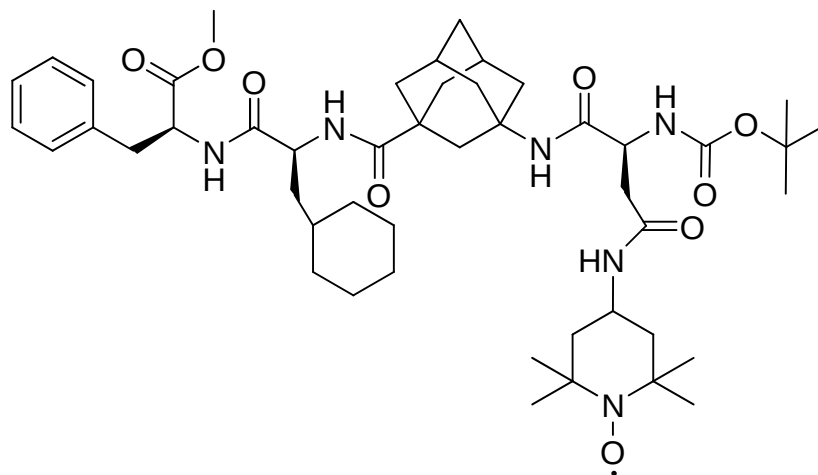


Oligopeptides as Organocatalysts for Selective Oxidations of Secondary Alcohols



Bachelor Thesis
Stefanie Dobitz

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Oligopeptides as Organocatalysts

- Kinetic resolution of mono-protected amino alcohols^[1]
- Secondary monoalcohols as well^[2]

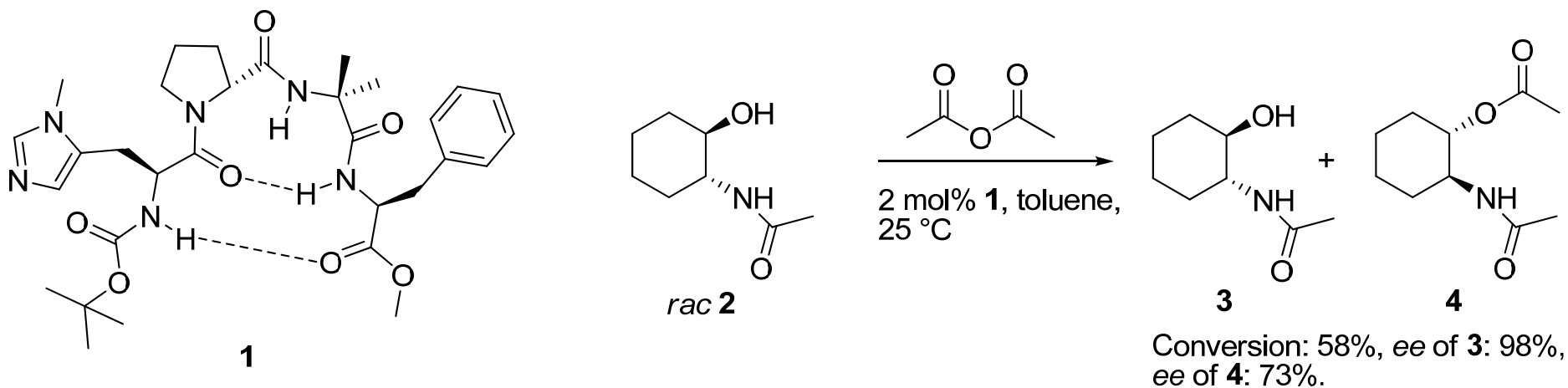
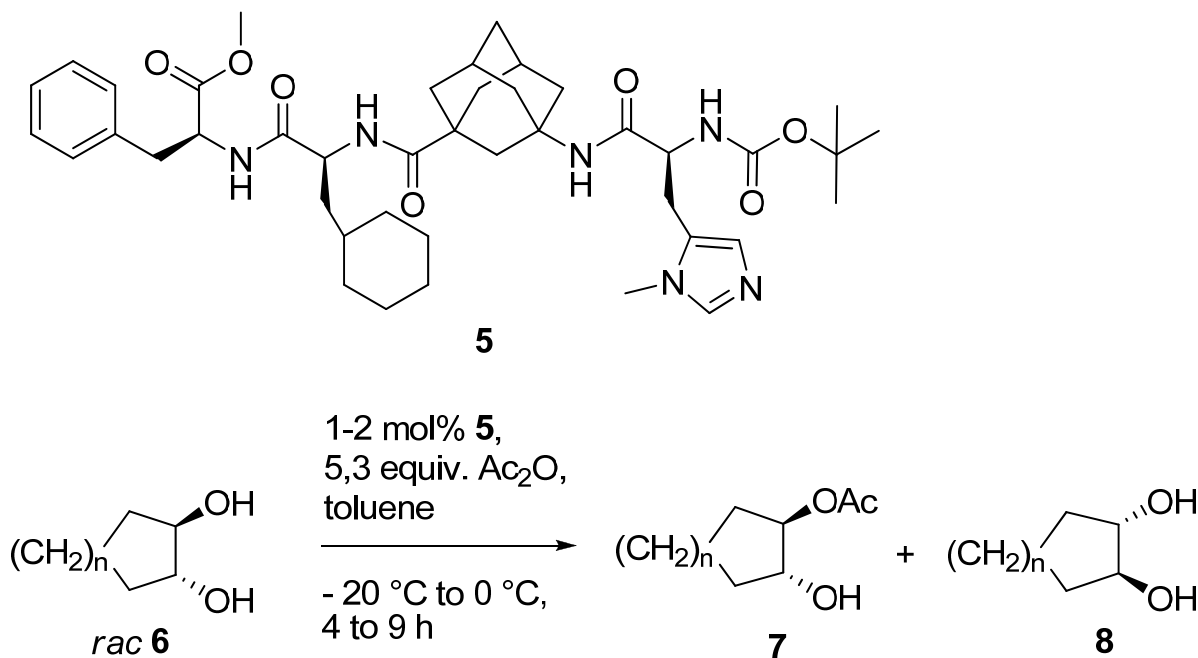


Figure 1: Kinetic resolution of **2** through acylation by Miller's peptide **1**.^[1]

Oligopeptides as Organocatalysts



- For example:
Racemic *trans*-cyclooctane-1,2-diol^[3]
- Yield of **8**: 44%
- ee of **7**: 85%
- ee of **8**: > 99%

Figure 2: Kinetic resolution of *trans*-cycloalkane-1,2-diols with Boc-L-(π -Me)His-^AGly-L-Cha-L-Phe-OMe **5**.

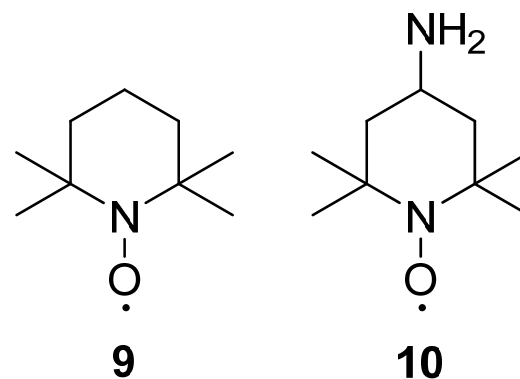
Oxidations through 2,2,6,6-Tetramethylpiperidine-1-oxyl

- Eco-friendly alternative to various metals^[4]
- Stoichiometrical use of oxoammonium salts since 1965^[5]
- *In situ* generation of oxoammonium cations through a primary oxidant, electrochemically or acid-catalysed disproportionation^[4]

Figure 3: 2,2,6,6-Tetramethylpiperidine-1-oxyl

9 (TEMPO) and 4-Amino-2,2,6,6-

Tetramethylpiperidin-1-oxyl **10** (TEMPO-Amin).



Motivation and Goal

- Synthesis of *N*-Boc-protected Adamantylglycine **11** (Boc-^AGly)
- Incorporate **9** into a chiral environment for enantioselective oxidations
- Preparation of Boc-L-Asp(NHTEMPO)-^AGly-L-Cha-L-Phe-OMe **12**

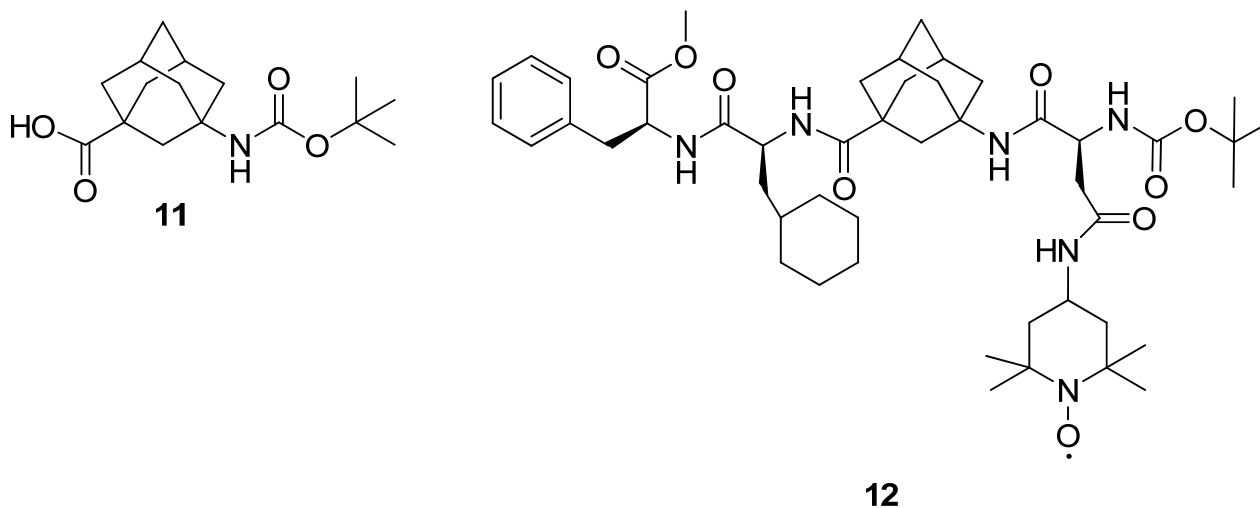


Figure 4: Boc-^AGly **11** and Boc-L-Asp(NHTEMPO)-^AGly-L-Cha-L-Phe-OMe **12**.

Motivation and Goal

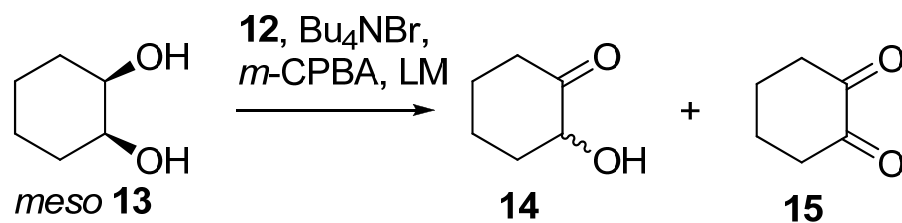
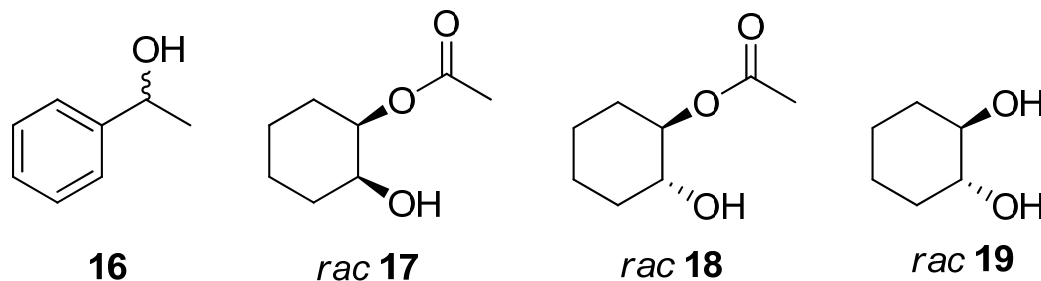


Figure 5: Desymmetrisation of cyclohexane-1,2-diol **13**.

Figure 6: Kinetic resolution of various substrates.



Mechanism of the Oxidation through 2,2,6,6-Tetramethylpiperidine-1-oxyl

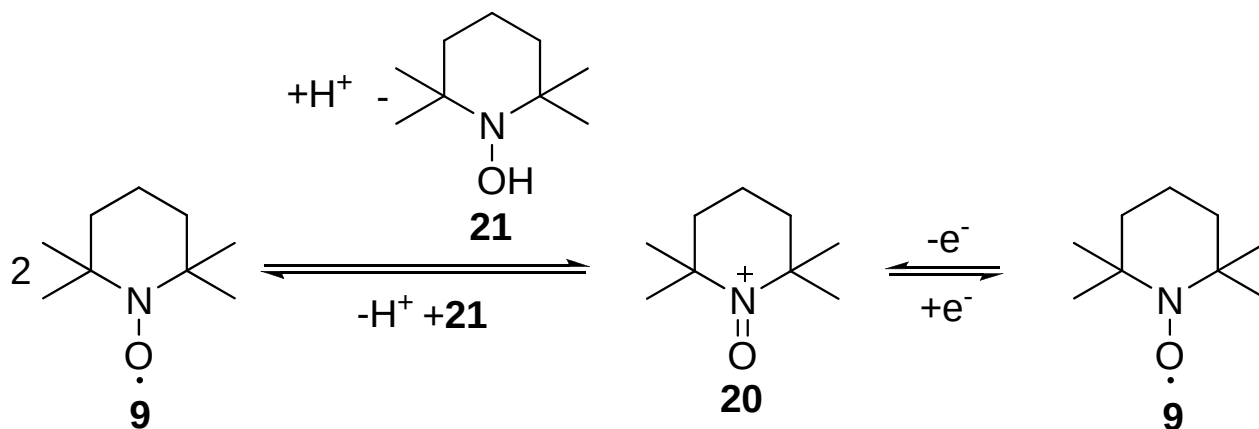
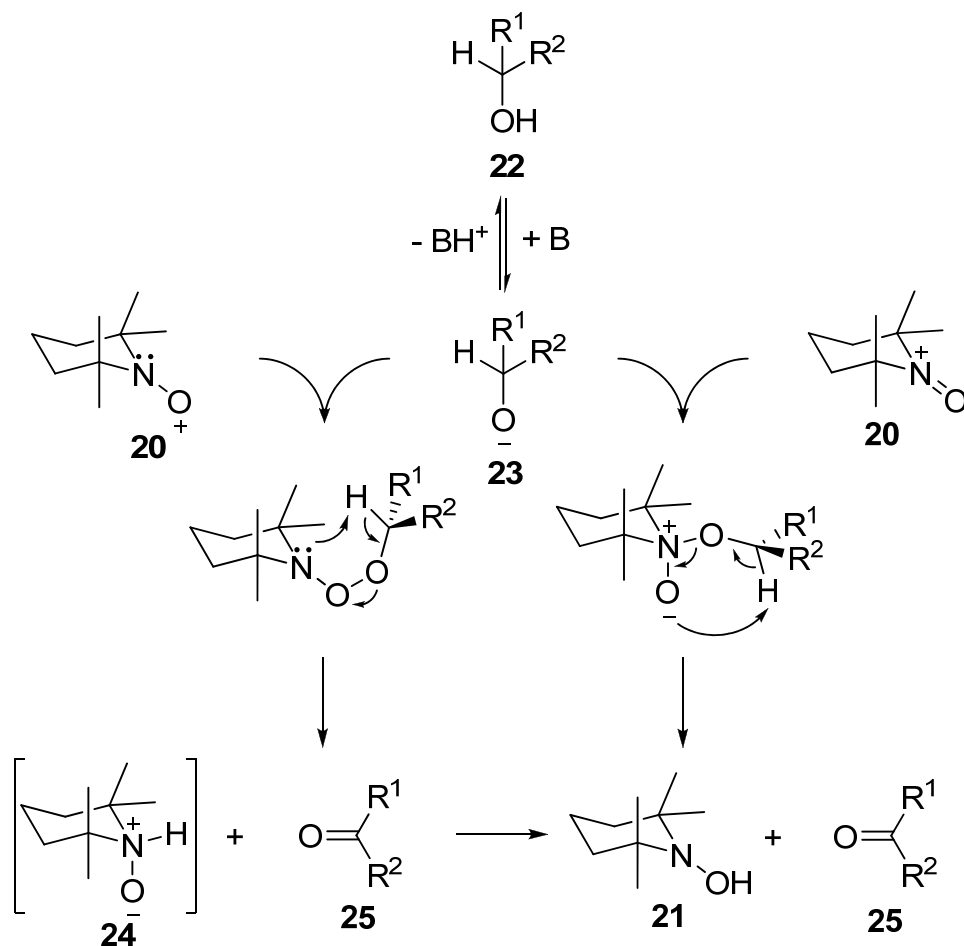


Figure 8: *In situ* generation of the oxo ammonium cation **20**.

- *In situ* generation through a primary oxidant^[6], electrochemically^[7] or acid-catalysed disproportionation^[8]

Mechanism of the Oxidation through 2,2,6,6-Tetramethylpiperidine-1-oxyl



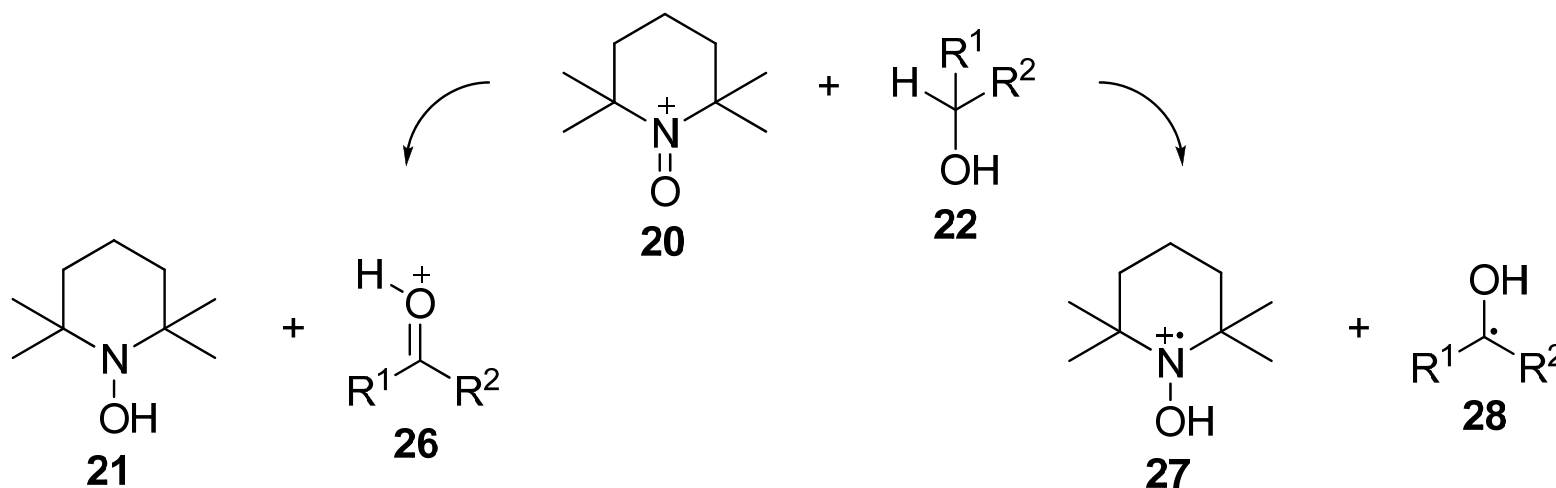
- Nucleophilic attack of an alcoholate anion on either the nitrogen atom or the oxygen atom

Figure 9: Two different ways to oxidize alcohols under basic conditions.^[5,9,10]

Mechanism of the Oxidation through 2,2,6,6-Tetramethylpiperidine-1-oxyl

- Hydride transfer or hydrogen atom transfer

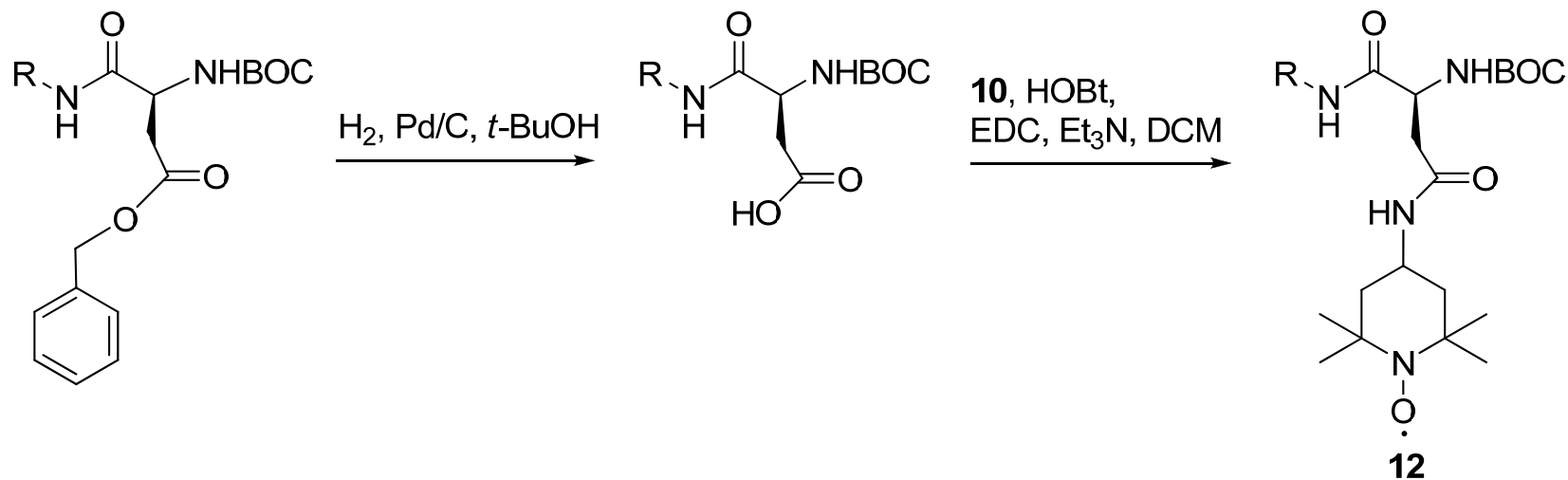
Figure 10: Two different ways to oxidize alcohols under acidic conditions.^[5,9,10]



Preparation of the Catalyst

- peptide coupling in solution with HOBt, EDC and Et₃N

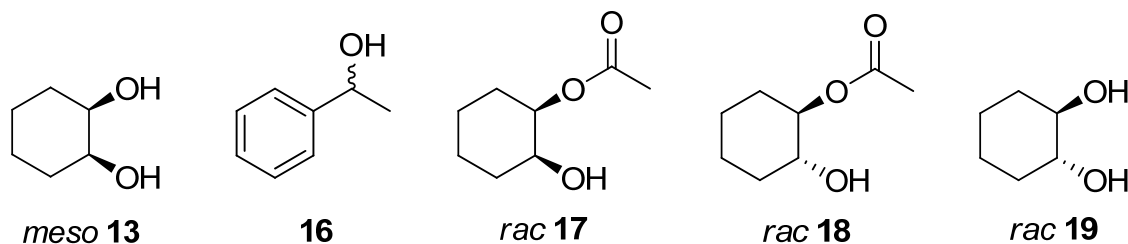
*Figure 7: Hydrogenation of the benzyl ester and coupling of **10**.*



Screening of Different Reaction Parameters

- Screening of temperature, solvent, amount of solvent, TEMPO/Bu₄NBr-loading, and *m*-CPBA-loading
- Temperature: 0 °C
- Solvents: Toluene and chlorobenzene
- Amount of solvent: 3 ml
- TEMPO/Bu₄NBr-loading: 5 mol% of both
- *m*-CPBA-loading: 2,15 equiv.

Screening of Different Reaction Parameters



conversion [%] ^a	64	32	96	72	100
ee [%] ^a	24	4	0	3	32

^a Determined by chiral gas chromatography.

Figure 11: Variation of the substrate with conversion and enantiomeric excess (ee).

Summary and Outlook

- Modification of the peptide sequence
- Change the amino acids
- Expansion of the substrates
- Computations for better understanding of reactivity and selectivity

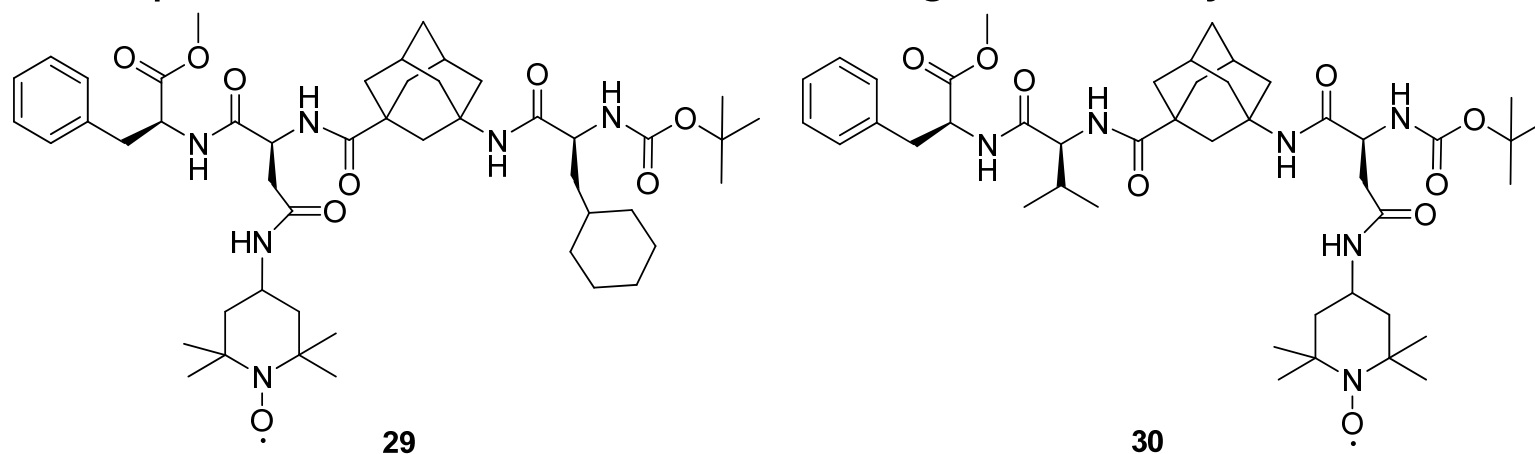


*Figure 12: Two new possible TEMPO-peptides **29** and **30**.*

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- Many thanks to Prof. Dr. Peter R. Schreiner for the opportunity to write my Bachelor Thesis in his research group
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Thank you for your kind attention!