

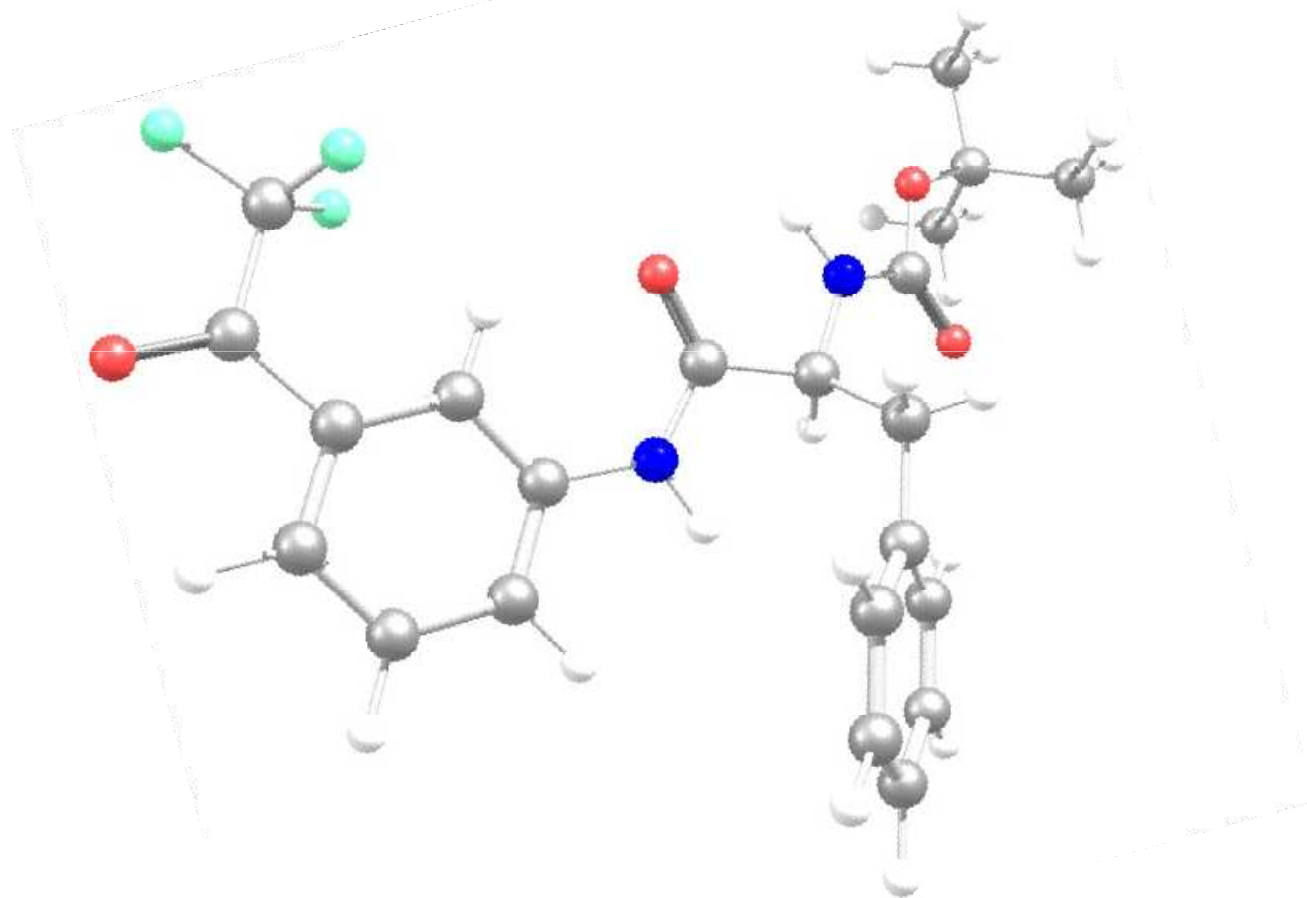
Actual State of Epoxidation Reactions via *in situ* Generated Dioxiranes

PRS Group Seminar

12th October 2012

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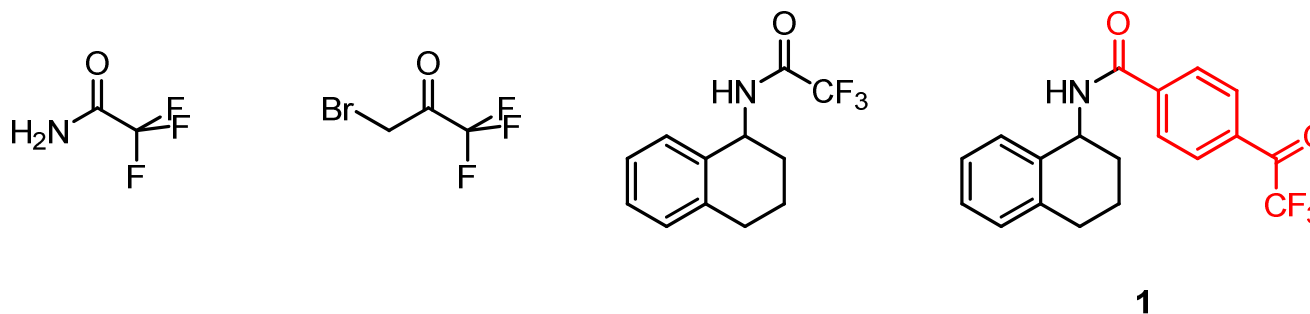




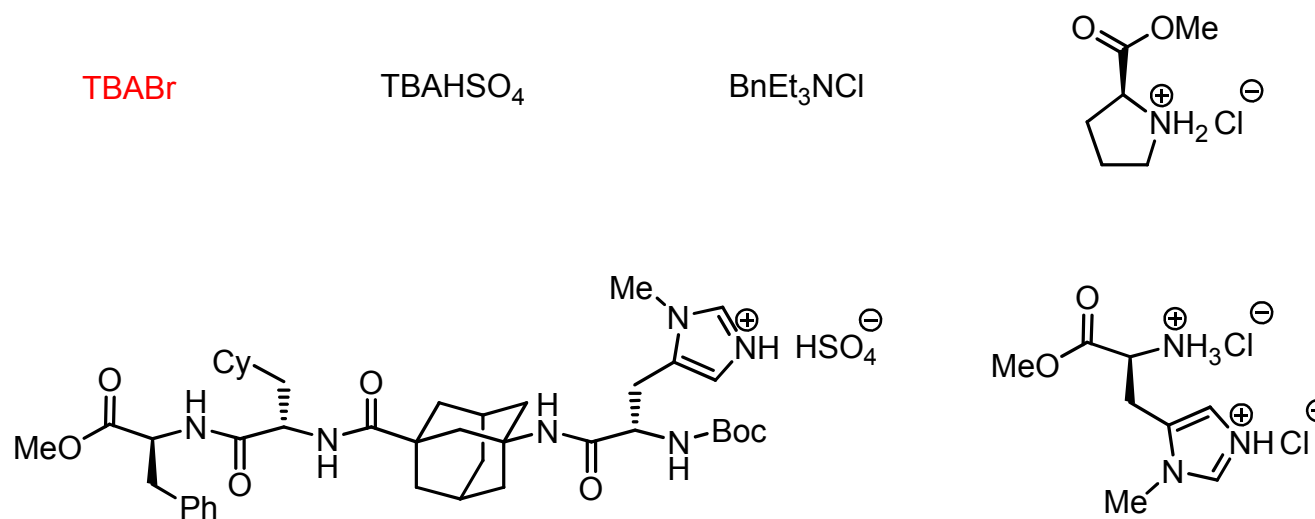
- Short Review
 - Optimization
 - Oxone/ NaHCO_3
 - $\text{H}_2\text{O}_2/\text{MeCN}$
 - Functionalization of Amino Acids
 - Missing *ee* – Methods of Resolution
 - Substance Library
 - Shorter Linker
 - Modifications of the Catalytic Moiety
 - Actual State of Epoxidation Reactions
 - Outlook
-

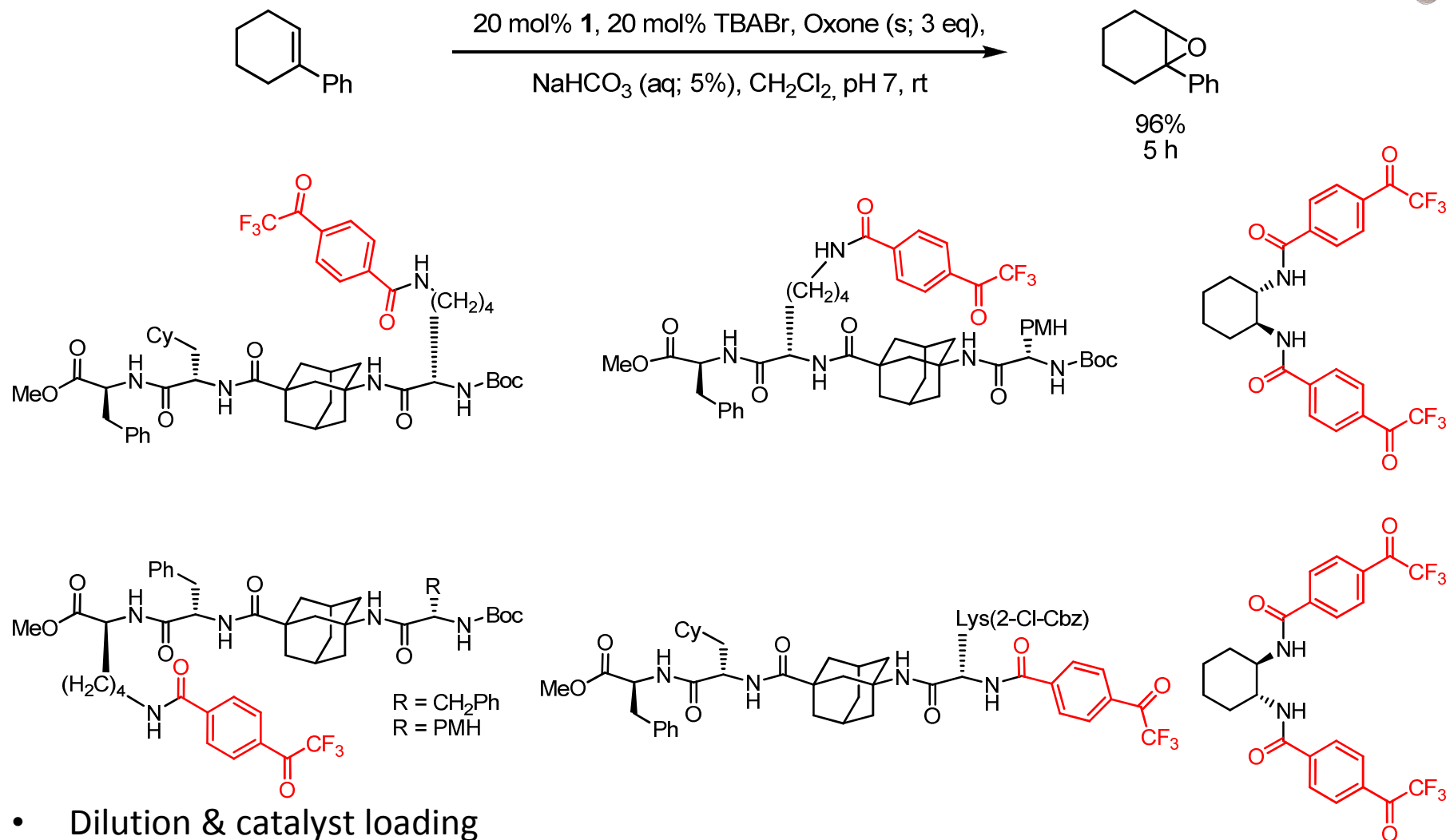


- Catalytic moiety:



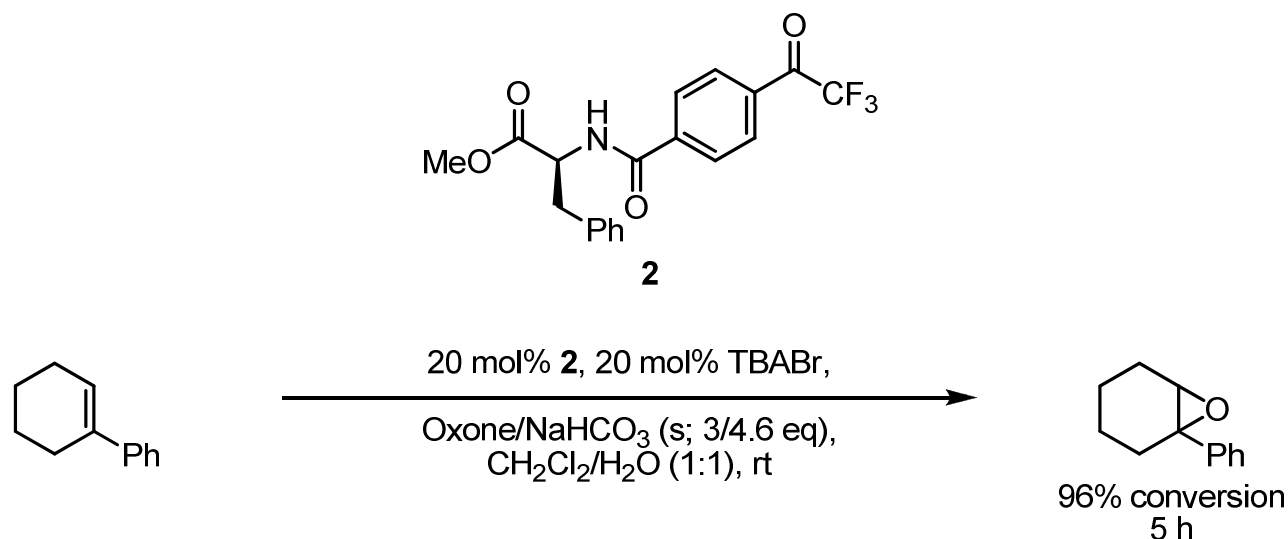
- Phase transfer catalyst:



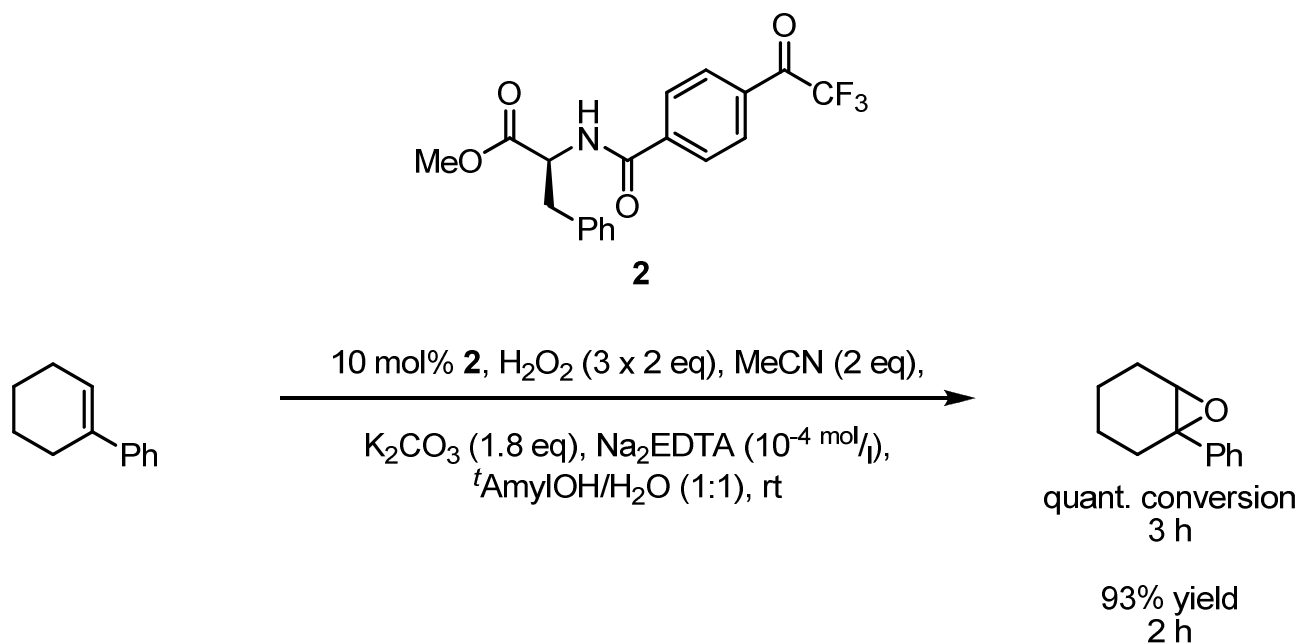


- Dilution & catalyst loading
- Difficult to keep the pH-value constant

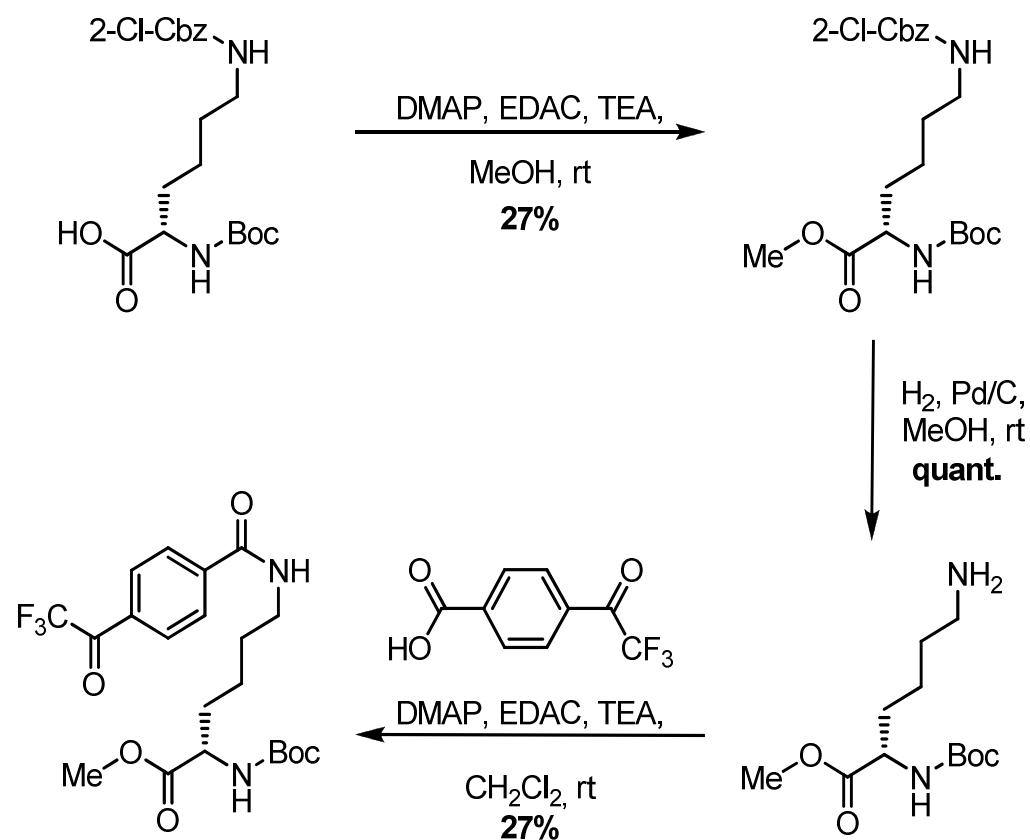
X. Peng, P. Li, Y. Shi, *J. Org. Chem.* **2011**, 77, 701-703; Y. Tu, Z.-X. Wang, Y. Shi, *J. Am. Chem. Soc.* **1996**, 118, 9806-9807; Z.-X. Wang, Y. Tu, M. Frohn, Y. Shi, *J. Org. Chem.* **1997**, 62, 2328-2329; Z.-X. Wang, Y. Tu, M. Frohn, J.-R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, 119, 11224-11235; O. A. Wong, Y. Shi, in *Asymmetric Organocatalysis*, Vol. 291 (Ed.: B. List), **2010**, pp. 201-232.



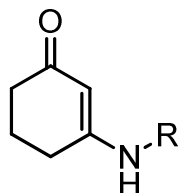
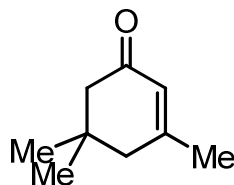
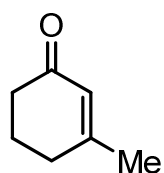
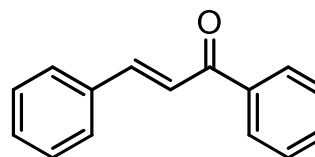
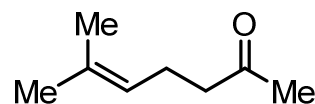
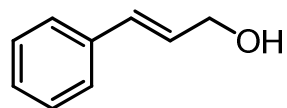
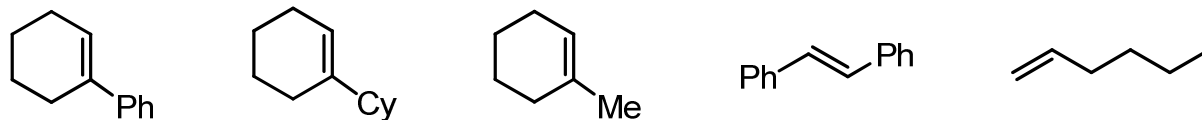
- Extremely pH-dependent
- Mixing Oxone/ NaHCO_3 and addition over 1 h
- 20 mol% catalyst necessary
- DCM optimal solvent
- PTC necessary



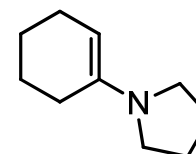
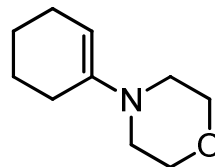
- H₂O₂ added in portions
- MeCN necessary
- Less catalyst: slower reaction, but more side reactions
- Very slow background reaction
- No PTC necessary



- Successful for lysine
- Not optimized yet
- Important in regard to automated peptide synthesis

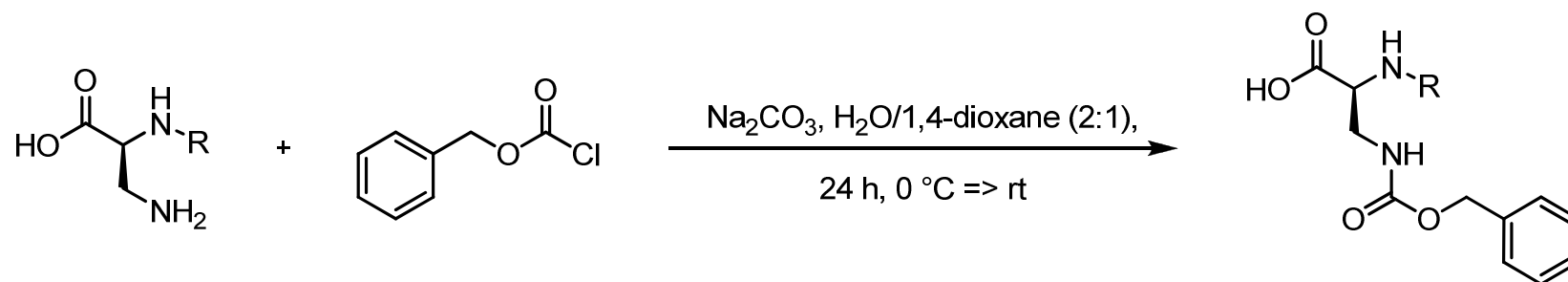


R = H
R = Ac
R = Cbz



- Cyclic compounds
- Linear compounds
- Conjugated systems
- Michael systems
- Isolated double bonds
- π - π -interaction
- Dispersion
- H-bond acceptors
- H-bond donors

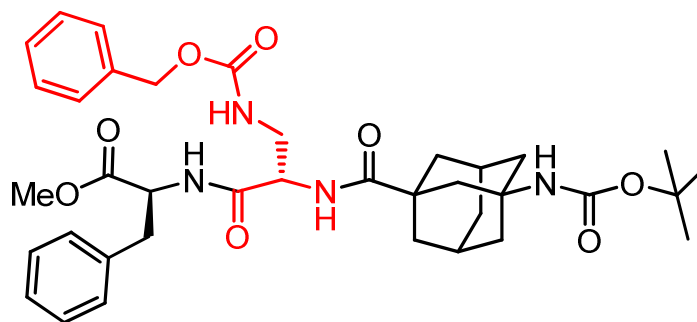
- Easier reaction screening
- Different kinds of interactions between substrate and catalytic backbone/moiety



R = Fmoc
R = Boc

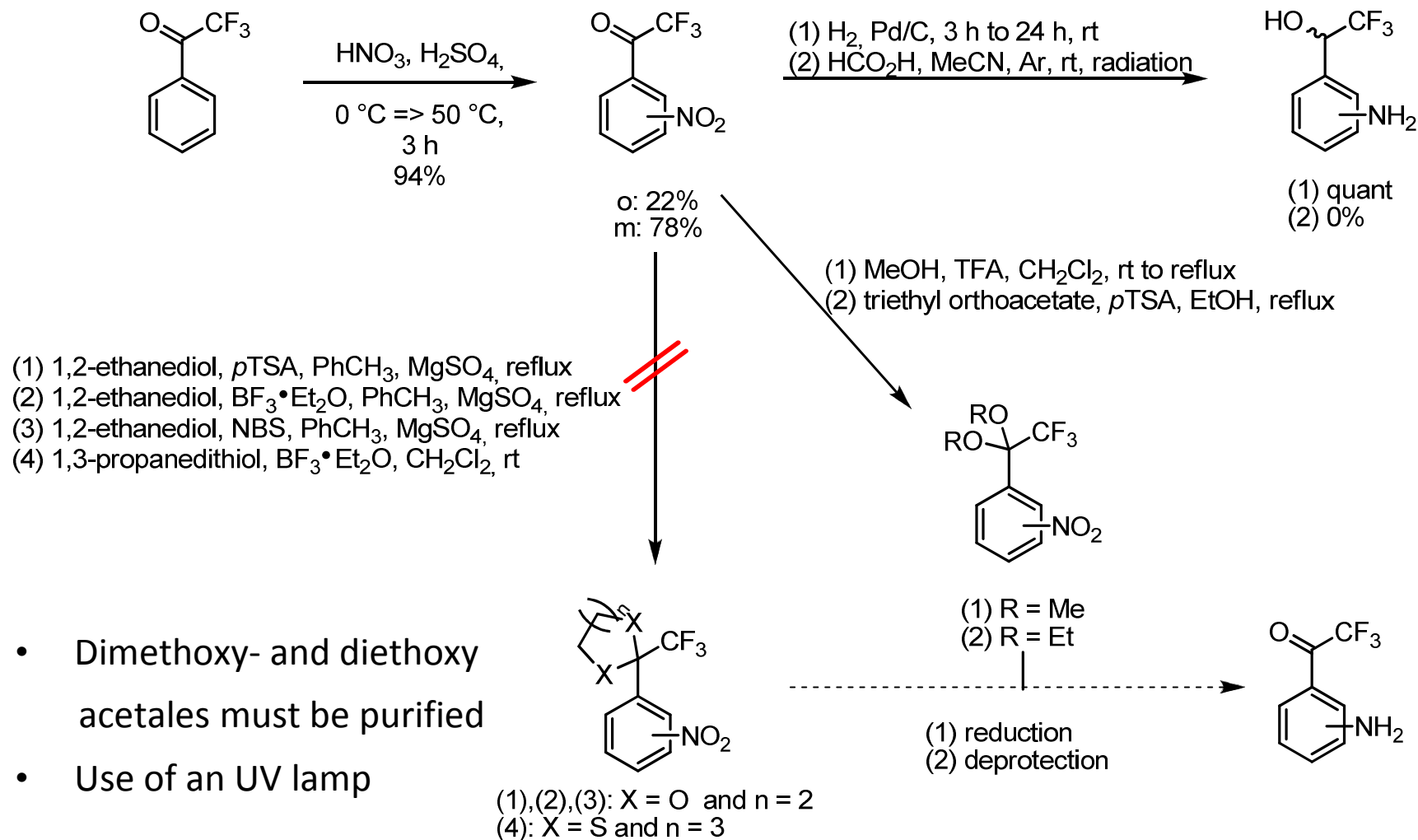
R = Fmoc: 68%
R = Boc: 0%

- Shorter distance between catalytic moiety and peptide backbone
- Purification



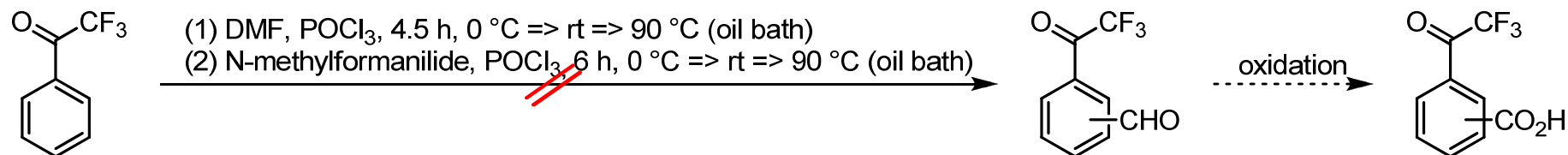
- Utilized in SPPS (23%)
- Coupling conditions must be optimized

Modifications of the Catalytic Moiety - Amine

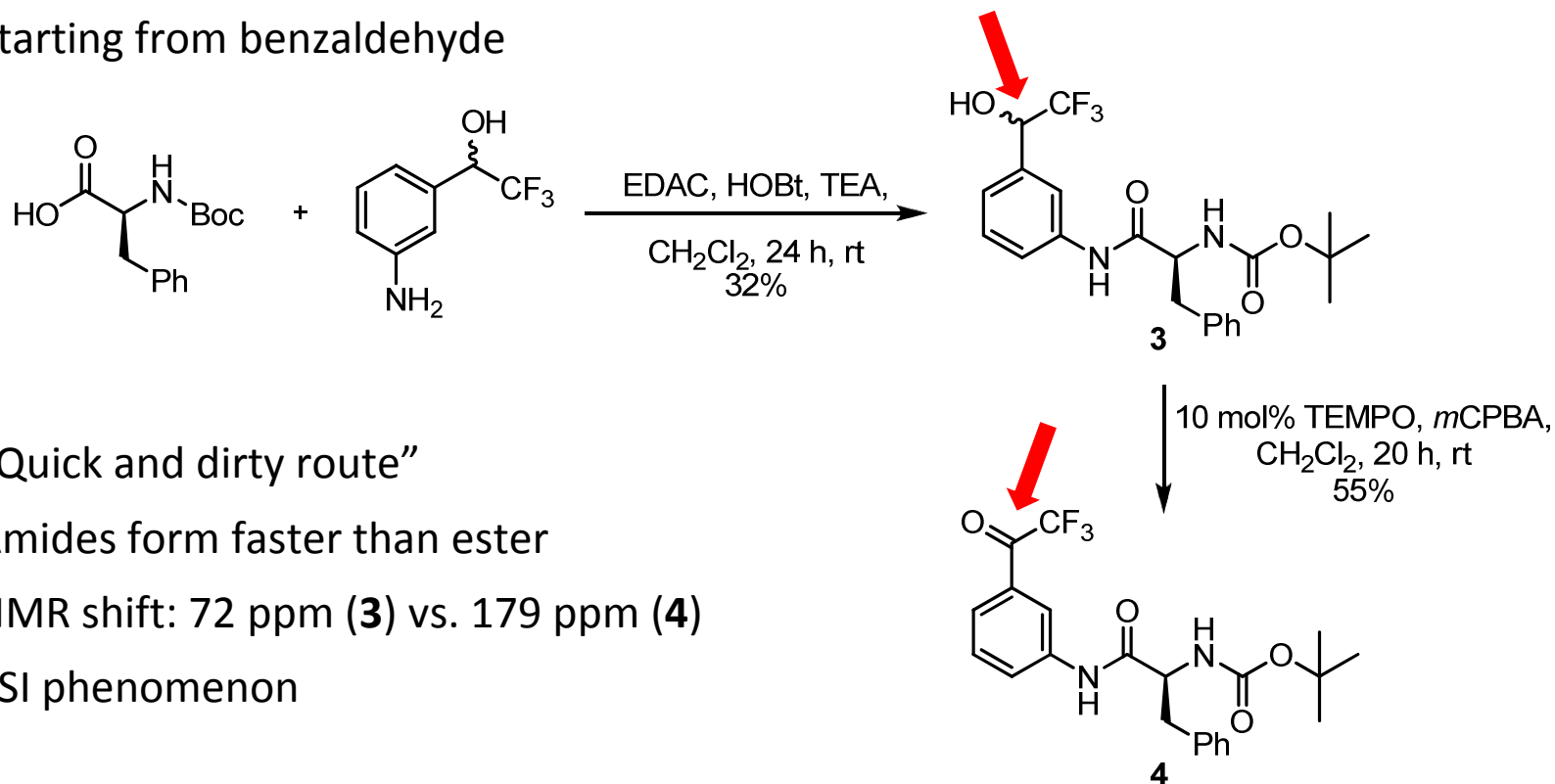


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Modifications of the Catalytic Moiety – Acid and Catalyst

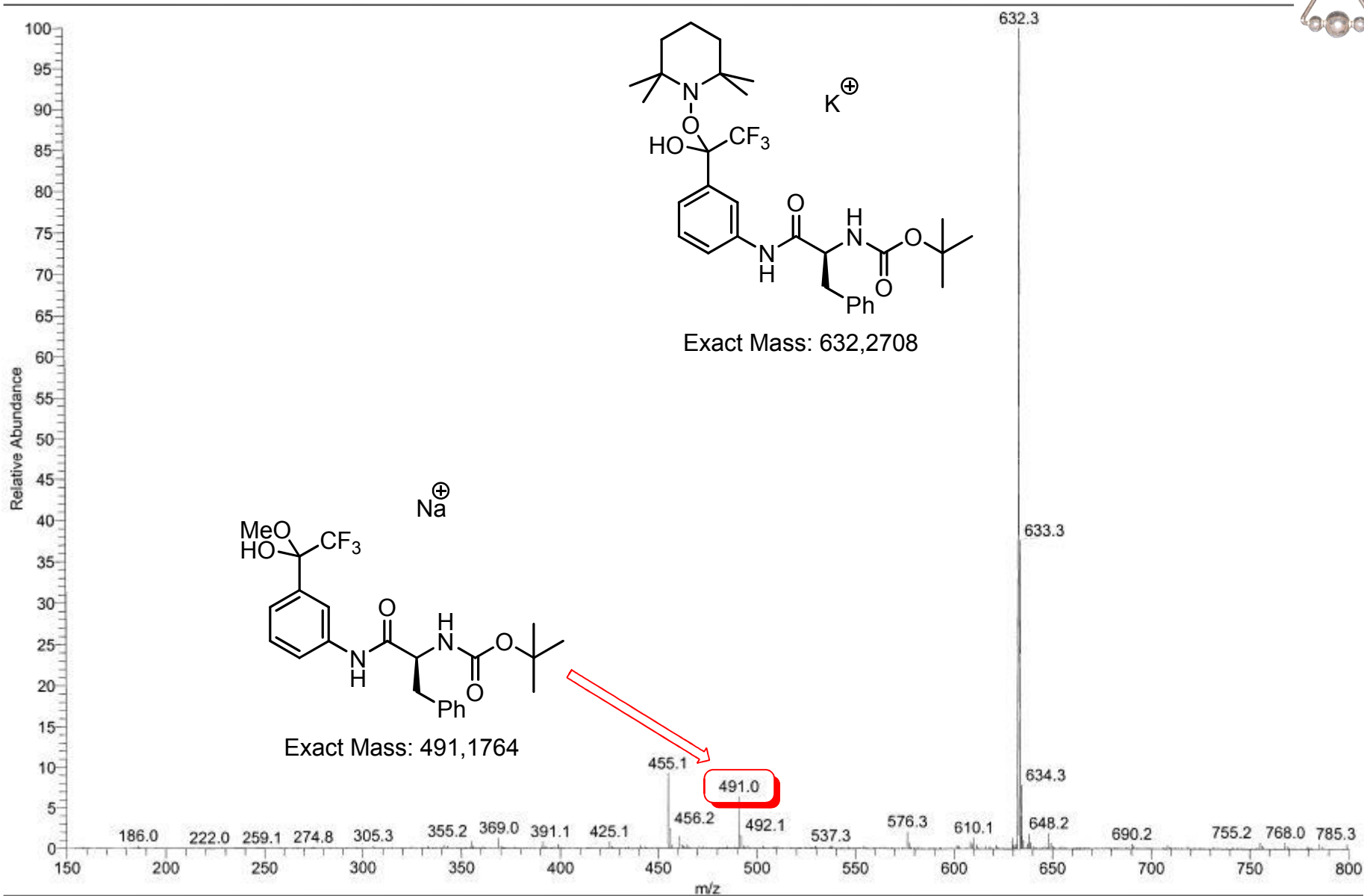


- Further formylation strategy
- Starting from benzaldehyde

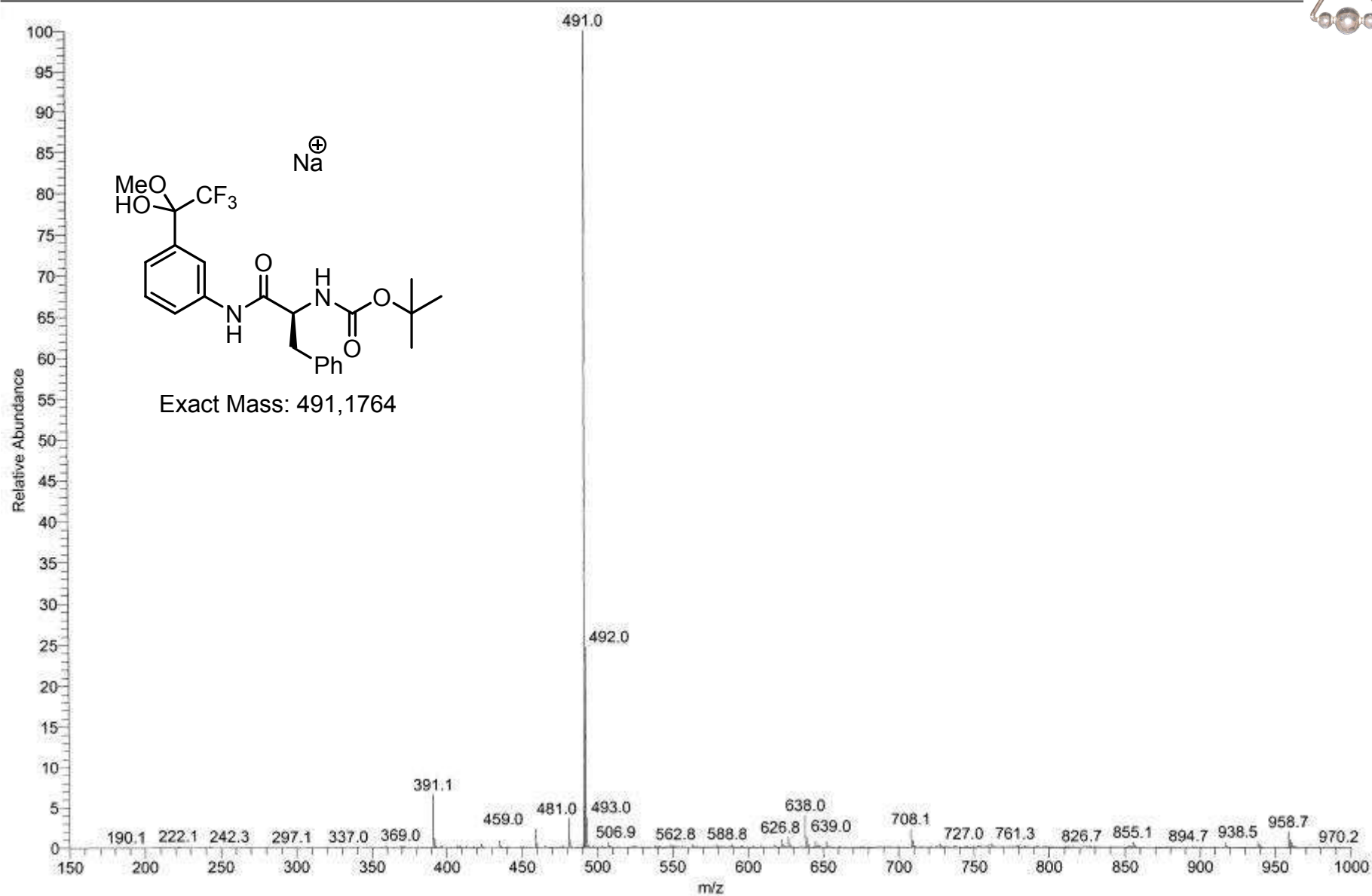
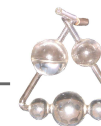


- “Quick and dirty route”
- Amides form faster than ester
- NMR shift: 72 ppm (**3**) vs. 179 ppm (**4**)
- ESI phenomenon

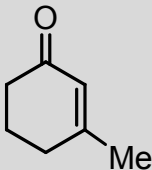
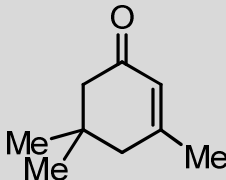
ESI Phenomenon

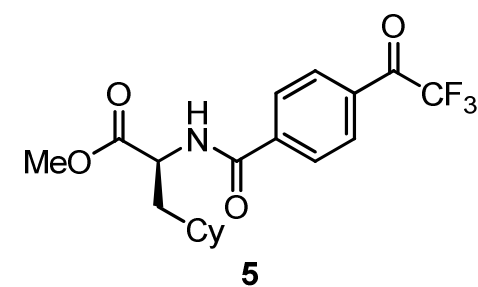
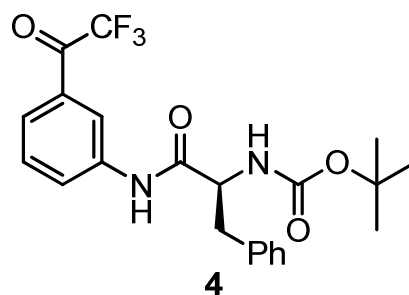
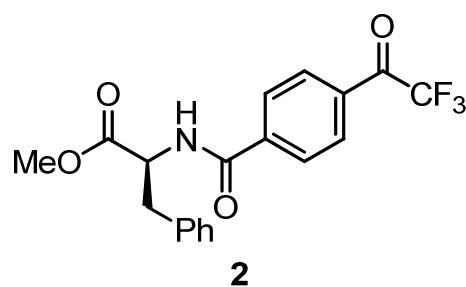


ESI Phenomenon





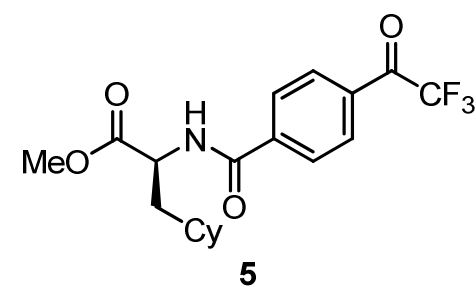
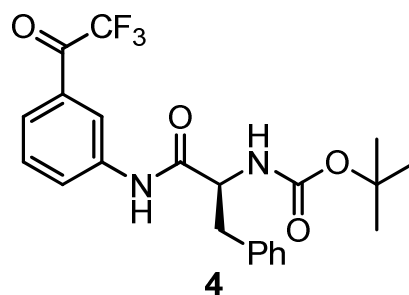
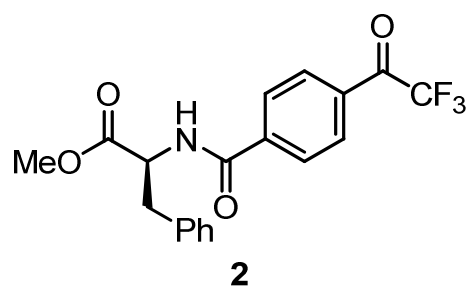
		
2	8 eq H ₂ O ₂ 96% conversion (7 h)	8 eq H ₂ O ₂ 36% conversion (24 h)
4	8 eq H ₂ O ₂ 98% conversion (7 h)	-
5	-	8 eq H ₂ O ₂ 34% conversion (24 h)



- Methyl cyclohexenone much faster than expected
- Thorpe-Ingold effect not the expected influence



2	2 eq H ₂ O ₂ 99% conversion (1 h)	2 eq H ₂ O ₂ quant. (1 h)
4	8 eq H ₂ O ₂ 23% conversion (6 h)	2 eq H ₂ O ₂ quant. (1 h)
5	8 eq H ₂ O ₂ 55% conversion (6 h)	2 eq H ₂ O ₂ quant. (1 h)

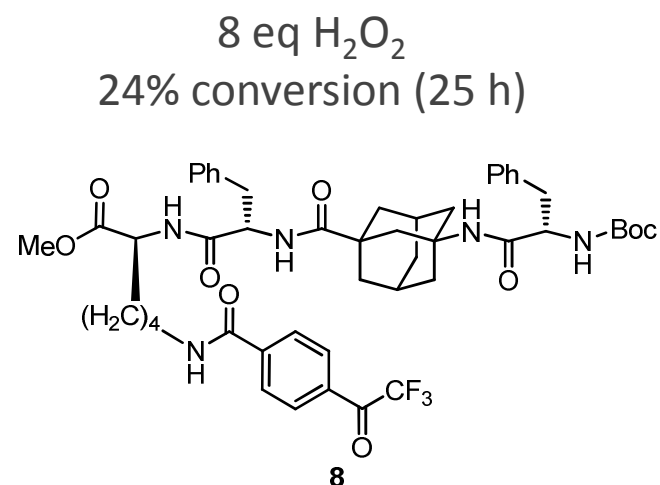
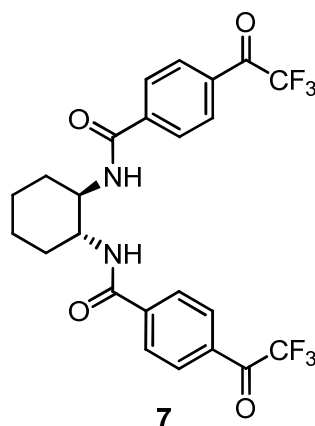
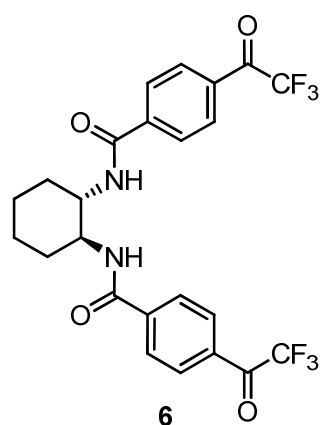


- π-π-interaction
- Weak or no dispersion effects

Results – Linear Compounds

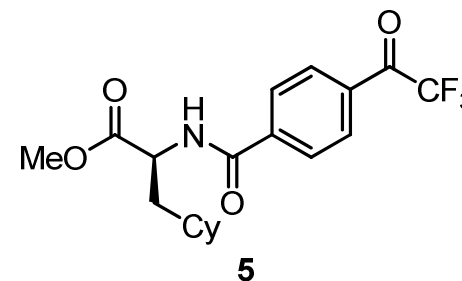
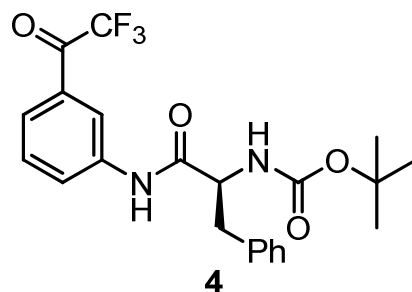
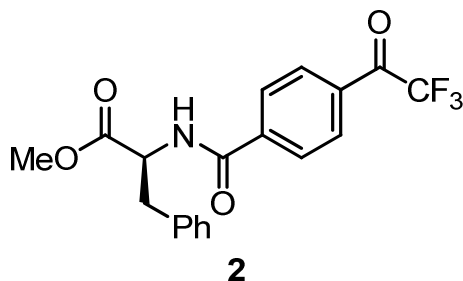


2	8 eq H ₂ O ₂ 64% conversion (25 h)	6 eq H ₂ O ₂ quant. (3 h)	8 eq H ₂ O ₂ 19% conversion (7 h)
4	8 eq H ₂ O ₂ 27% conversion (25 h)	8 eq H ₂ O ₂ 46% conversion (25 h)	8 eq H ₂ O ₂ 16% conversion (7 h)
6	-	2 eq H ₂ O ₂ quant. (1 h)	-
7	-	4 eq H ₂ O ₂ quant. (2 h)	-



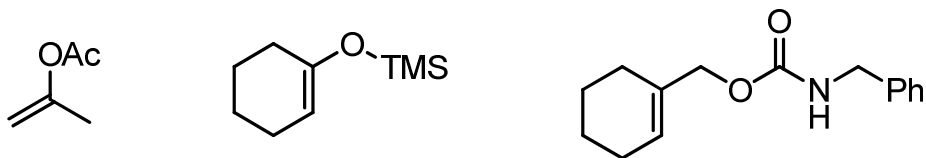


- Substrates:
 - Steric less demanding Michael systems can be epoxidized
 - Electronic properties of the double bond are important (electroneutral/-rich vs. electron-poor)
 - More flexible substrates are slower epoxidized
- Interactions:
 - Statements concerning possible interactions are difficult (e.g. **2** vs. **5**)
 - No tendency is yet recognizable
- Substitution patterns:
 - *Meta*-position less reactive or sterically more hindered (**2** vs. **4**)
 - Exact comparison of **2** and **4** difficult

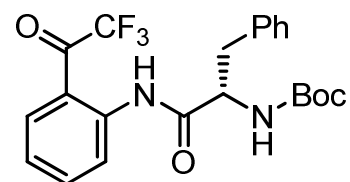




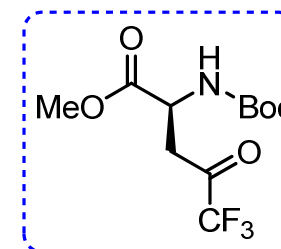
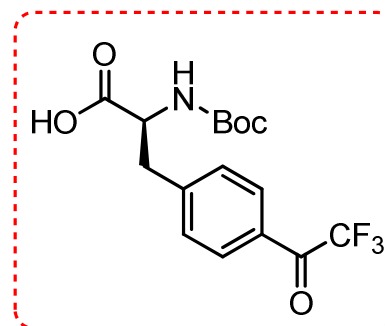
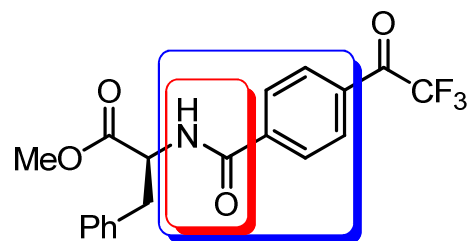
- Expansion of the substance library



- Synthesis of the missing catalyst analog

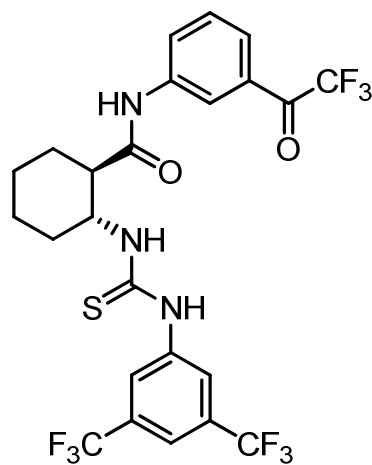


- Direct modification of amino acids





- Selective reduction method to shorten the synthesis of the catalytic moiety
- Otto, Otto, Otto, ...
- Thiourea backbone





My thanks go to ...

... Prof. Peter R. Schreiner

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... Katharina Lippert, Lukas Wanka, and Mareike Machuy

... Sascha Combe, Dominik Niedek, and Weike Newe

Thank you for your attention!