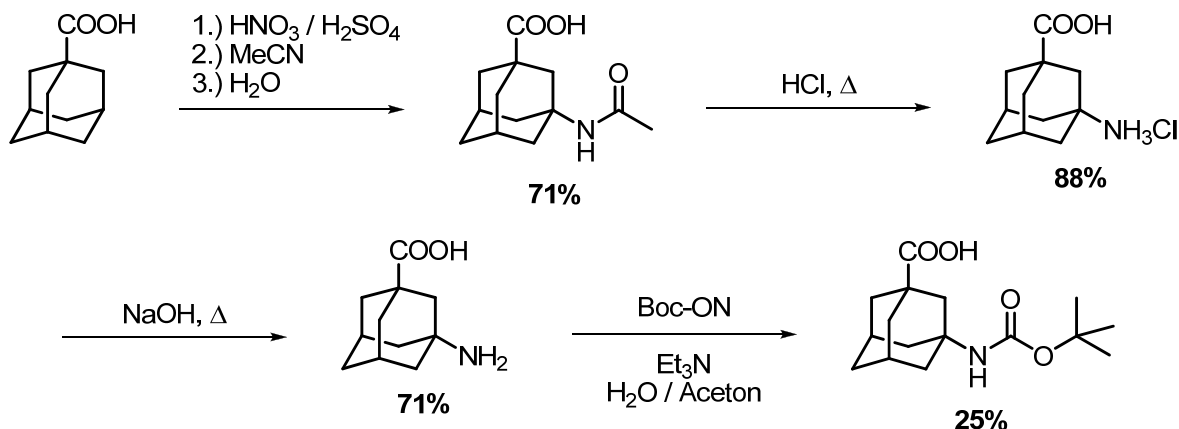


the **acetamide group** is quite similar to the Boc protecting group but should be more stable under this reaction conditions

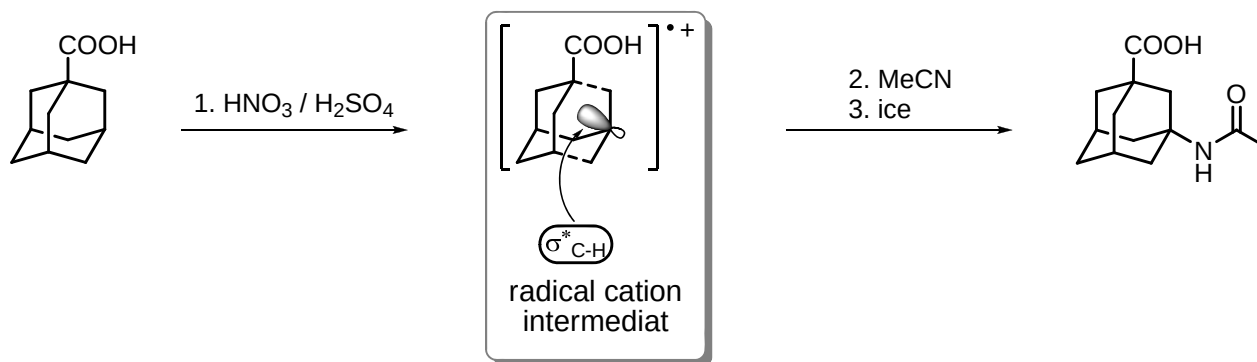


- coupling of the tripeptide with Ac-(π -Me)-His
- introduction of the acetyl protecting group into the already prepared peptide

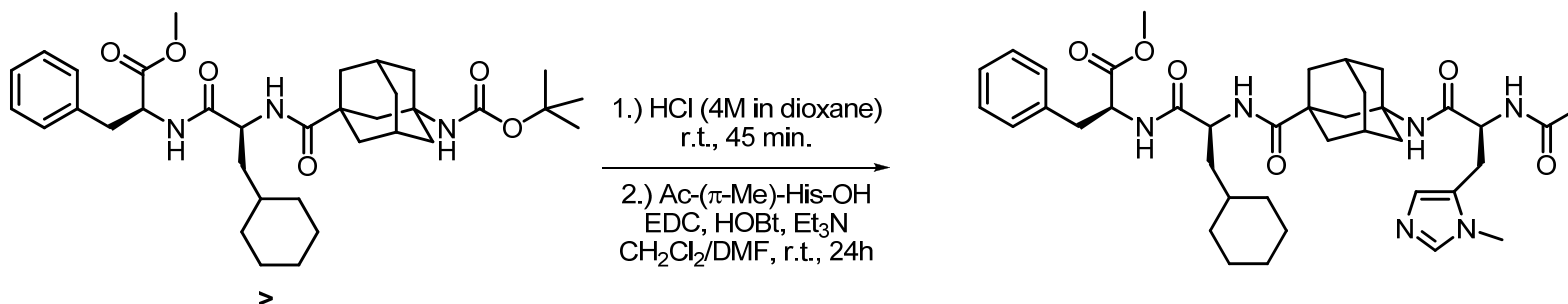
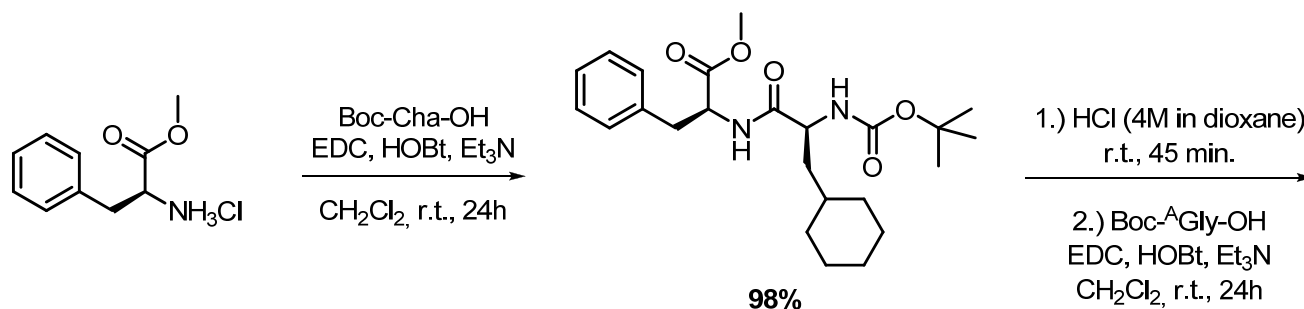
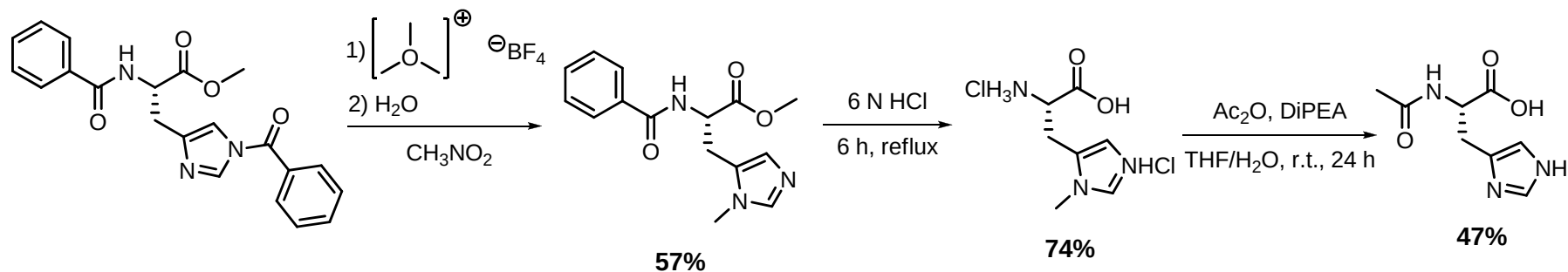




key step of the synthesis: activation of the tertiary C-H bond by Ritter-type reaction

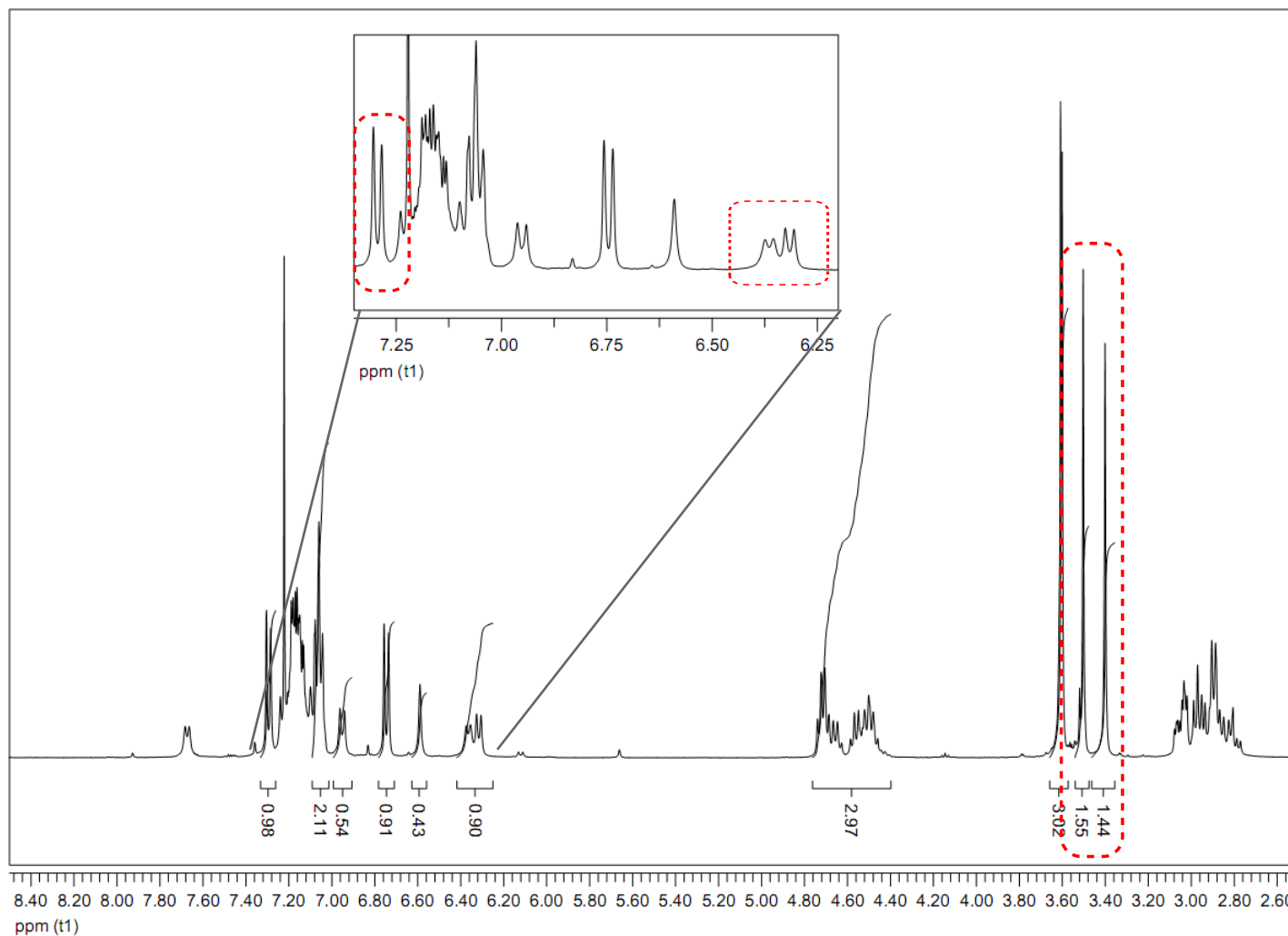
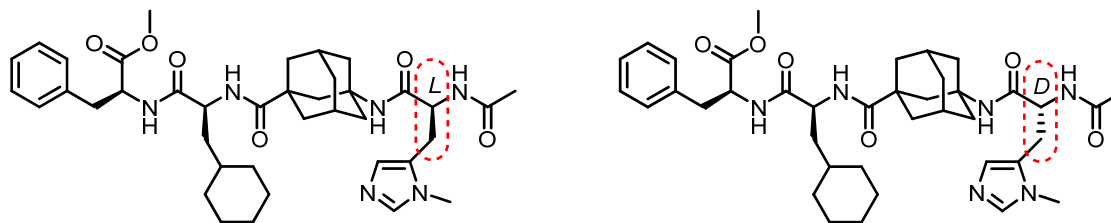


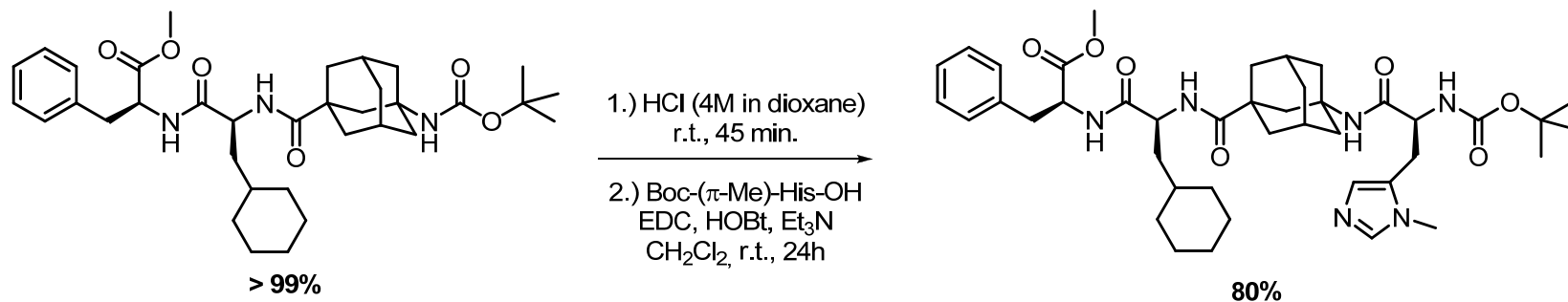
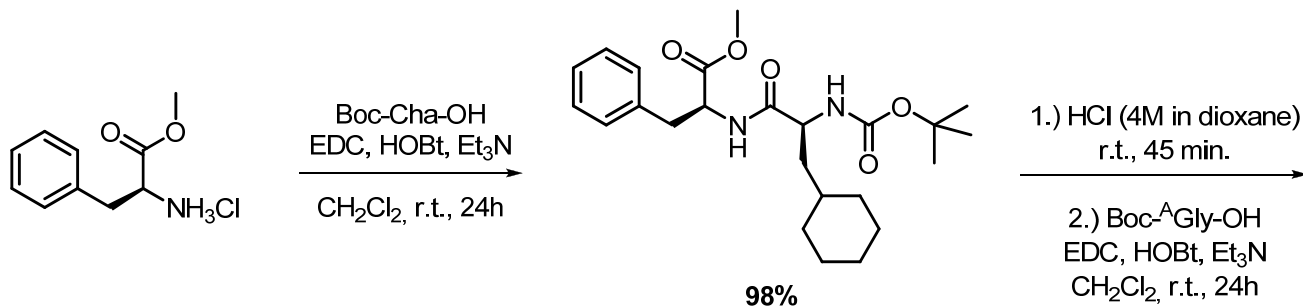
Catalyst preparation – Synthesis of Ac-(π -Me)-His and coupling with the tripeptide



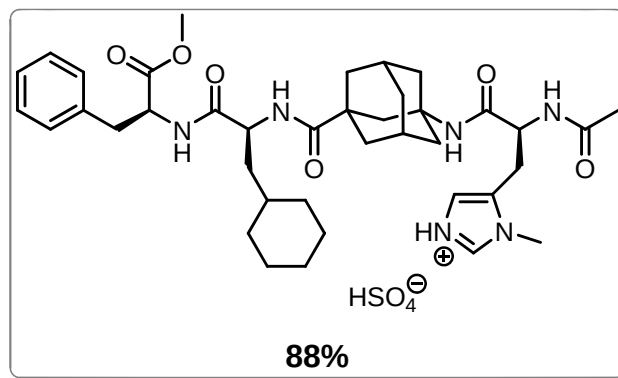
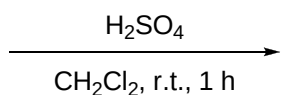
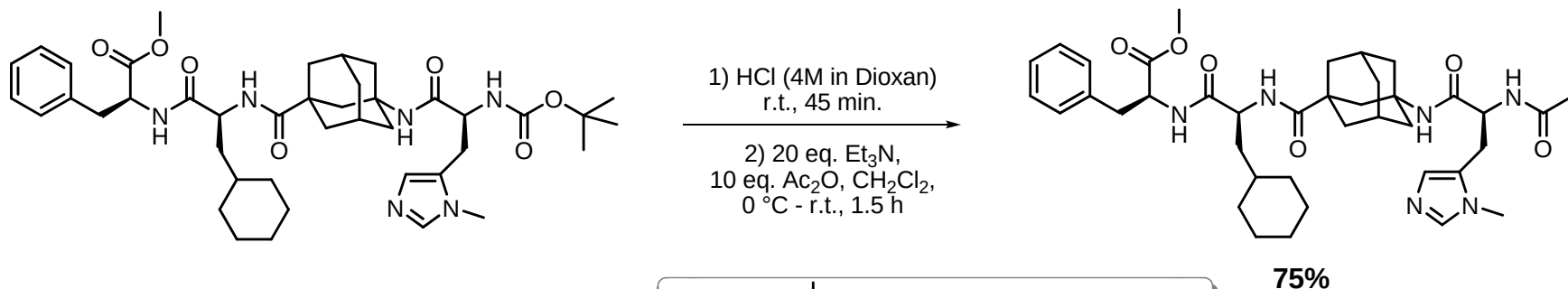
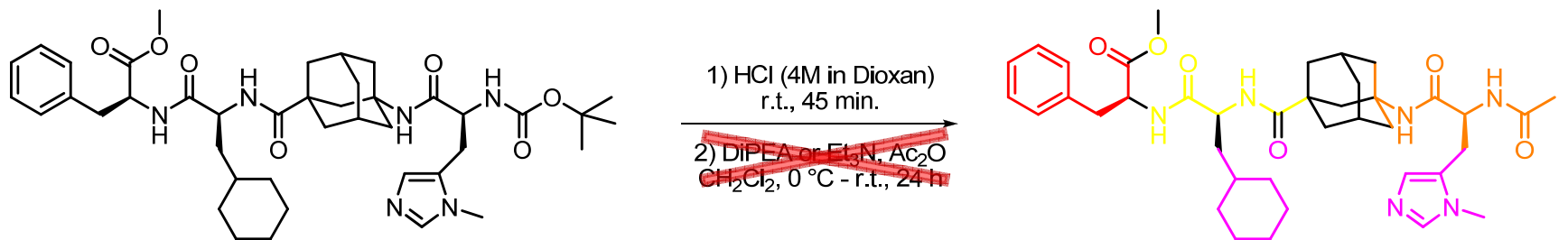
only **low yield** for the obtained peptide and probably **racemization** after the last coupling step

Catalyst preparation – Synthesis of Ac-(π -Me)-His and coupling with the tripeptide

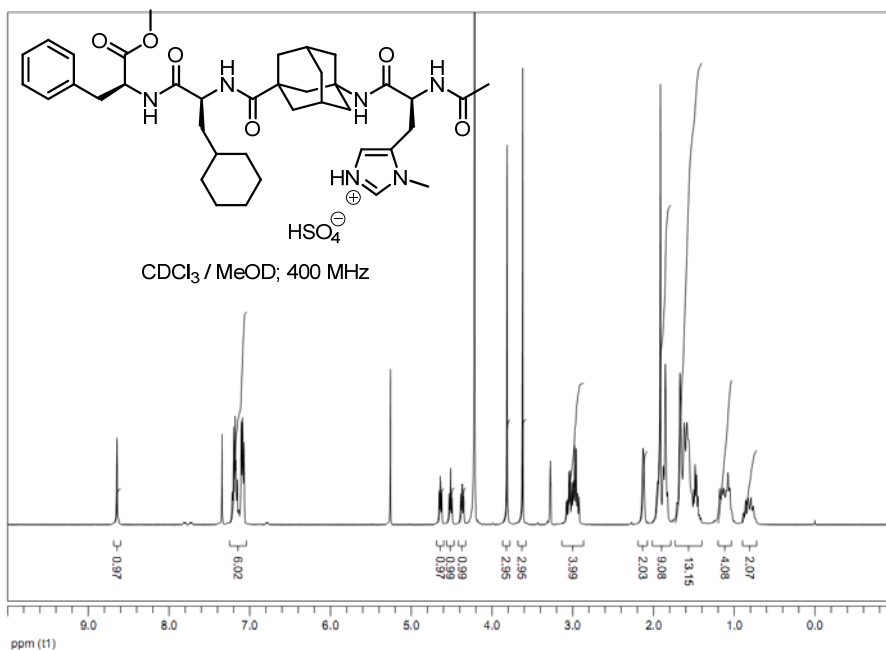
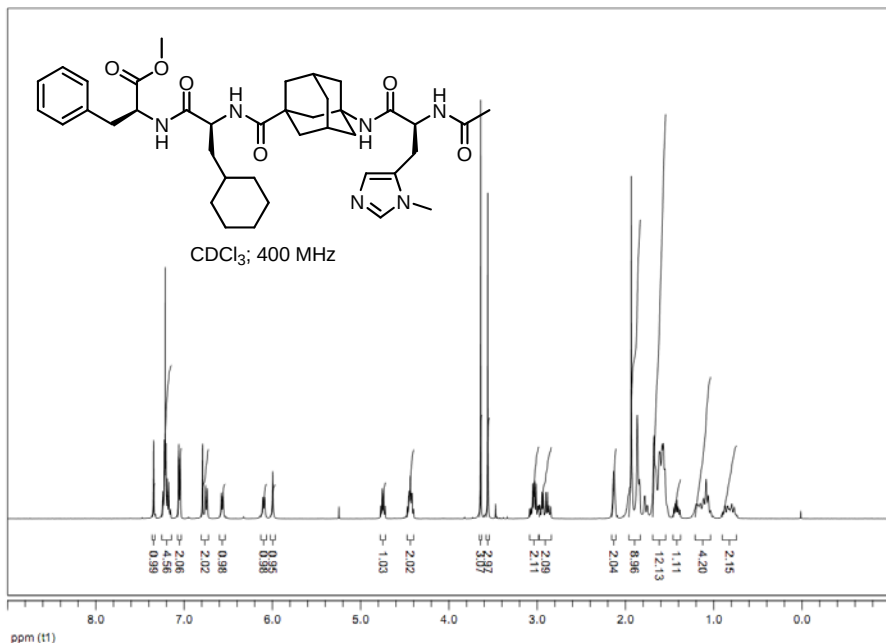




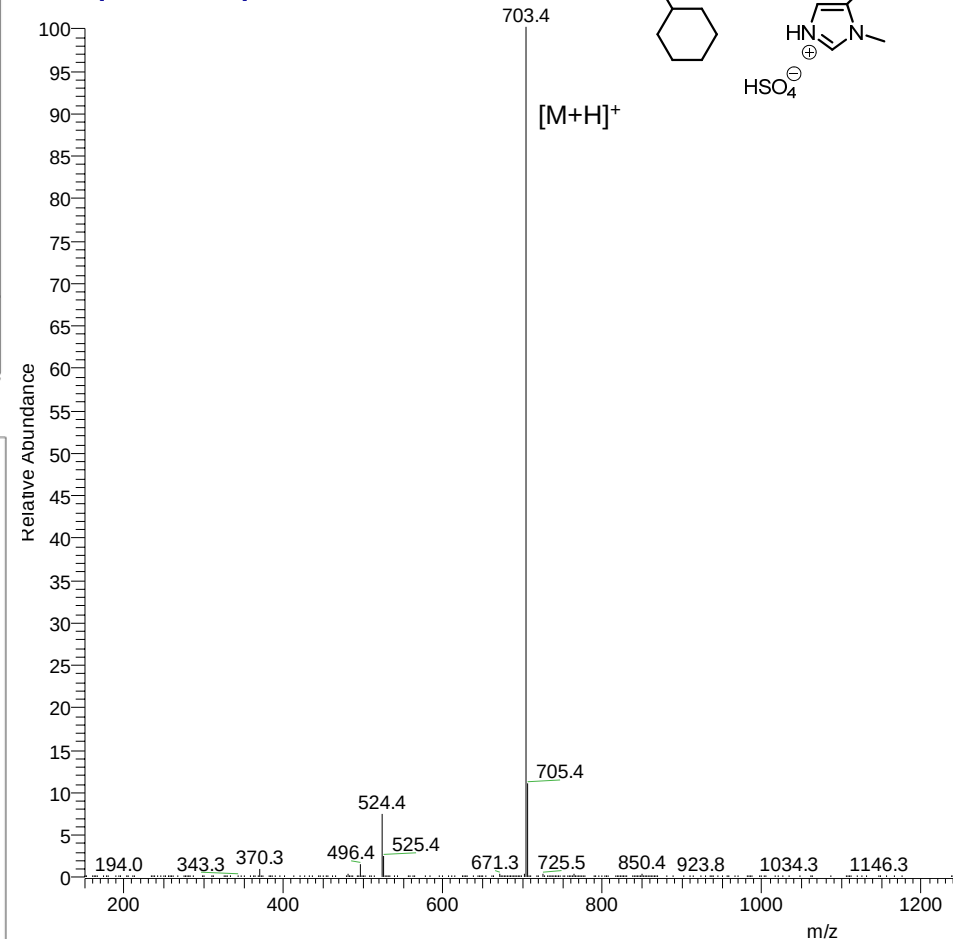
Catalyst preparation – Introduction of the acetyl protecting group and salt formation



Catalyst preparation – Introduction of the acetyl protecting group and salt formation

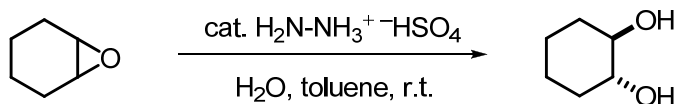


Rcw_104 #1-6 RT: 0.02-0.16 AV: 6 NL: 1.49E7
T: + c ms [150.00-2000.00]





studies on the influence of catalyst loading and water on the efficiency of the epoxide opening reaction with hydrazine sulfate

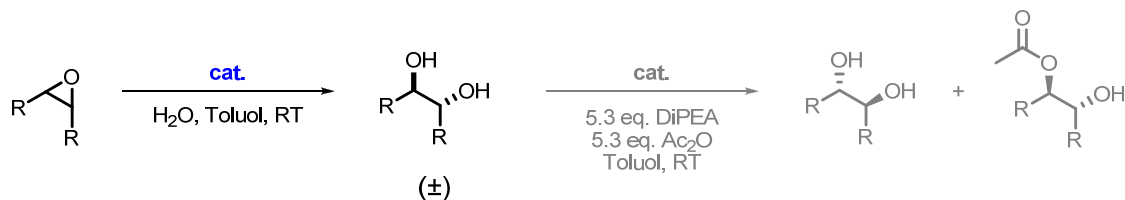


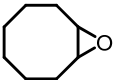
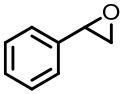
entry	mol% cat.	eq. H ₂ O	time [h]	conv. [%] ^[a]
1	1	10	24 (42)	73 (95)
2	1	20	24	99
3	2	10	24 (42)	89 (> 99)
4	2	20	18	> 99
5	5	10	18	> 99

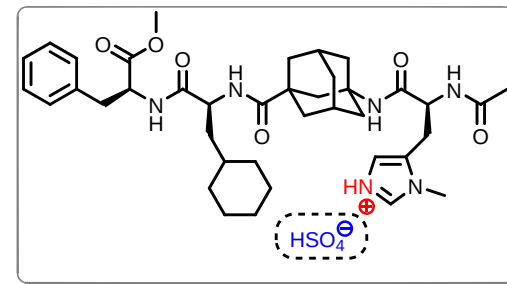
[a] determined by GC-MS using *n*-dodecane as internal standard.

hydrazine sulfate shows a very good performance as catalyst in epoxide opening reactions

Catalysis – Epoxide opening reactions



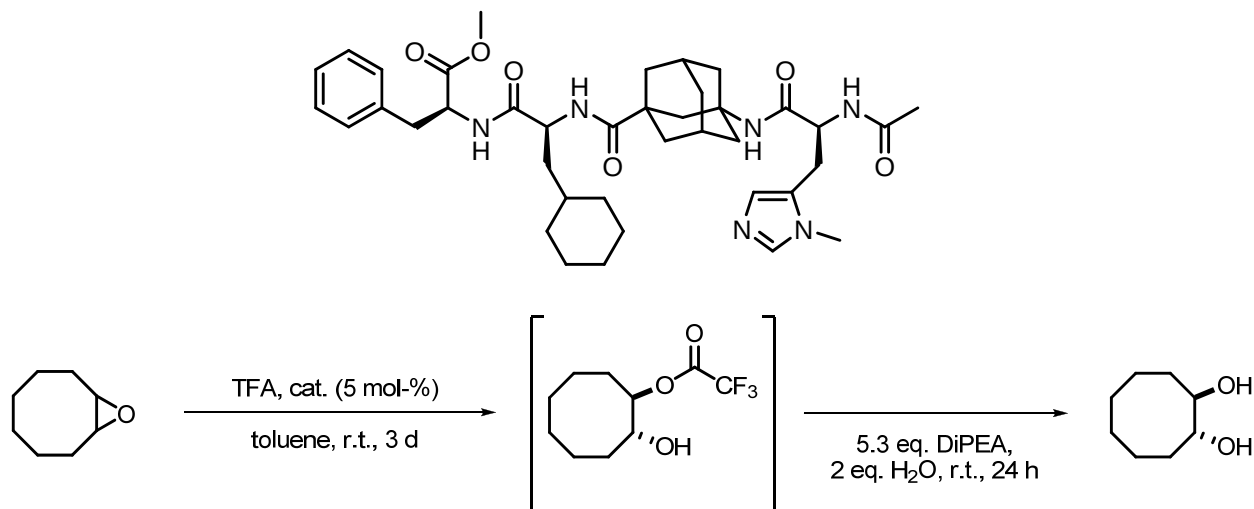
substrate	mol% cat.	eq. H ₂ O	time [h]	conv. [%] ^[a]
	1	20	24 (42)	58 (65)
	2	20	24 (42)	80 (84)
	5	10	24 (42)	79 (85)
	5	20	18	> 99
	2	20	24	89
	5	20	18	> 99
	2	20	42	51
	5	20	42	83
	2	20	72	8
	5	20	24	> 99
 [b]	5	20	24	> 99
	5	20	72	61
	5	10	18	> 99
	5	20	6,5	> 99



epoxides are efficiently opened by the peptide salt

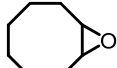
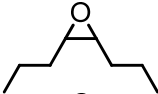
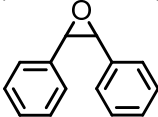
[a] Determined by GC-MS using *n*-dodecane as internal standard.

[b] Obtained from epoxidation of 3-hexene with *m*-CPBA and added to the reaction mixture as 1M solution

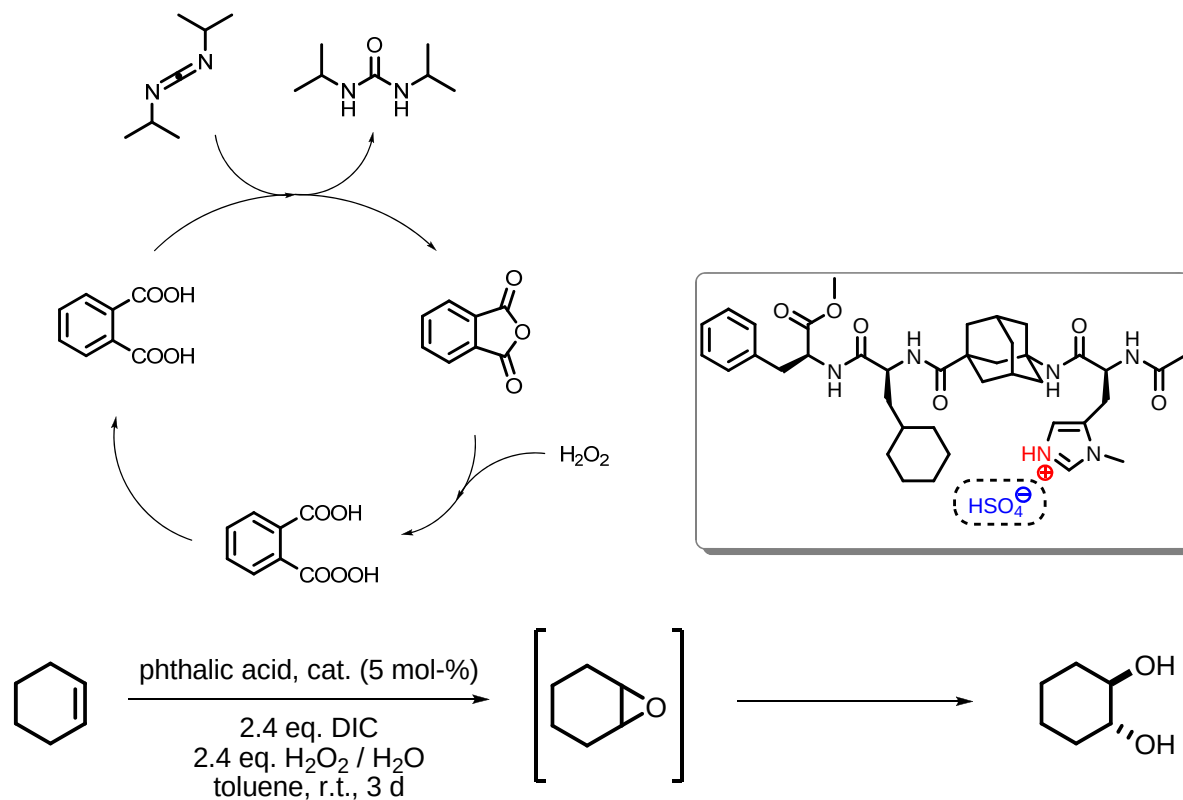


epoxides which were not opened by the peptide salt, can be opened by trifluoroacetic acid

the resulting TFA-ester hydrolyzes readily to the corresponding diol in the presence of base and water

substrate	conv. [%] ^[a]
	76
	> 99
	> 99

[a] determined by GC-MS using *n*-dodecane as internal standard.

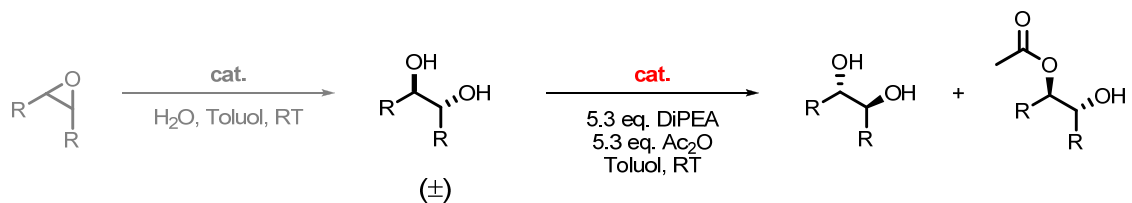


epoxidation through *in situ* formation of a peracid prior to epoxide opening

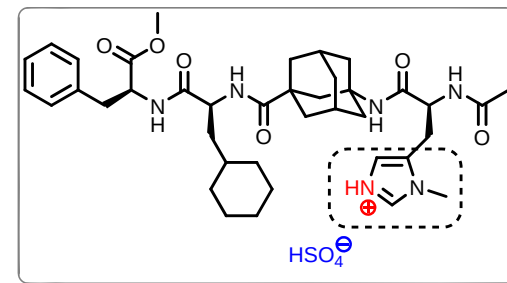
substrate	mol% phthalic acid	conv. [%] ^[a]
	5	76
	10	> 99

[a] determined by GC-MS using *n*-dodecane as internal standard.

Catalysis – Subsequent kinetic resolution of the *trans*-1,2-diols



substrate		mol% cat.	time [h]	conv. [%]	ee [%] (+)-diol	ee [%] (-)-ac. diol	<i>S</i> ^[a]
	[b]	2	3,5	59	> 99	69	39
		2	3	59	> 99	68	38
		5	1,5	57	> 99	74	48
	[c]	5	3	58	> 99	73	45
		2	65	65	67	37	4
		5	42	71	78	32	4
		5	2	59	> 99	70	40
	[d]	5	2,5	62	> 99	61	29
	[c]	5	4	68	> 99	48	19
	[d]	5	5	68	> 99	48	19
		5	2,5	41	4	6	1
	[d]	5	24	—	47	—	—



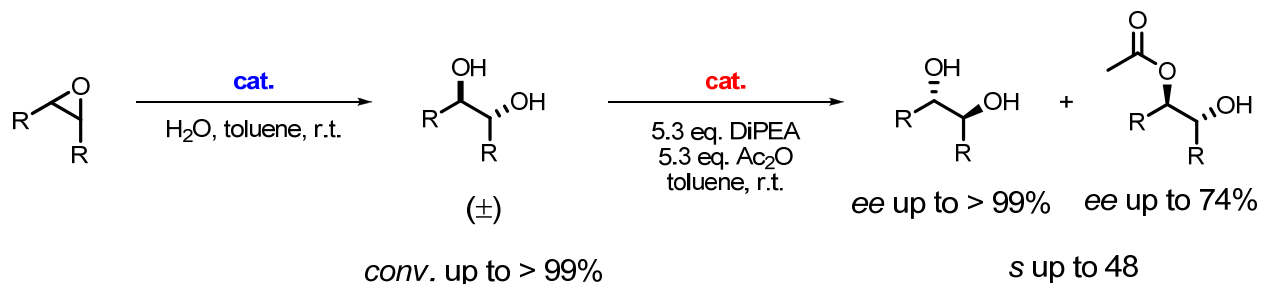
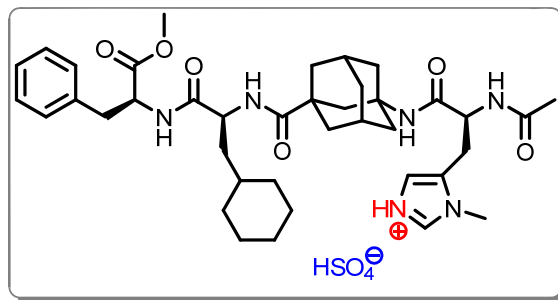
***kinetic resolution of the
obtained diols proceeds
without loss in selectivity***

[a] Determined using the method of Kagan and Fiaud.

[b] Without previous epoxide opening.

[c] Obtained from epoxidation with phthalic acid with subsequent epoxide opening.

[d] Obtained from epoxide opening with TFA.



Advantages:

mild reaction conditions

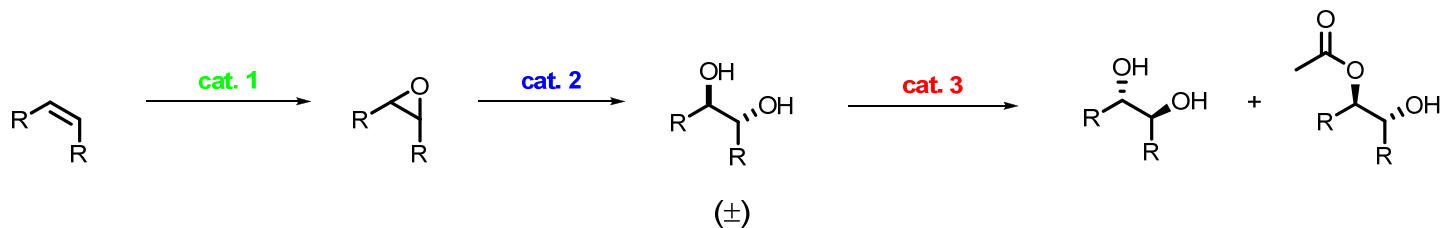
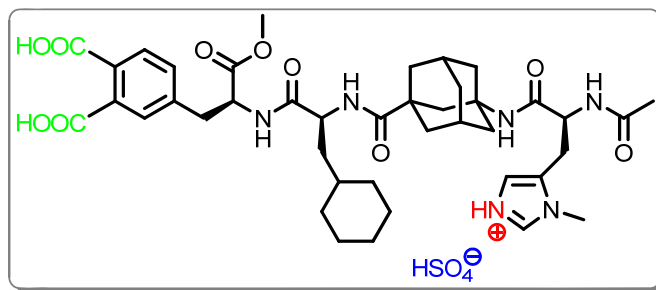
minimization of work load (synthetic operations, no isolation, purification, ... of intermediates)

no significant change in reaction conditions needed

avoidance of toxic hydrazine sulfate



further modification of the developed catalyst



***enantiomerically pure and enantioenriched products from
readily available, simple starting materials***



Many thanks to...

Prof. Dr. Peter R. Schreiner

Dr. Radim Hrdina

Christian E. Müller

Daniela Zell

analytical department

the rest of my colleagues