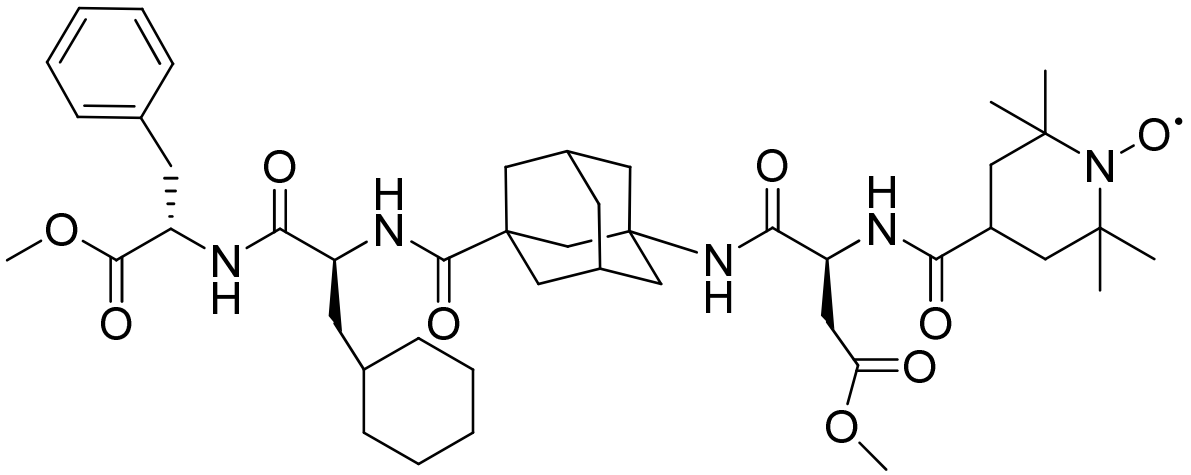
Studies on enantioselective Oxidation of Alcohols with Oligopeptidecatalysts



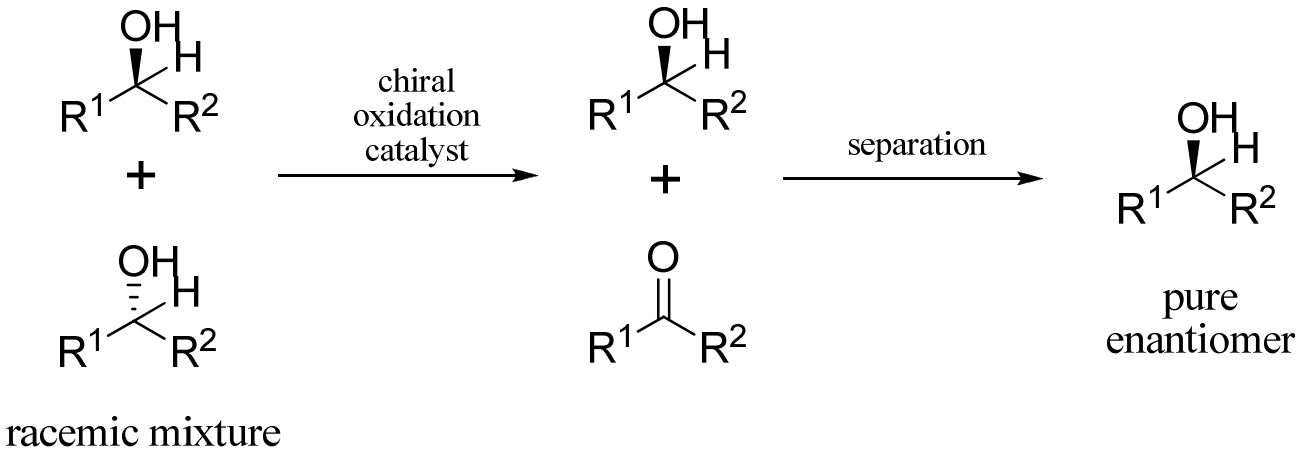
Bachelor Thesis

Martina Rümenapp

Table of Contents

Kinetic Resolution and Kagan´s S-value

- R^1 unequal R^2



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

C = conversion

ee = enantiomeric excess starting material

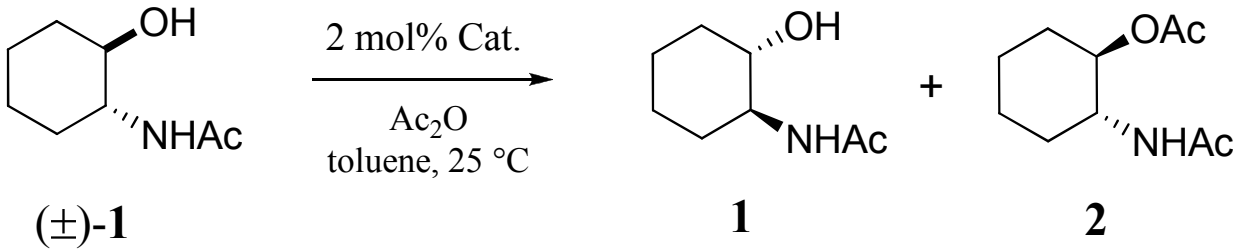
$ee´$ = enantiomeric excess product

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

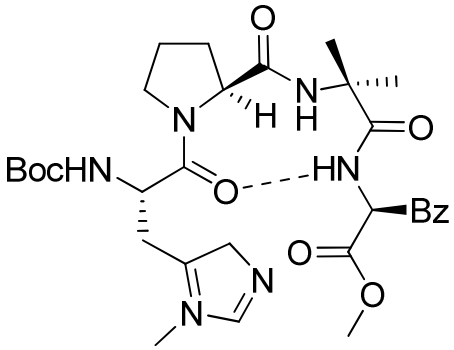
$$C = \frac{ee}{ee+ee'} \cdot 100$$

Kagan, H. B.; Fiaud, J. C.; *Top. Stereochem.*, **1988**, *18*, 249-330.

Kinetic Resolution of mono-protected Amino Alcohols

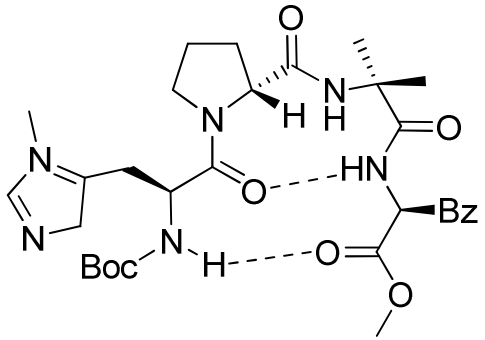


(±)-**1** **1** **2**



A

S = 3,1
56%, *ee* of **1** = 44%
ee of **2** = 34%

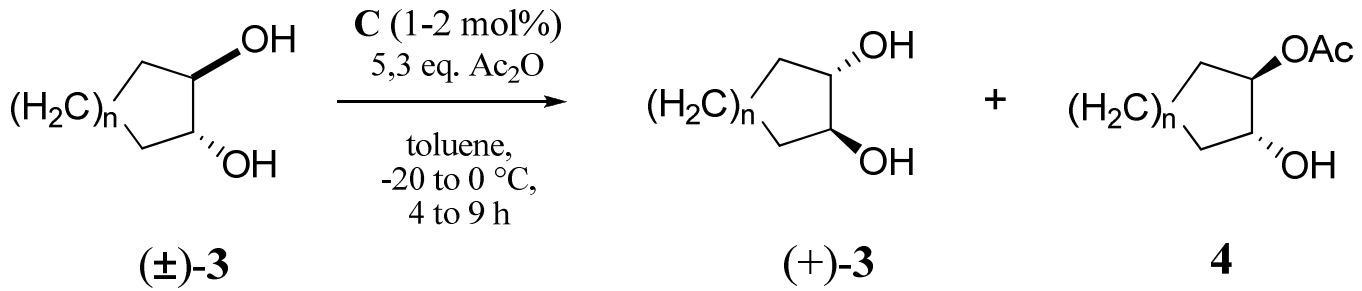


B

S = 28
58%, *ee* of **1** = 98%
ee of **2** = 73%

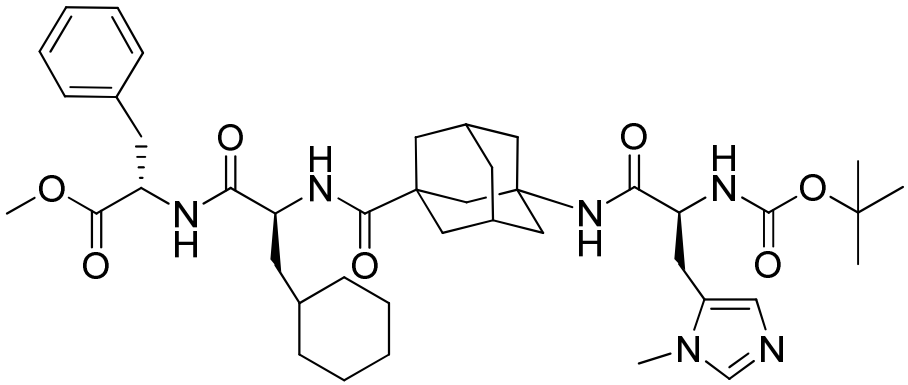
Jarvo, E. R., Copeland, G. T.; Papaioannou, N.; Bonitatebus Jr., P. J.; Miller, S. J., *J. Am. Chem. Soc.*, **1999**, *121*, 11638-11643.

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



(±)-3 **(+)-3** **4**

S > 50
n = 2: 57%, *ee* of **3** > 99%
ee of **4** = 75%

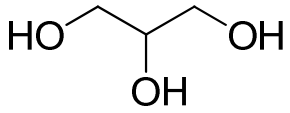


C

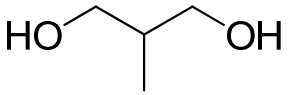
Müller, C. E.; Wanka, L.; Jewell, K.; Schreiner, P. R.; *Angew. Chem.*, **2008**, *120*, 6275-6278.

Goal

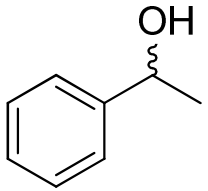
- Oxidation of the alcohols Glycerol **5**, 2-Methyl-1,3-Propanediol **6** and 1-Phenylethanol **7**



5

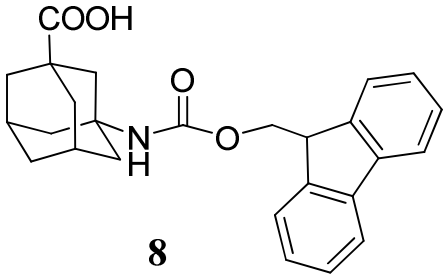


6

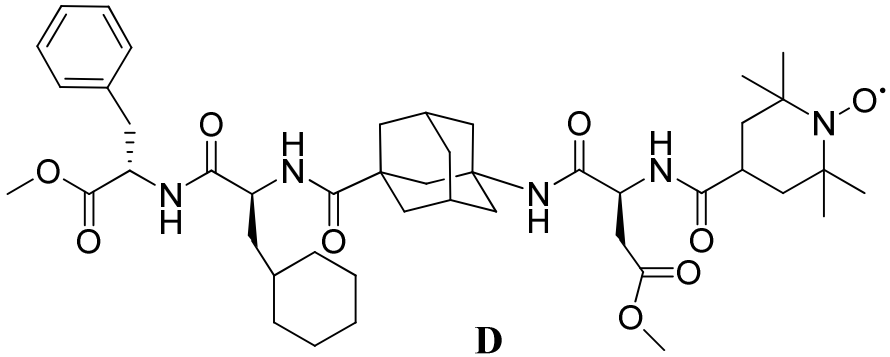


7

- Synthesis of *N*-Fmoc-protected Adamantylglycin **8**
- Preparation of Boc-L-Asp(NHTEMPO)-^{A}Gly-L-Cha-L-Phe-OMe **D** through SPPS



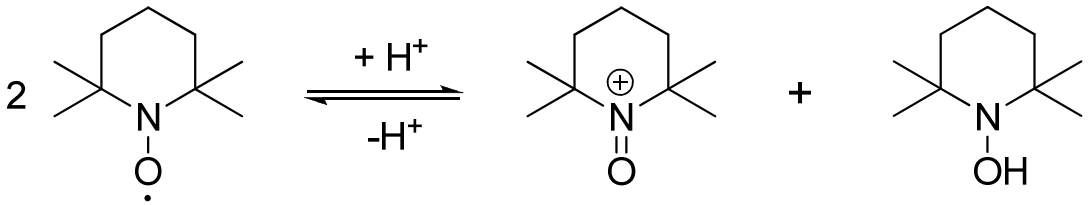
8



D

Oxidation through 2,2,6,6-Tetramethylpiperidine-1-oxyl (TEMPO)

- TEMPO **9** = nitroxid, nitroxylradical
- Eco friendly
- Oxommoniumcation **10** is the reactive spezies
- *In situ* gerneration through primary oxidants, electrochemically or acid-catalysed disproportionation

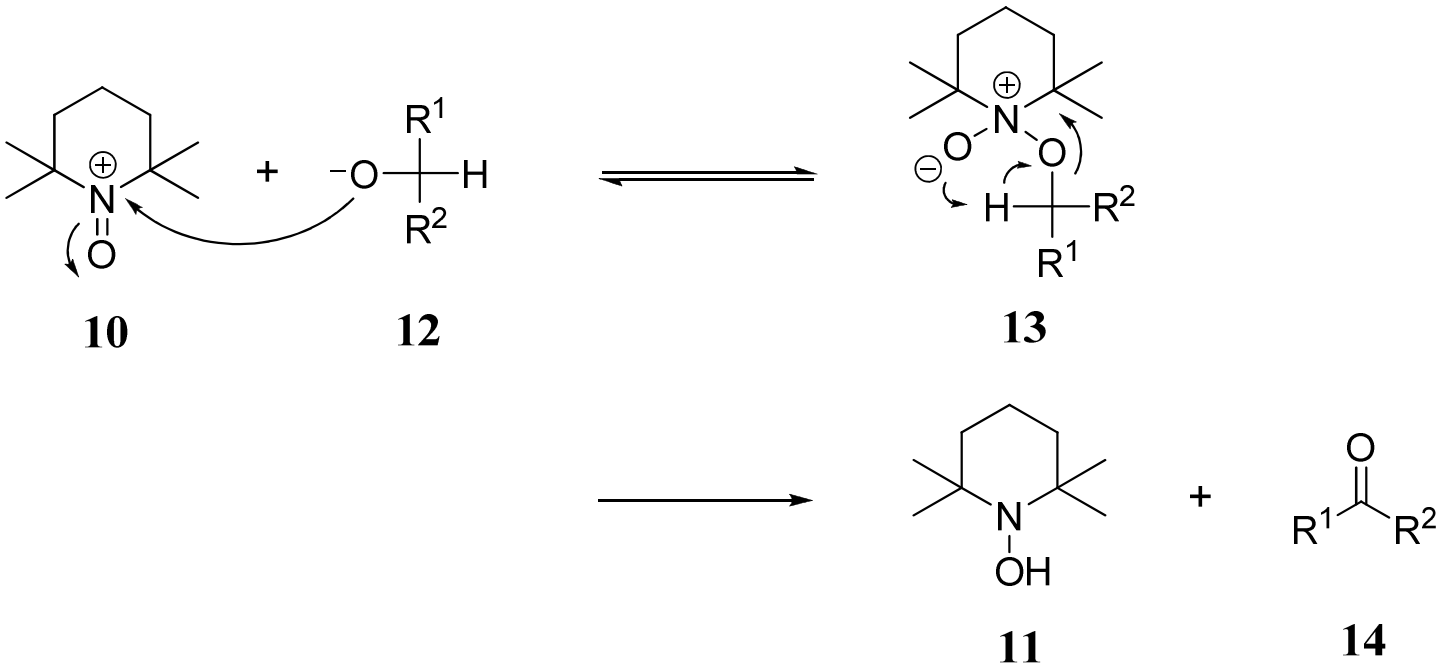


9 **10** **11**

Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H.; *Synthesis,* **1996**, *10*, 1153-1174.

Mechanism

- Alkaline: primary alcohols preferred
- nucleophilic attack of alcoholat anion on nitrogen atom
- formation of reactive komplex **13**
- Cope-like cyclic elimination to **11** and **14**



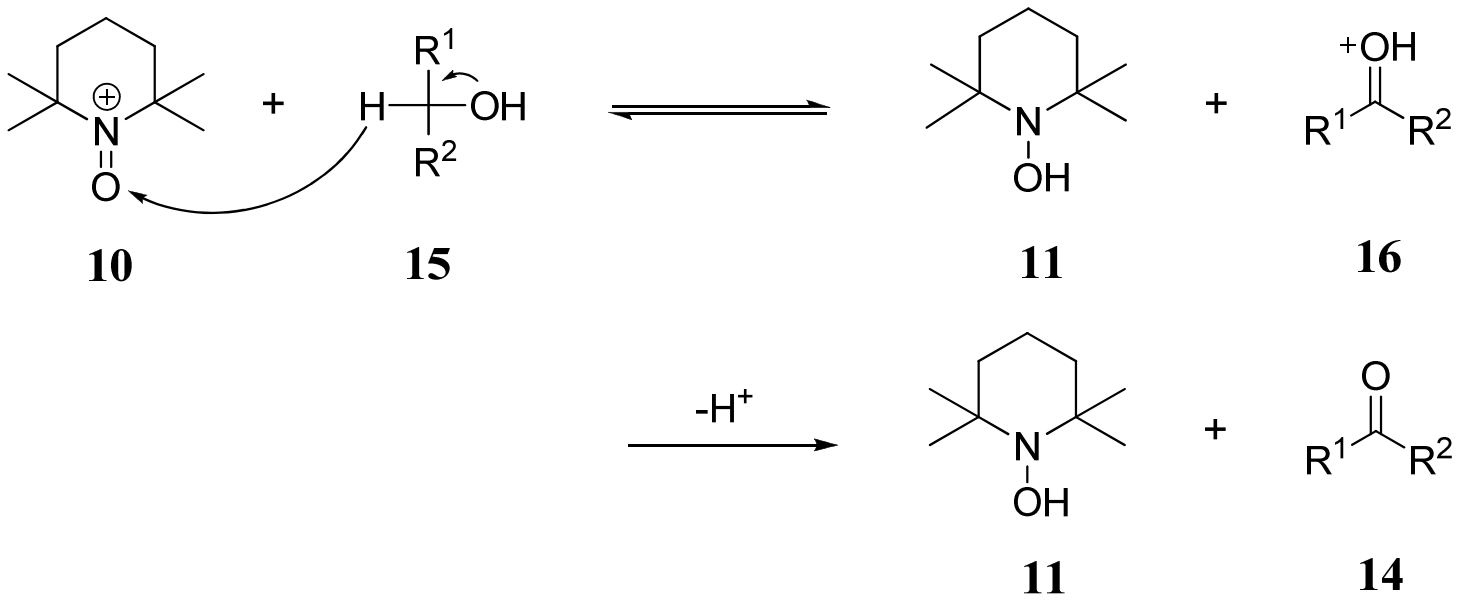
10 **12** **13**

11 **14**

Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H.; *Synthesis,* **1996**, *10*, 1153-1174.

Mechanism

- Acid: secondary alcohols preferred
- hydride transfer of alcohol **15** to **10**
- formation of **11** and protonated cation **16**
- deprotonation of **16** to **14**



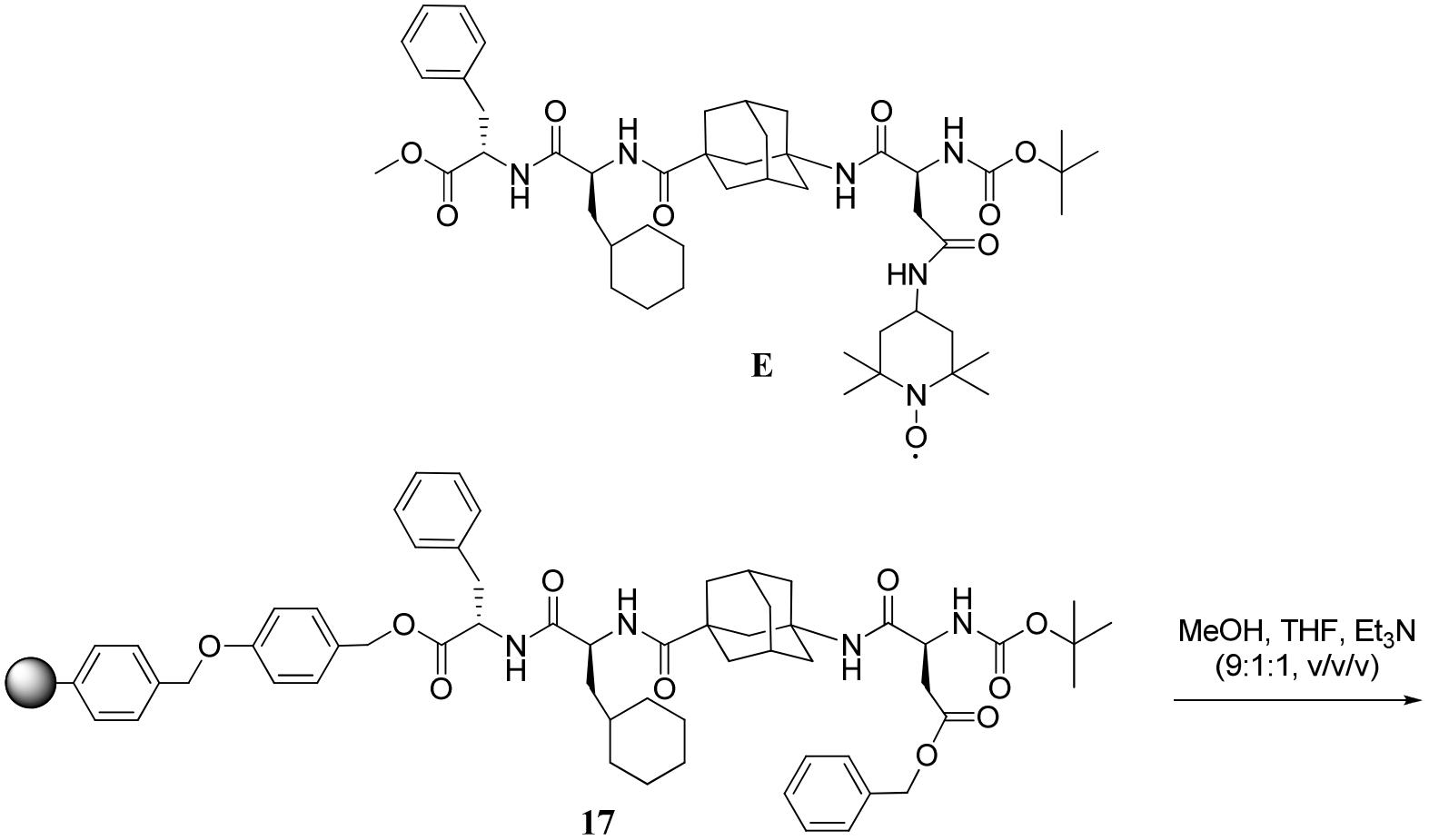
10 **15** **11** **16**

11 **14**

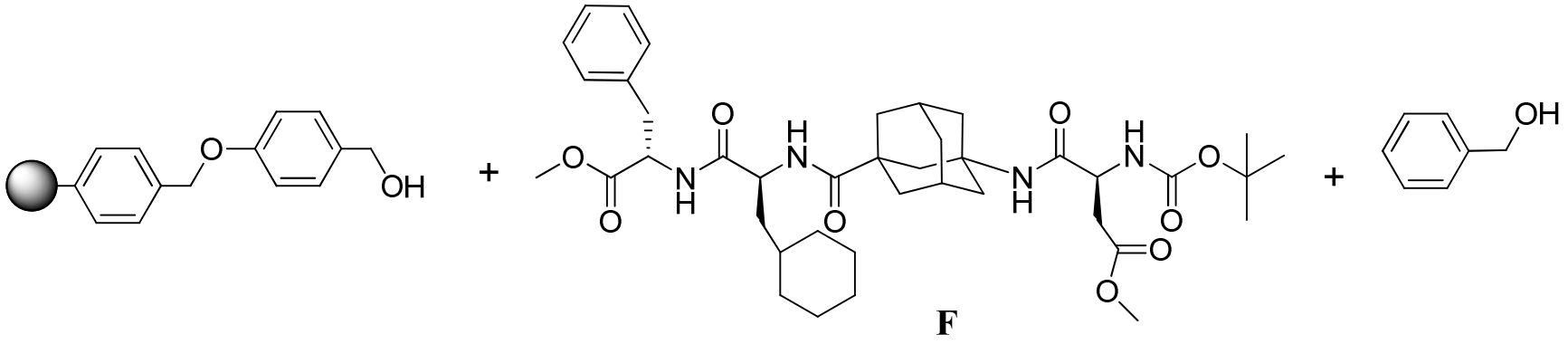
Nooy, A. E. J.; Besemer, A. C.; Van Bekkum, H.; *Synthesis*, **1996**, *10*, 1153-1174.

Preparation of the Catalyst

- Peptide coupling through SPPS with HBTU, HOBt and DIPEA

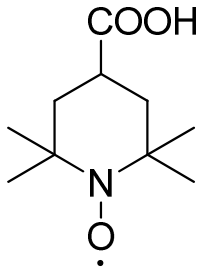


Preparation of the Catalyst

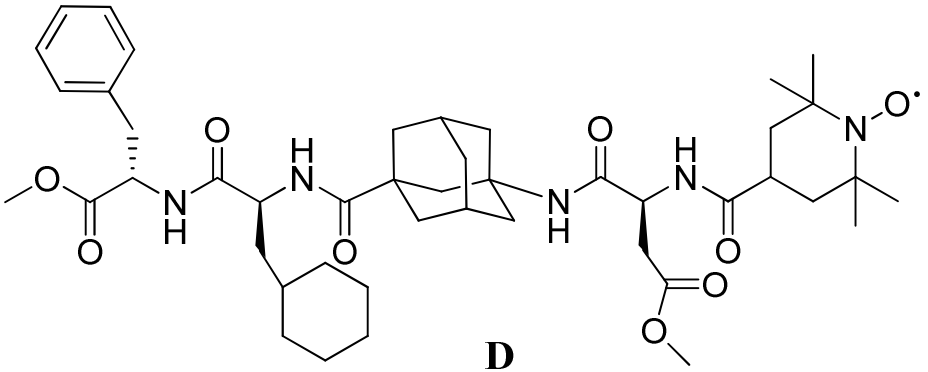


F

- Deprotection of Boc in **F** and coupling with 4-Carboxy-TEMPO **18** to form catalyst D



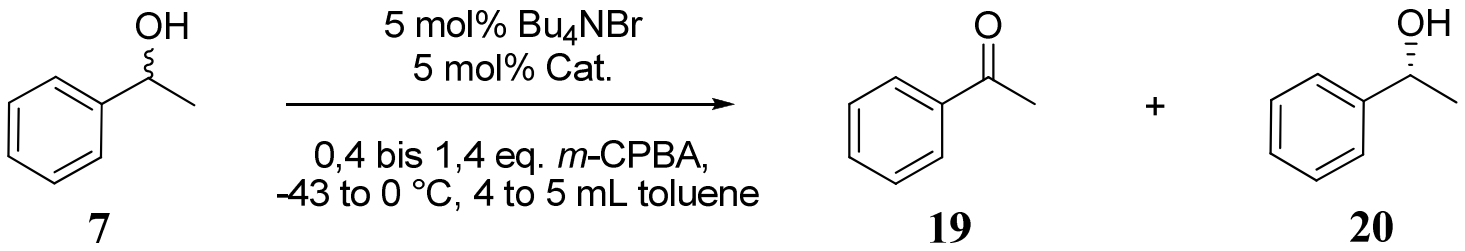
18



D

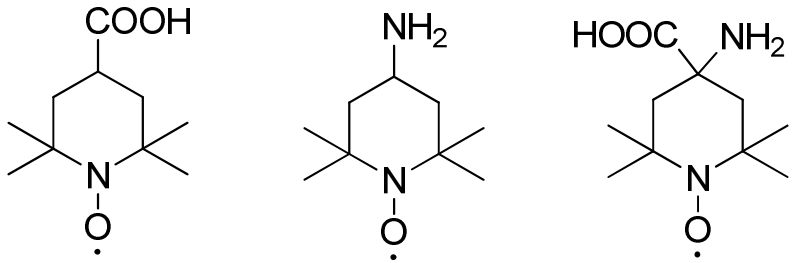
Results

- Oxidation of Glycerol and 2-Methyl-1,3-Propanediol didn´t work well



7 **19** **20**

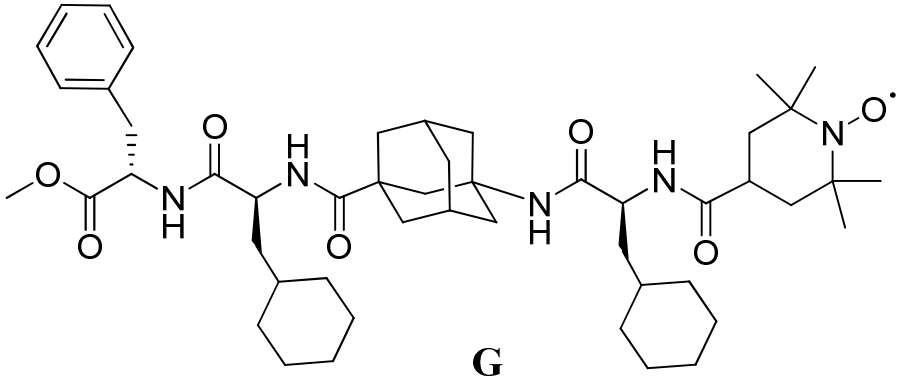
- Screenings with catalysts including **19**, 4-Amino-TEMPO **22** and 4-Amino-4-Carboxy-TEMPO (TOAC) **23**



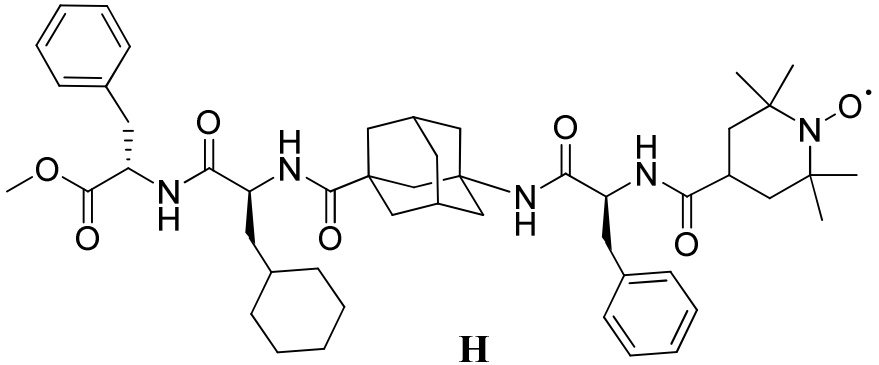
18 **21** **22**

Results

- best results with 4-Carboxy-TEMPO-catalysts **G** and **H** and 0,7 eq. *m*-CPBA, -18 °C, 5 mL toluene



G



H

Results

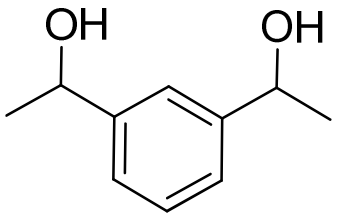
Catalysts	Conversion [%] [a]	ee (20) [%] [a]	S [%] [a]	Conversion [%] [b]	ee (20) [%] [b]	S [%] [b]	*m*-CPBA [eq.]	T [° C]
Cat. G	39	14	1,8	40	14	1,7	0,55	0
Cat. G	58	25	1,8	59	29	1,9	0,7	-18
Cat. G	42	15	1,7	45	19	1,9	0,7	-28 to -35
Cat. G	72	37	1,8	93	75	1,9	1	-18
Cat. G	59	23	1,7	70	35	1,8	1	-38 to -43
Cat. H	53	22	1,8	61	29	1,9	0,7	-18
Cat. H	57	18	1,5	56	21	1,7	1	-38 to -43

[a] Determined by chiral gas chromatography after 1 h reactiontime. [b] Determined by chiral gas chromatography after 3 h reactiontime.

- highest *ee* 75%, 93% conversion
- best S-value = 1,9

Outlook

- Oxidation of primary alcohols under basic conditions
- Expansion of the substrates, e.g. 1,3-Bis(1-hydroxyethyl)benzene



23

- Computations of conformers for better understanding of placing the reactive groups

Acknowledgement

Many Thanks to :

- Prof. Dr. Peter R. Schreiner
- Christine Hofmann
- the whole research group

Thank you for your attention!