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Enantioselective Synthesis of β^2 -Amino Acids by Organocatalytic *Mannich* Reaction



Master Thesis





Table of content

- Introduction
 - β^2 -amino acids
 - Organocatalysis

- Practical part
 - Process optimization
 - Cbz-N,O-acetal
 - Fmoc- β^2 -homo-serine
 - Fmoc- β^2 -homo-threonine
 - Fmoc- β^2 -homo-cysteine

- conclusion





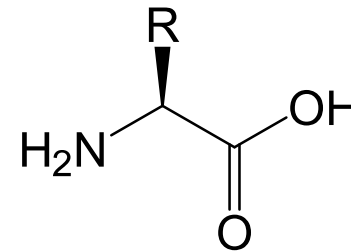
β^2 -amino acids



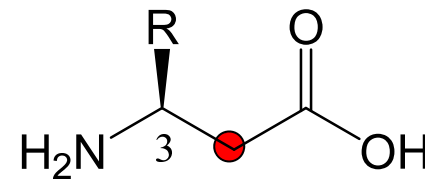


β -aminosäuren: nomenclature

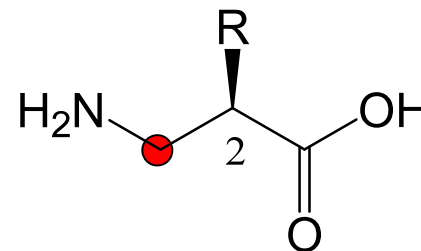
α -amino acids



β^3 -amino acids



β^2 -amino acids





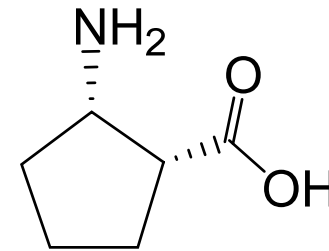
β -amino acids: characteristics

- secondary metabolites
- proteolytic and metabolic stabilization of peptides
- β^3 -amino acids \rightarrow homologisation
- β^2 -amino acids \rightarrow enantioselective reactions

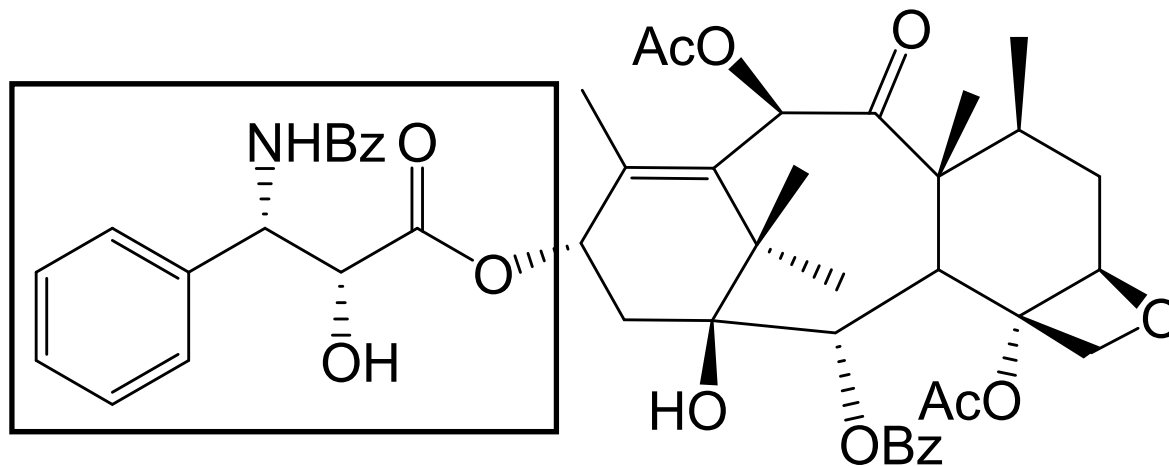


β -amino acids: applications

- **Cispentacin:** fungicide

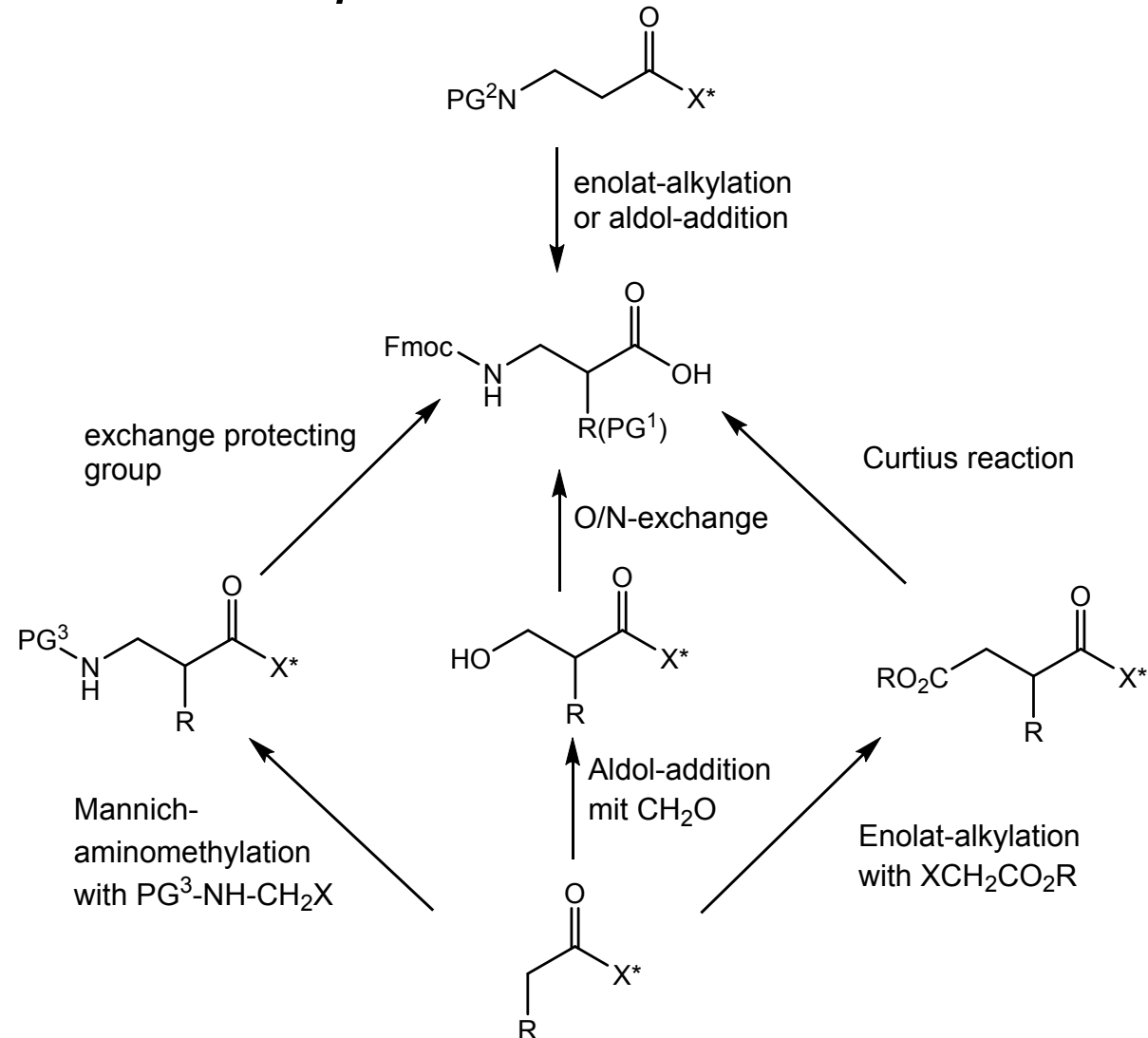


- **Taxol:** antitumor agent





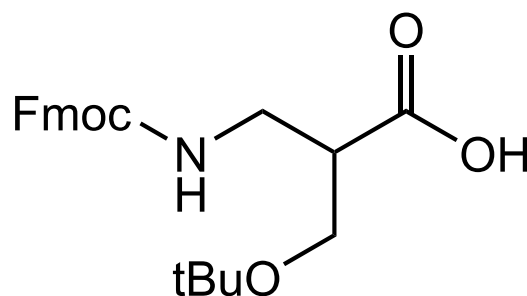
Synthesis Fmoc- β^2 -amino acid



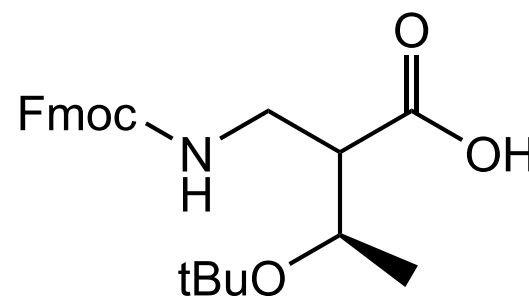


Steps for β^2 -amino acid with β -leaving groups

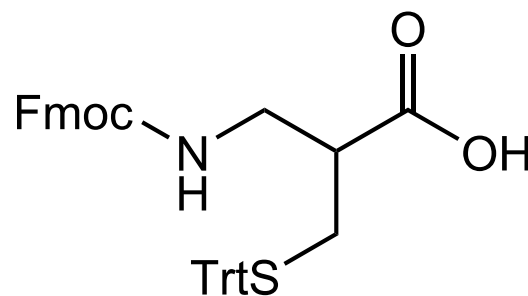
β^2 -serine (9)



β^2 -threonine (13)



β^2 -cysteine (10)



D. Seebach et al., Synth. 2009, 1, 1

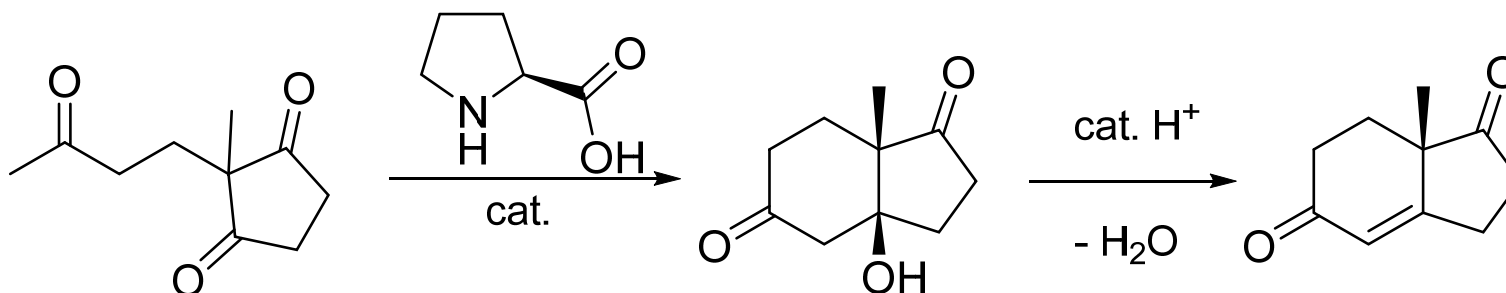


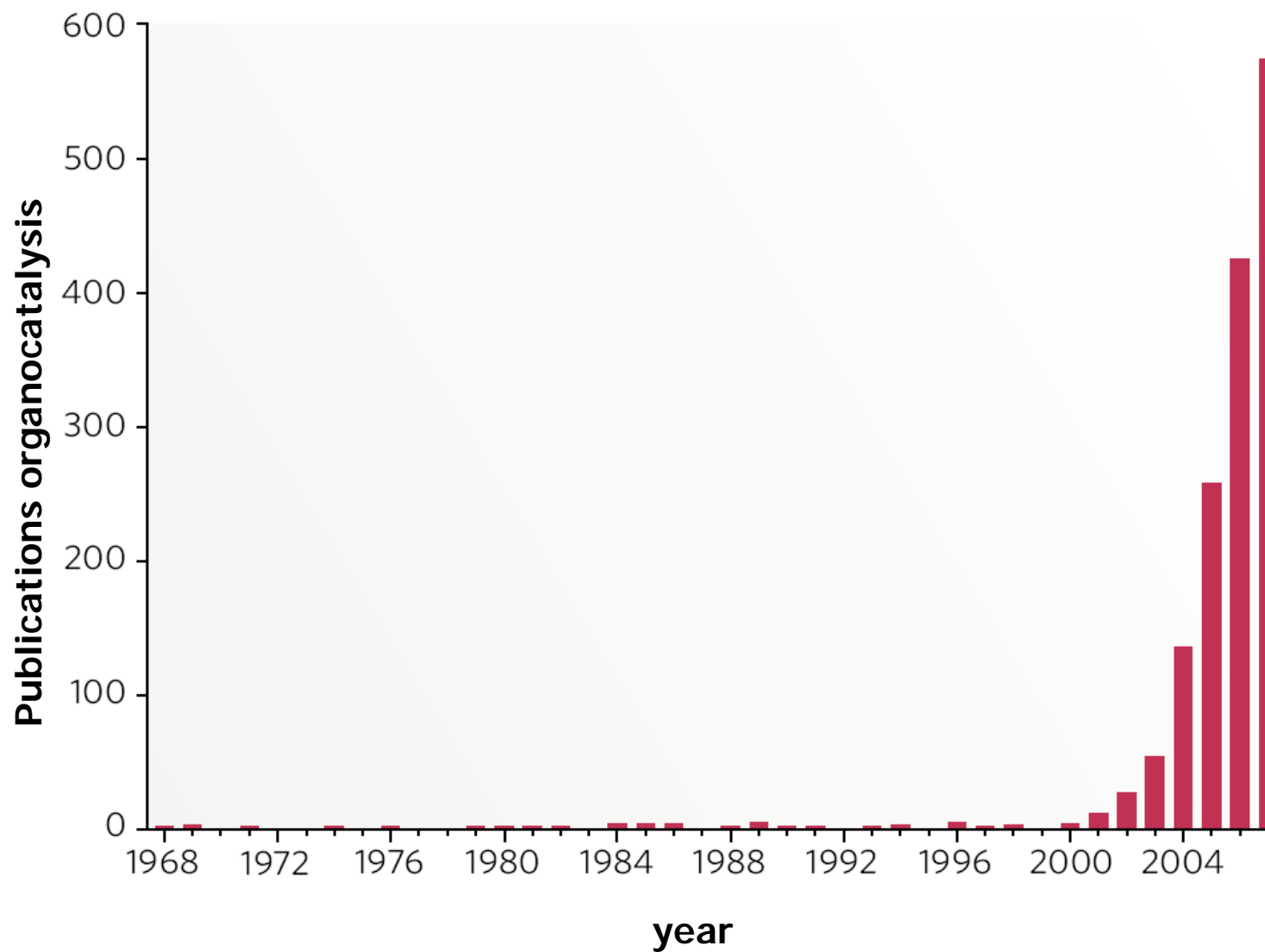
Organocatalysis



Organocatalysis

- Previous metallorg. catalysts for synthesis of enantiomerically pure compounds
- Hajos-Parrisch-reaction (1971)

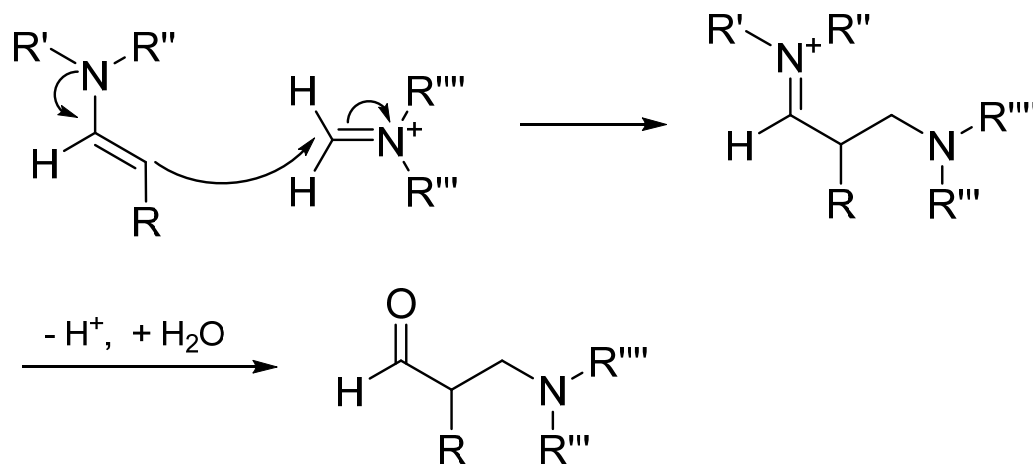
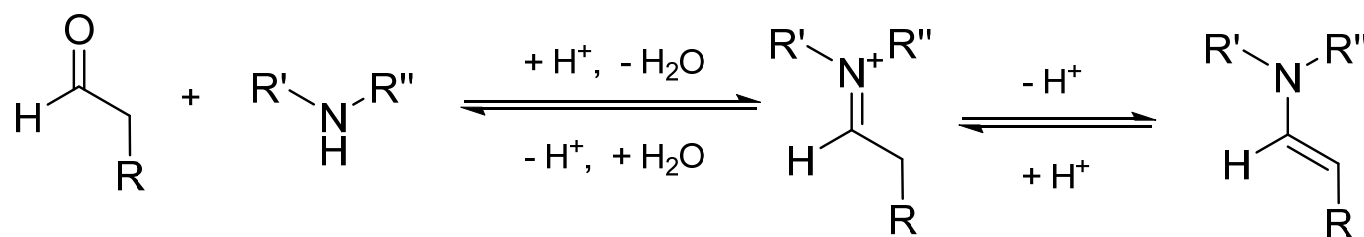




D. W. C. MacMillan, *Nature* **2008**, *455*, 304.

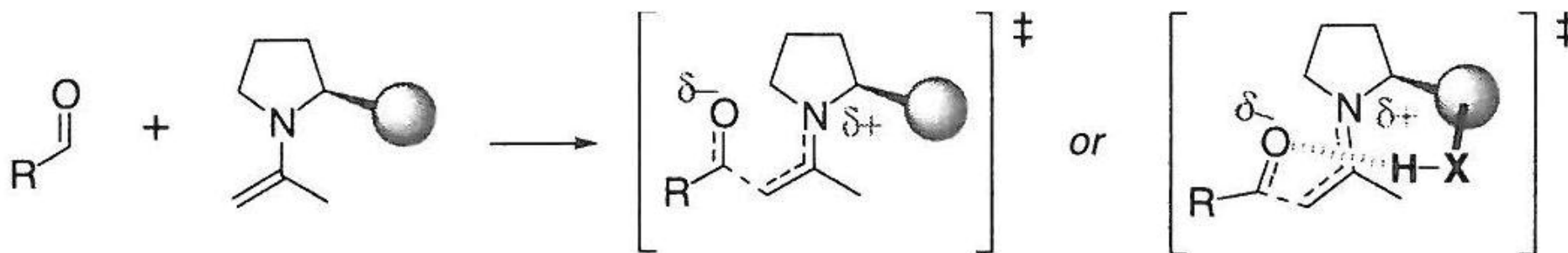


Mannich reaction





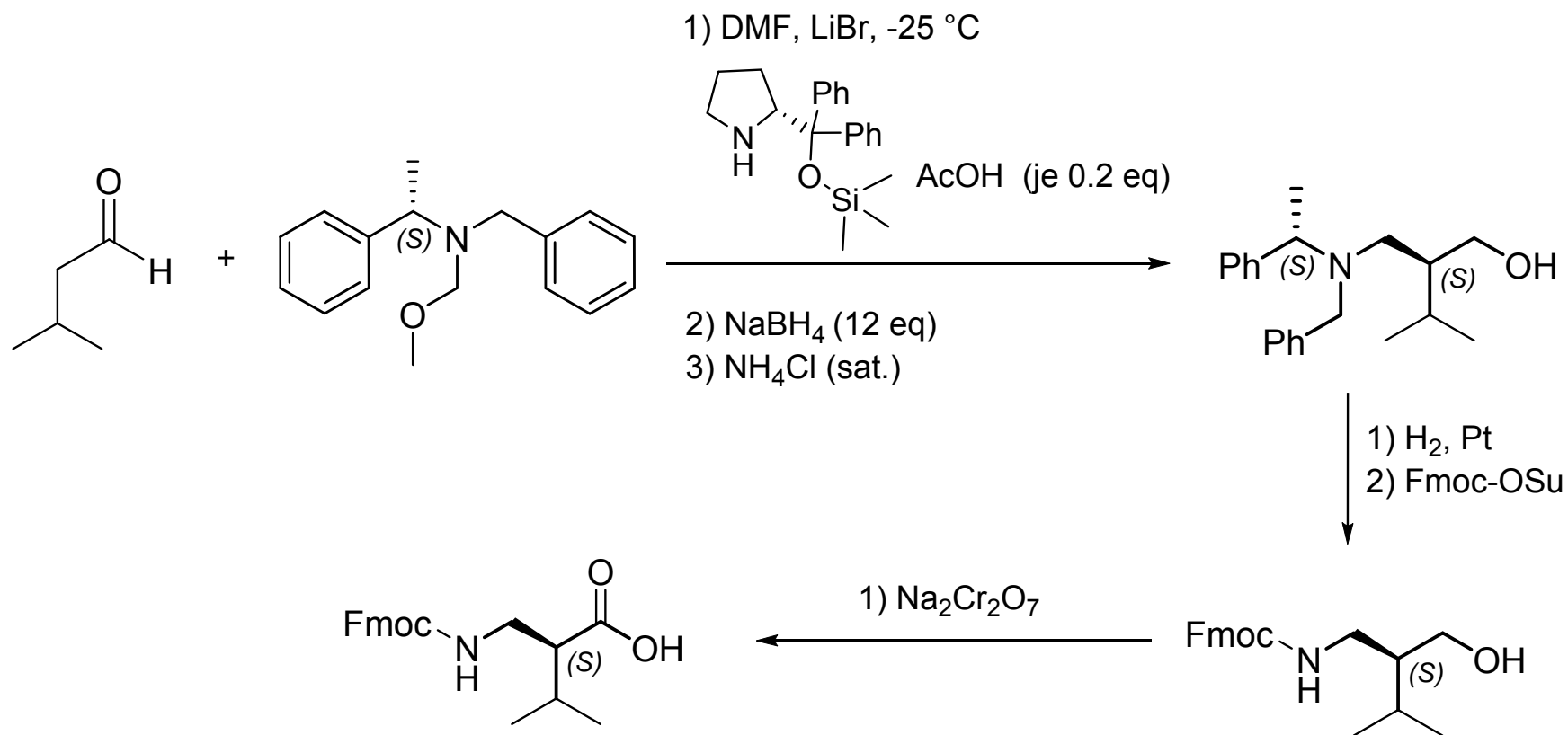
Organocatalysis: Enamin-transition states



- steric
- activation with H-bridge

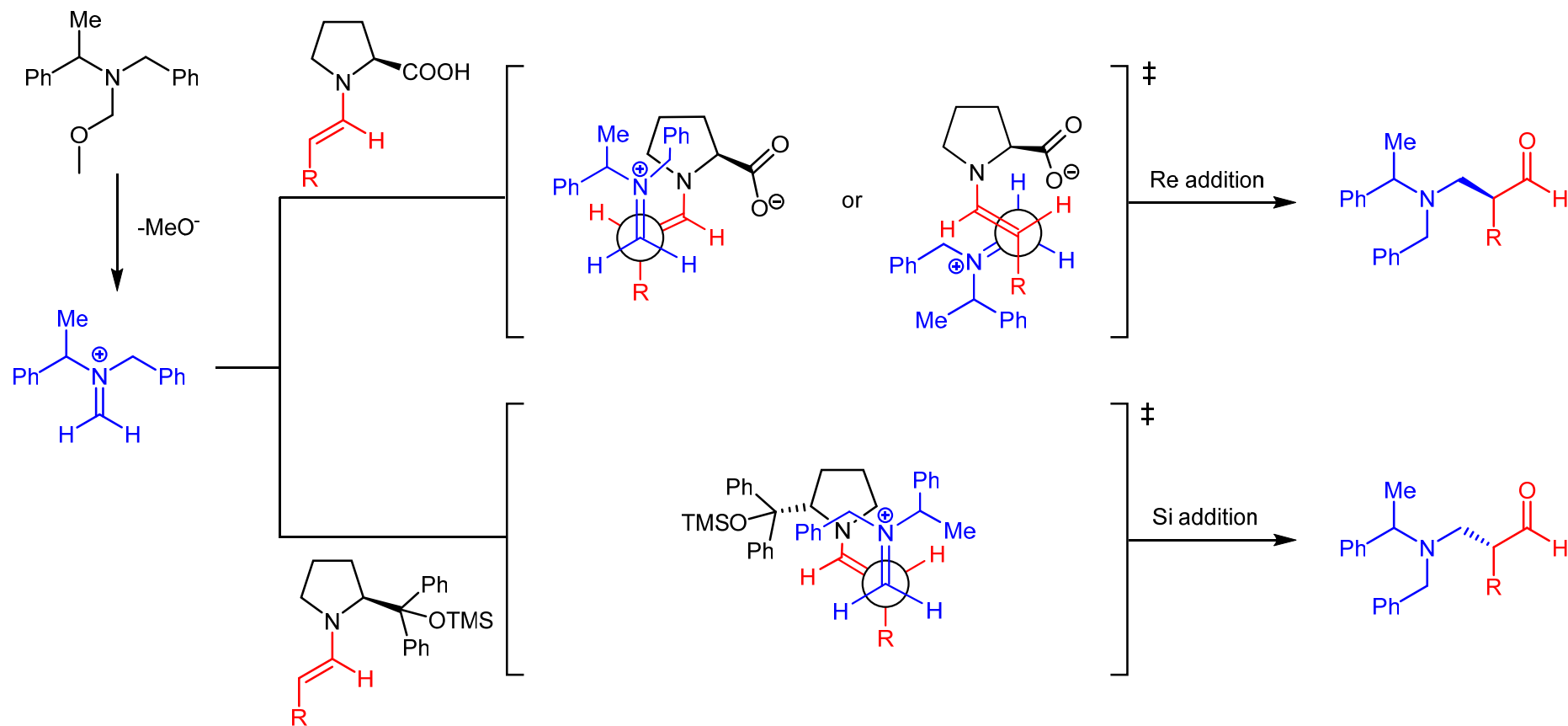


Reaction overview





Transition states



D. Seebach et al., *Helv. Chim. Acta* **2007**, *90*, 425.



Goals

- Optimization of the process
- Catalyst-screening
- Cbz-N,O-acetal as imine-source
- Transfer aldehydes with labile side chains
 - Serine
 - Threonine
 - Cysteine

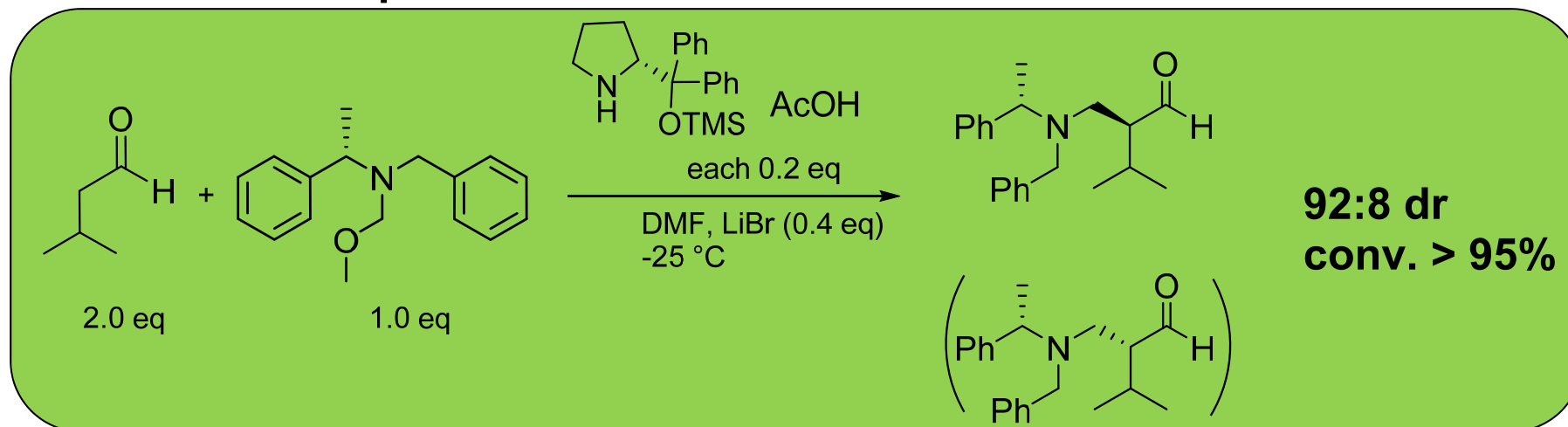




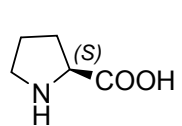
Practical part



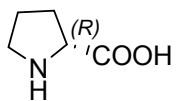
Prozess optimization



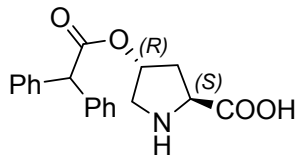
- Quantity cat. → dr unchanged, conversion change
- H⁺ catalysis → dr lower with < pK_A
- Temperature → -35°C: 92:8 dr; -15°C 86:14 dr
- iPr-N,O-acetal → 92:8 dr; conv. > 95%



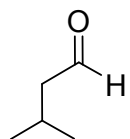
C1
82:18 dr



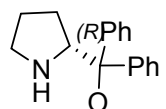
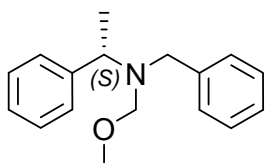
C2
26:74 dr



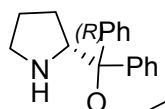
C3
69:31 dr



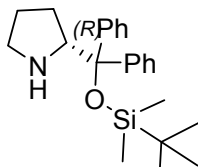
+



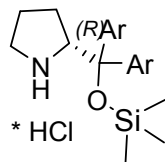
C4
92:8 dr



C5
92:8 dr

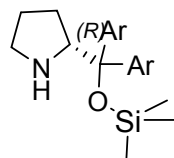


C6
94:6 dr



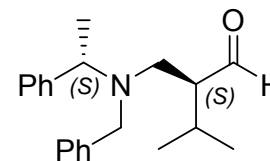
Ar = 3,5-Me₂-C₆H₃

C7
89:11 dr

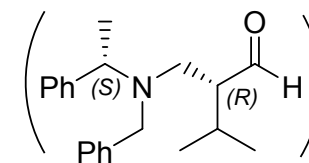


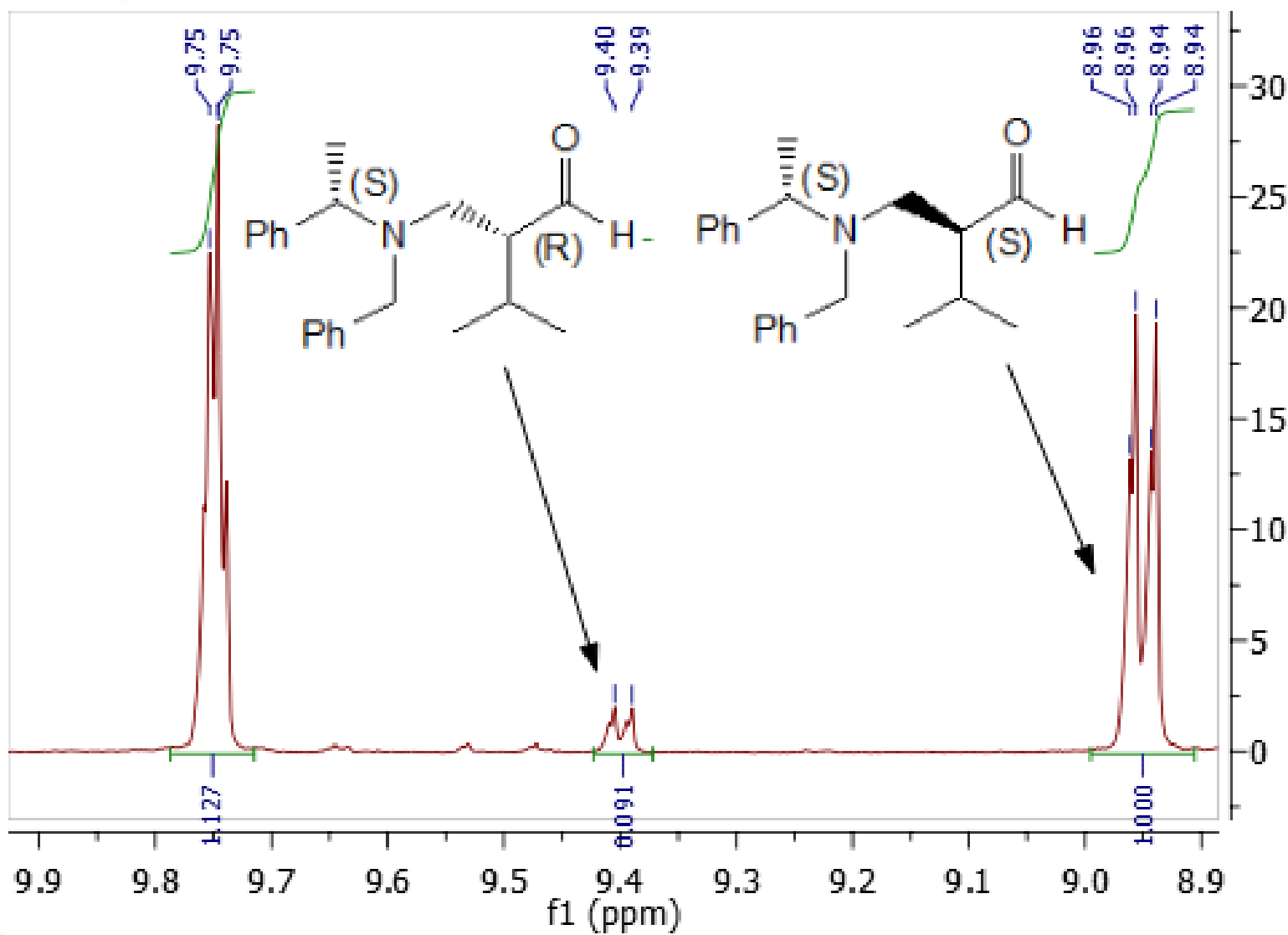
Ar = 3,5-CF₃-C₆H₃

C8
90:10 dr



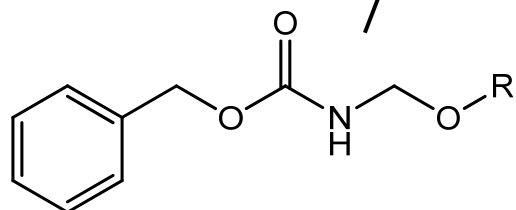
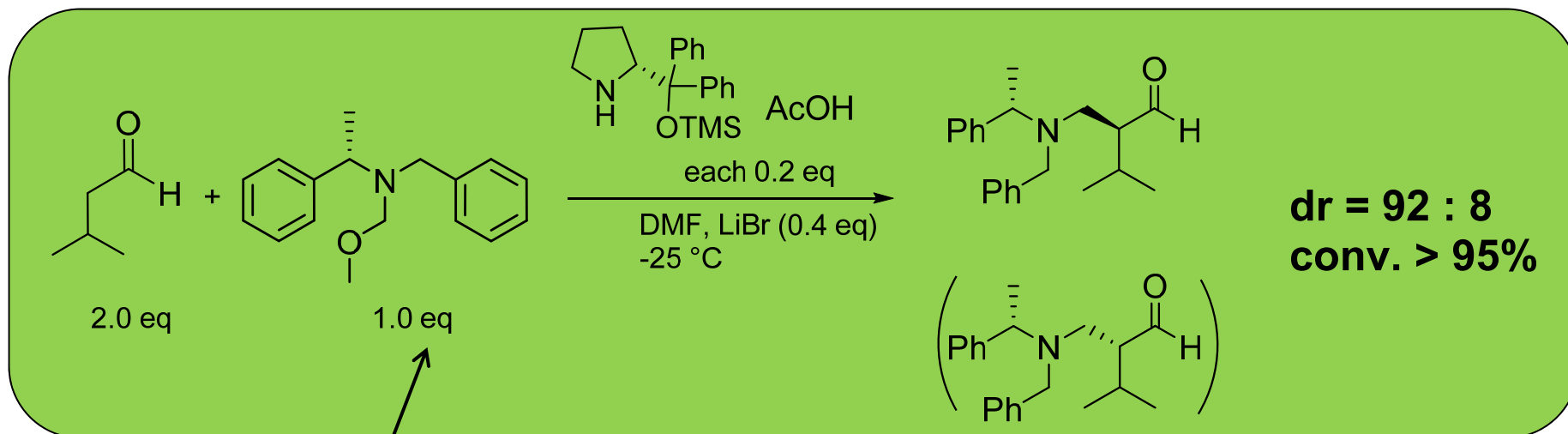
+







Cbz-N,O-Acetal

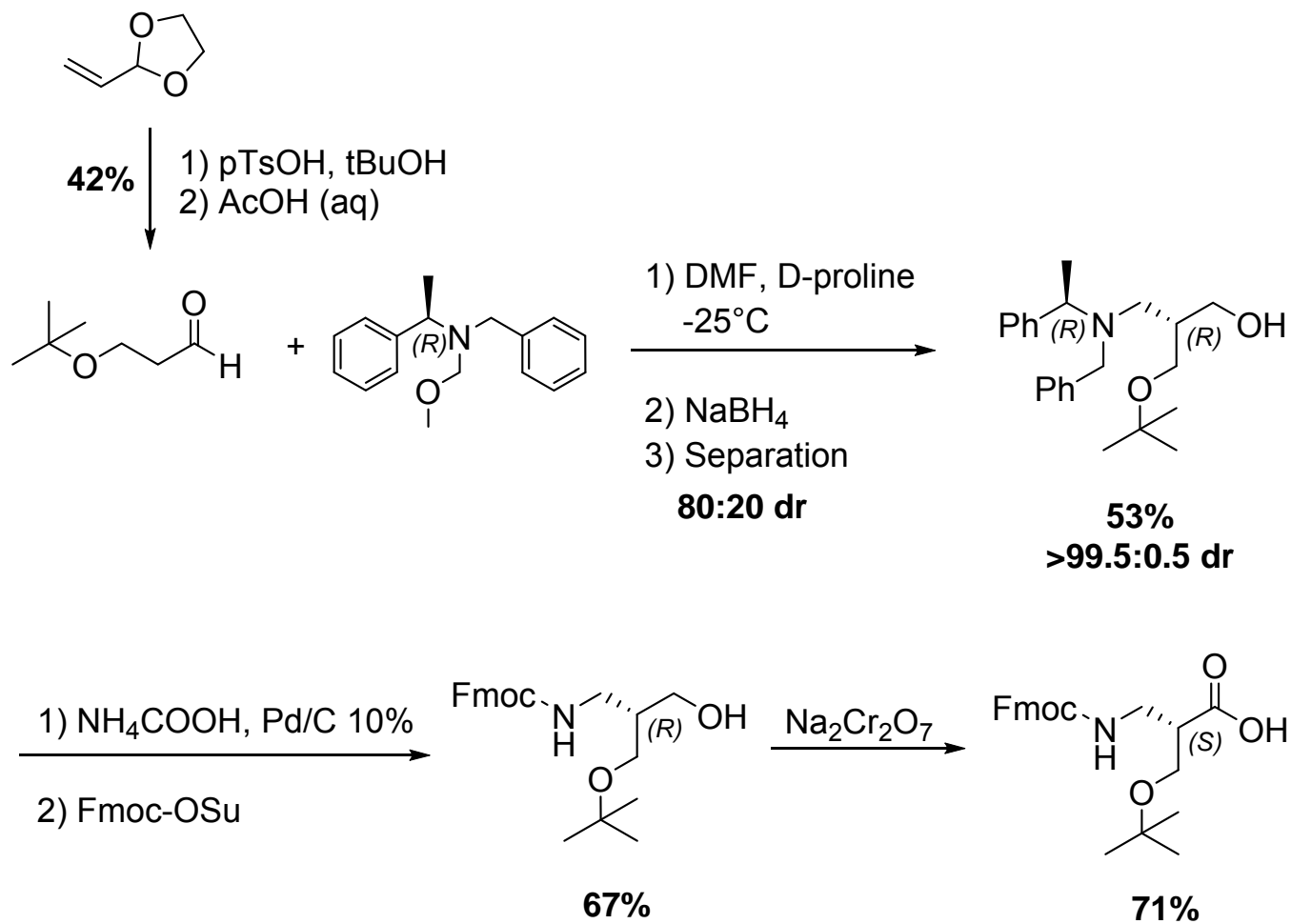


- No exchange of protecting group
- No reaction



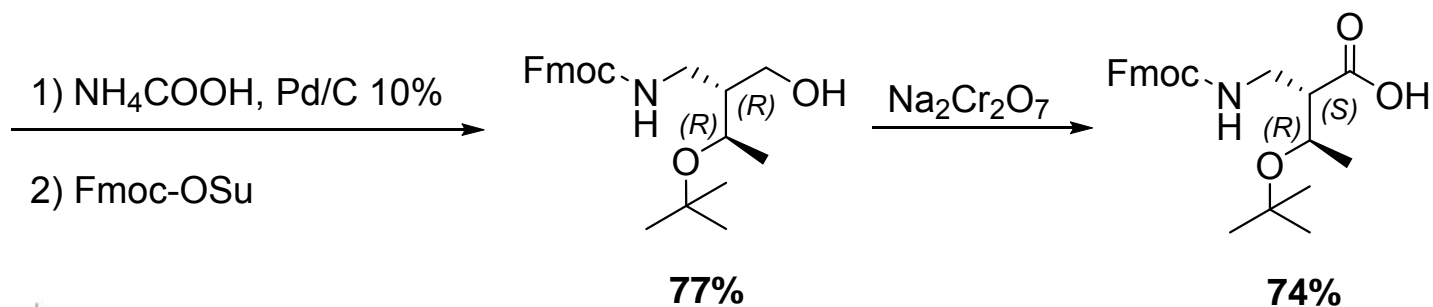
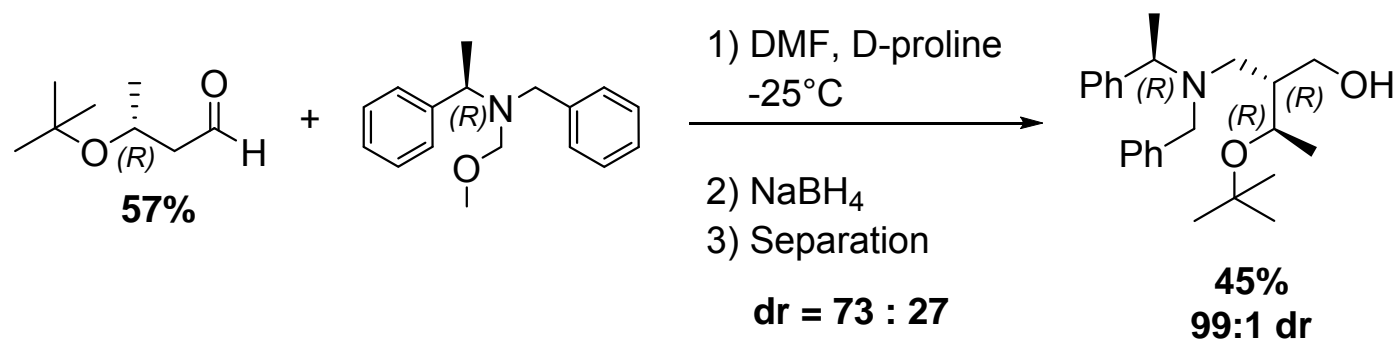
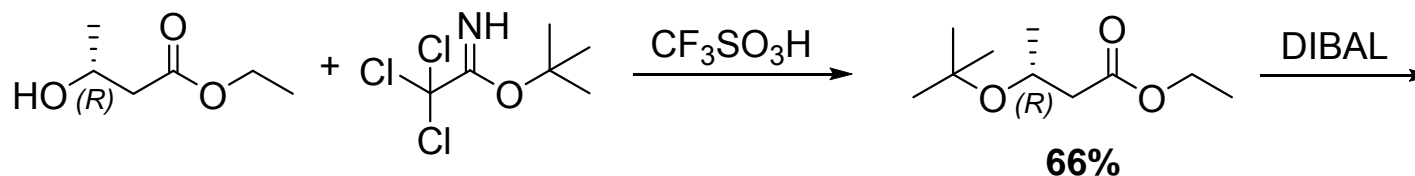


Fmoc- β^2 -homo-serine



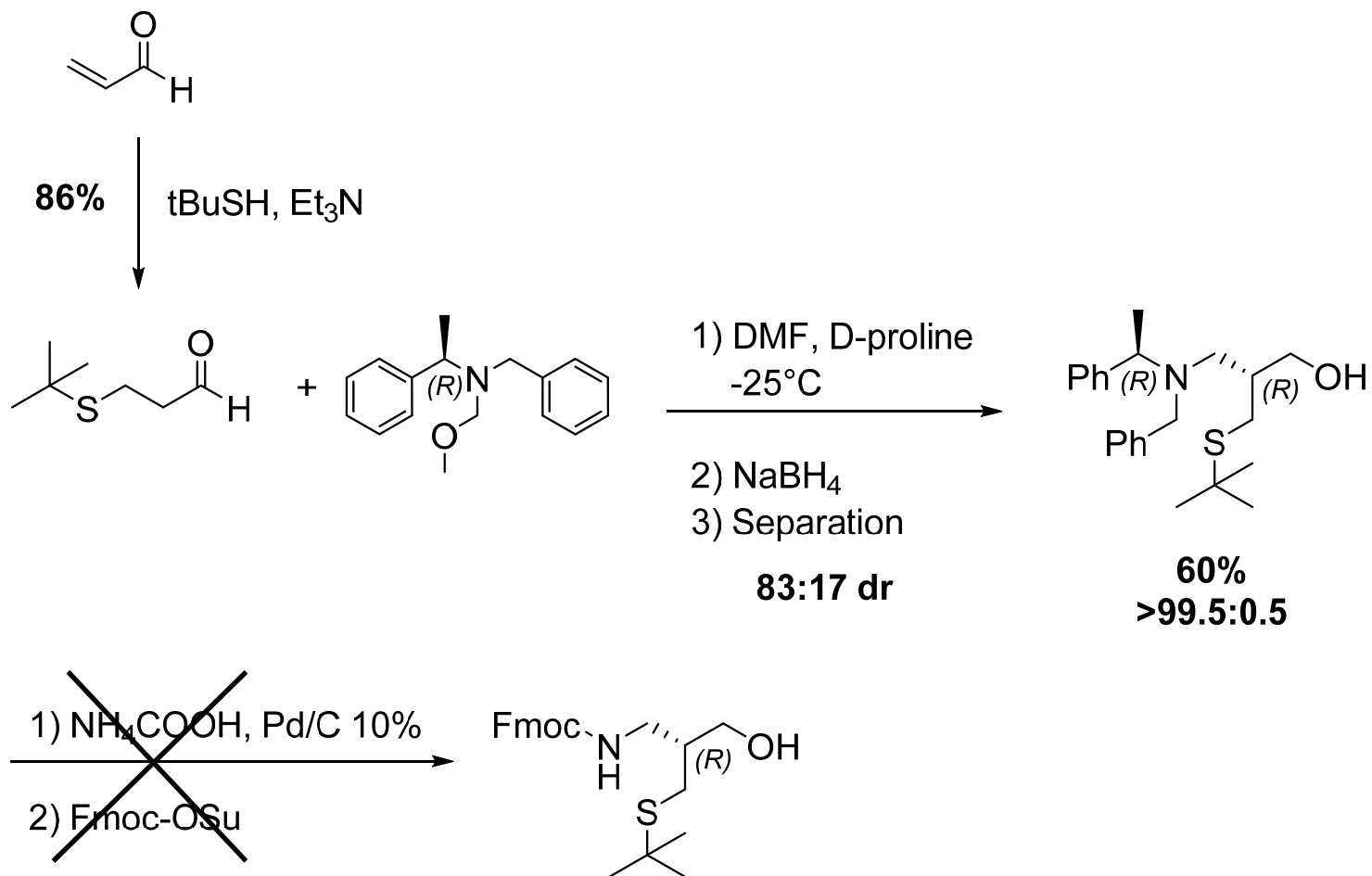


Fmoc-β²-homo-threonine



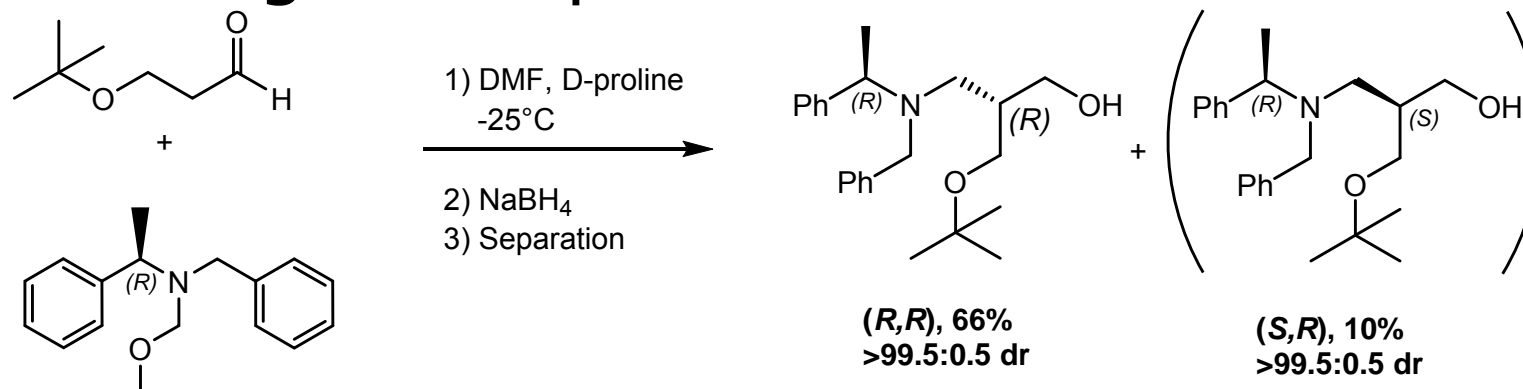


Fmoc- β^2 -homo-cysteine

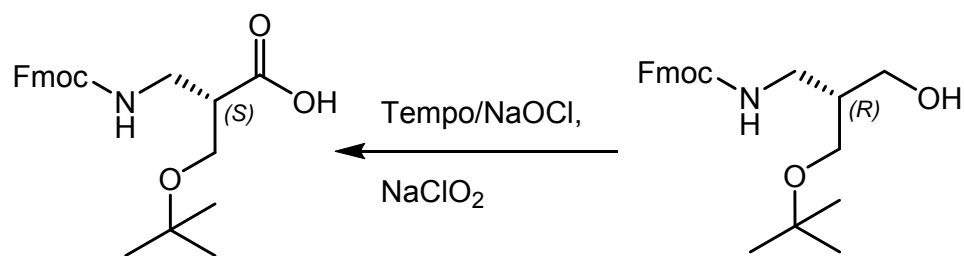




Up-scaling Fmoc-β²-serine



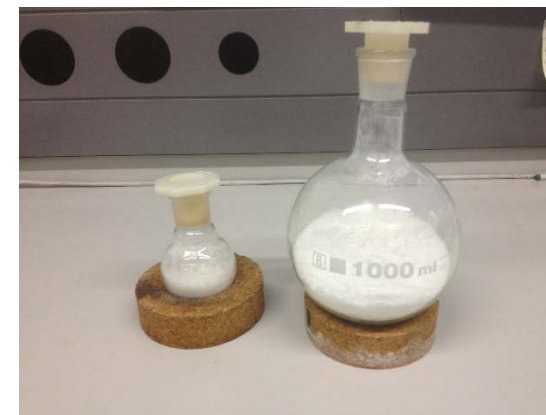
1) NH₄COOH,
Pd/C 10%
2) Fmoc-OSu



(S), 90%; 99:8:0.2 er

(R), 88%; 99:6:0.4 er

(R), 97%; (S), 95%





Conclusion

- Optimization of α -aminomethylation
- Diastereoselective *Mannich* reaction on aldehydes with β -leaving groups
- Multigram synthesis of Fmoc-(*S*)- β^2 -Ser(tBu)-OH (46 g)
- Fmoc- β^2 -Ser(tBu)-OH and Fmoc- β^2 -Thr(tBu)-OH in 6 steps in overall yield of 24% and 10%



