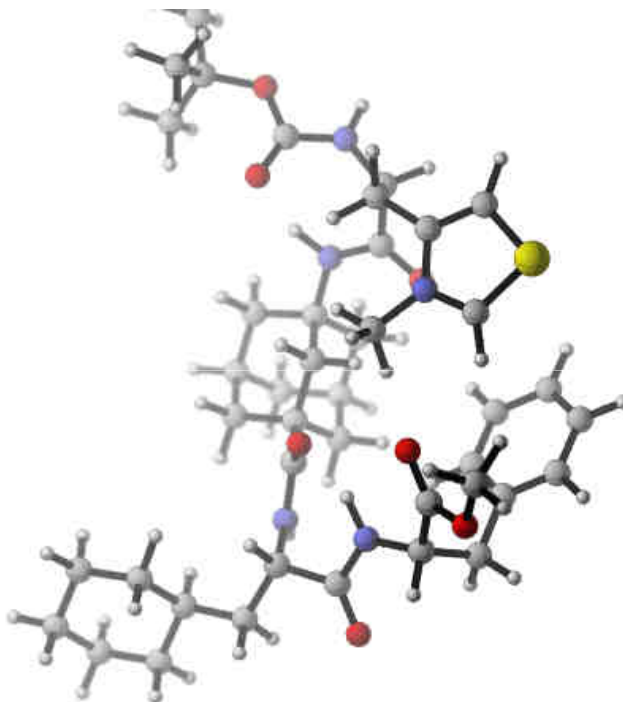


Towards Asymmetric Catalysis Using NHC-Peptide Catalyst

Seminar talk presented by
Friederike Gasiorek

27.04.2012

*Institute of Organic Chemistry
Justus-Liebig University Giessen*



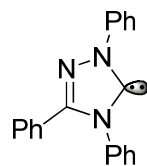


- Carbenes
- Asymmetric Benzoin condensation
- Asymmetric Stetter reactions
- Amino acids and peptides as catalysts
- Synthesis of the peptides
- Outlook

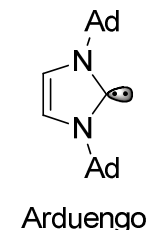


- Carbene: neutral, bivalent carbon atom with electron sextet
- First reports of NHC's by Wanzlick, Bertrand and Arduengo

commercially available stable carbene:

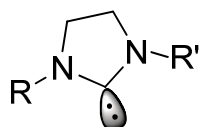


Enders

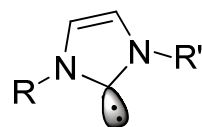


Arduengo

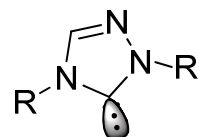
- General structure of nucleophilic carbenes:



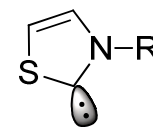
imidazolinylidene



imidazolylidene



triazolylidene

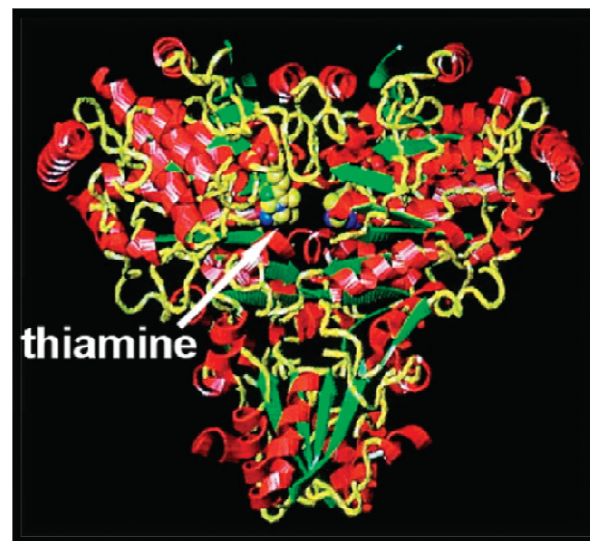
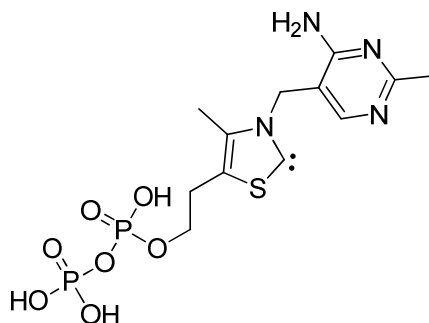


thiazolylidene

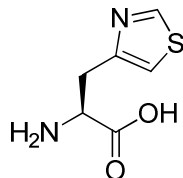
- Excellent ligands for metal-based catalysis (e.g. for Suzuki-coupling)
- Increasing use in metal-free catalysis, which is often more economical and environmentally friendly



- Coenzyme thiamine pyrophosphate (vitamine B₁):
natural thiazolium salt
catalyzes nucleophilic acylation by transketolase enzymes



- Cofactor is embedded in a narrow channel in the center of the enzyme
- High selectivity in catalytic reaction
- Development of catalysts with nonproteinogenic amino acid thiazolylalanine to mimic this enzymatic system



Benzoin Condensation



1832: found by Liebig and Wöhler

Cyanide-catalyzed coupling of benzaldehyde to benzoin (α -hydroxyketone)

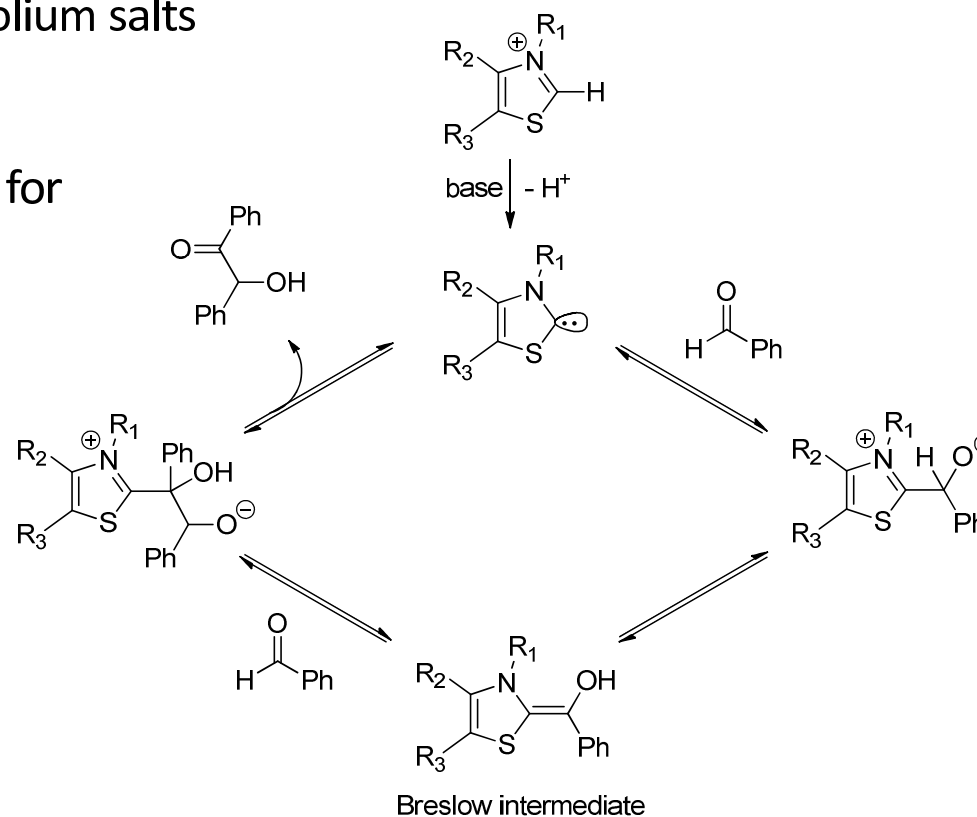
“Umpolung”-concept by Seebach:

carbonyl carbon with inverted nucleophilic reactivity (a^1 to d^1)

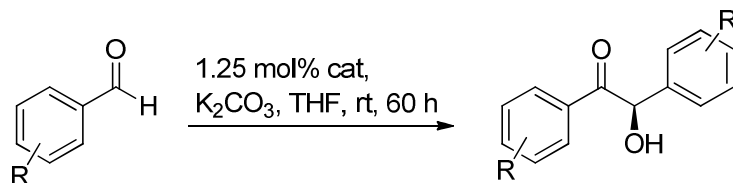
1943: Ugai et al. recognized that thiazolium salts could also be used as catalyst

1958: Breslow proposed a mechanism for the thiazolium salt-catalyzed benzoin condensation

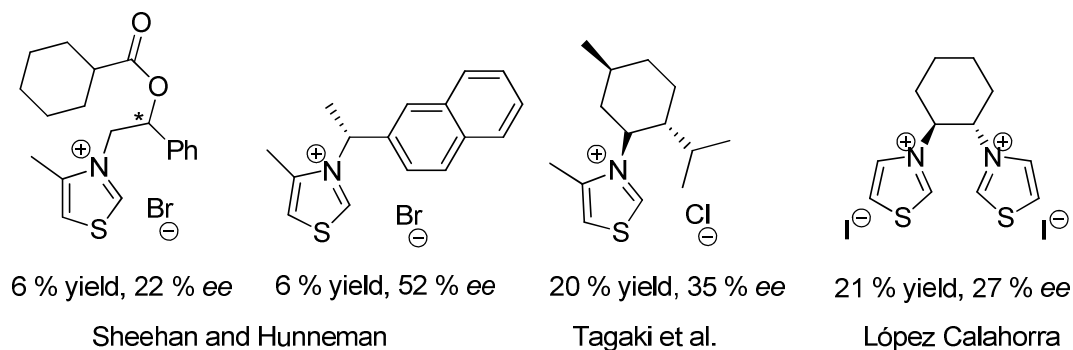
Breslow intermediate:
 d^1 -synthon



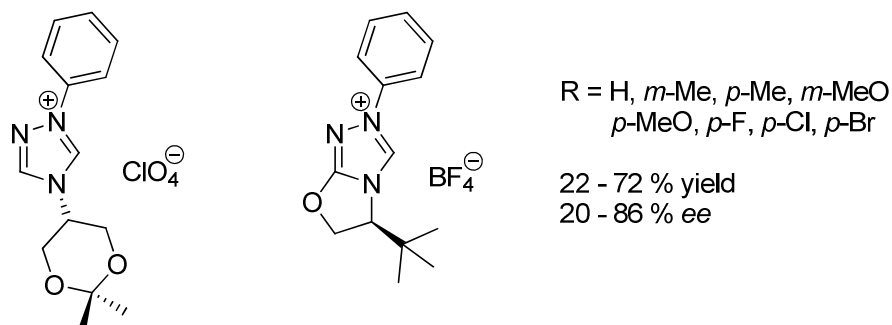
Asymmetric Benzoin Condensation



- Chiral thiazolium salts to catalyze the benzoin condensation:



- Enders: chiral triazolium-salt



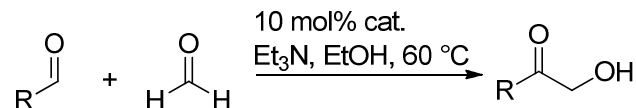
- Base: K₂CO₃, KO^tBu

J. Sheehan, D. H. Hunneman *J. Am. Chem. Soc.* **1966**, *88*, 3666-3667; J. Sheehan, T. Hara *J. Org. Chem.* **1974**, *39*, 1196; W. Tagaki, Y. Tamura, Y. Yano *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478-480; C. Zhao, S. Chen, P. Wu, Z. Wen *Huaxue Xuebao* **1988**, *46*, 784-790; J. Martí, J. Castells, F. López Calahorra *Tetrahedron Lett.* **1993**, *34*, 521-524; D. Enders, K. Breuer, J. H. Teles *Helv. Chim. Acta* **1996**, *79*, 1899-1902



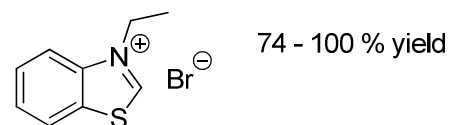
Asymmetric Benzoin Condensation

- Crossed benzoin condensation

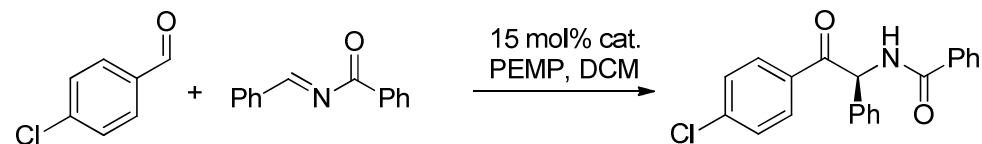


Problem of mixture of all possible symmetric and asymmetric acyloins

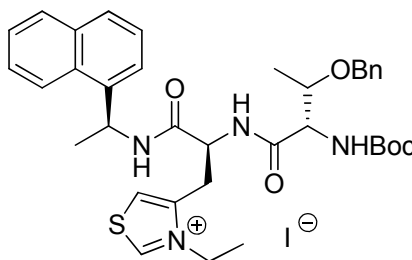
- Selective cross-acyloin condensation by Inoue and coworkers using thiazolium salt



- Intermolecular aza-benzoin reaction by Miller et al. using small peptide catalyst



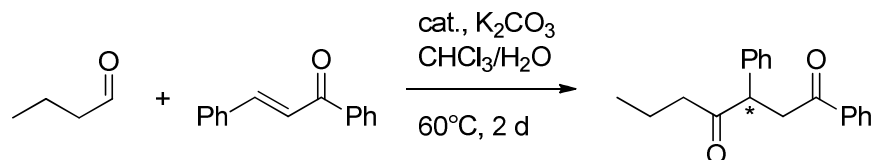
90 % yield
87 % ee





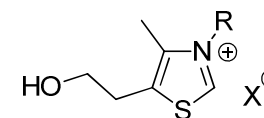
Asymmetric Stetter Reaction

- Intermolecular Stetter reactions



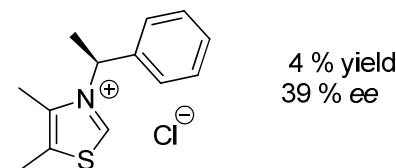
Catalytic 1,4-addition of aldehydes to a Michael acceptor

1976: Stetter and coworkers found thiazolium salts for catalysis



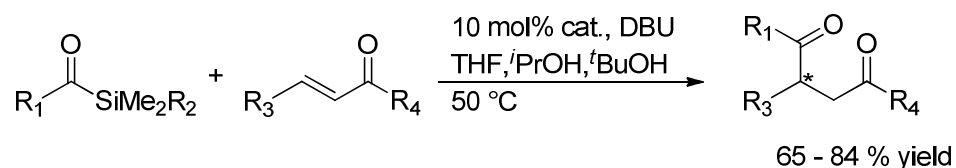
- a) $R_1 = Bn, X = Cl$
- b) $R_2 = Me, X = I$
- c) $R_3 = Et, X = Br$
- d) $R_4 = (CH_2)_2OEt, X = Br$

1989: Enders et al. first asymmetric Stetter reaction
poor yield and *ee*



Problem: self-condensation of the aldehyde and benzoin as side product

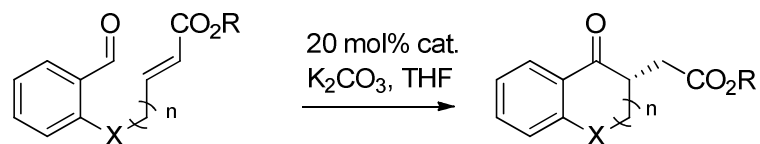
- Sila-Stetter reaction by Scheidt and coworkers, cat. c)





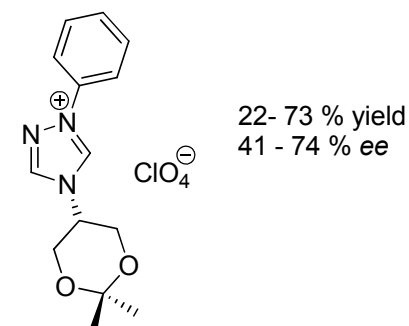
Asymmetric Stetter Reaction

- Intramolecular Stetter reactions

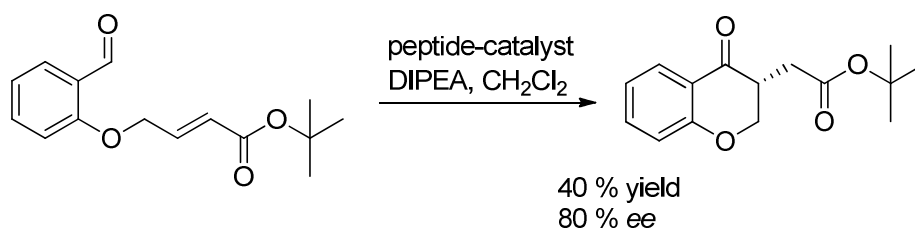


(*E*)-alkenes gave better yields than (*Z*)-alkenes
Five- and six-membered rings are available

1996: Enders et al. first asymmetric reaction with triazolium salt



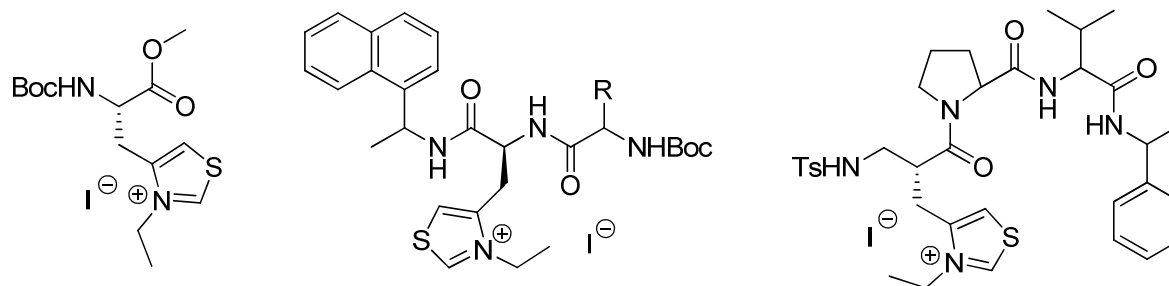
2005: Miller et al. first used small peptide organocatalysts



Amino acids and peptides as catalysts



- Miller et al: single amino acids to tetrapeptides as precatalysts for asymmetric Stetter Reaction



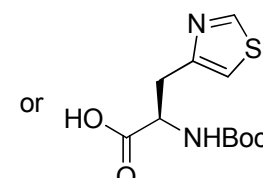
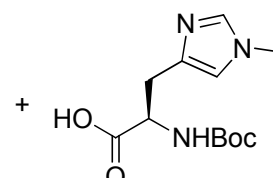
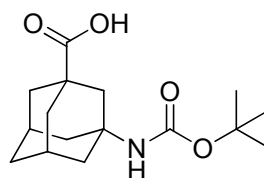
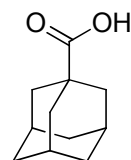
- Single derivatives show selectivity in cyclization, but poor yield due to catalyst decomposition when NHC is not sufficiently protected from dimerization
- Taz location at N- or C- terminus of a tetrapeptide lead to less enantioselectivity
- Taz at internal position gave better yield (up to 67 %) and *ee* (80 %)

Experimental

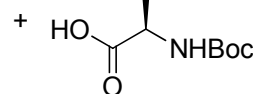
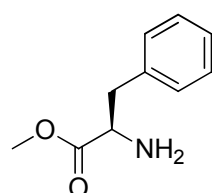


Synthesis of the tetrapeptides:

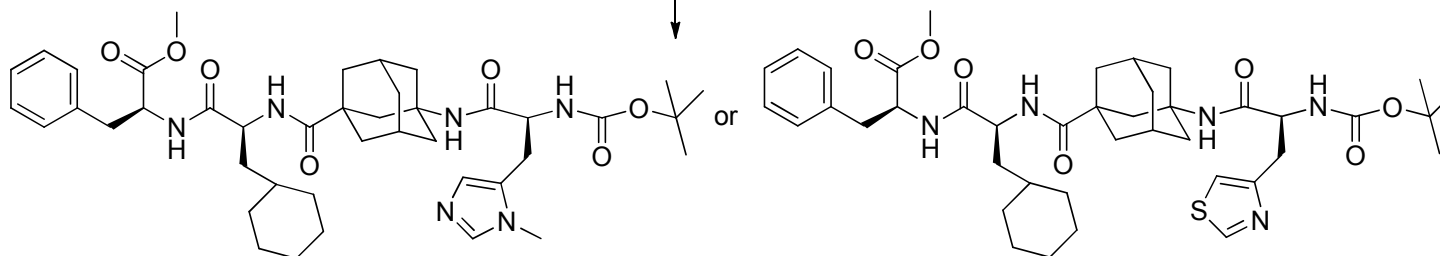
Modifying and protecting adamantane-1-carboxylic acid:



Peptide synthesis in solution:



EDC, HOBT
Et₃N
DCM



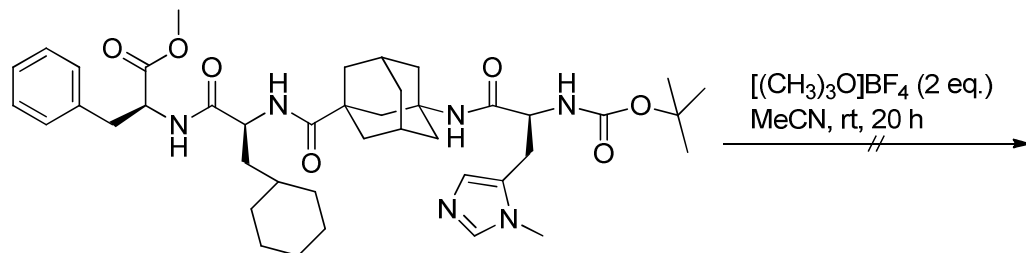
Boc-L-(π -Me)-His-^AGly-L-Cha-L-Phe-OMe

Boc-L-Taz-^AGly-L-Cha-L-Phe-OMe

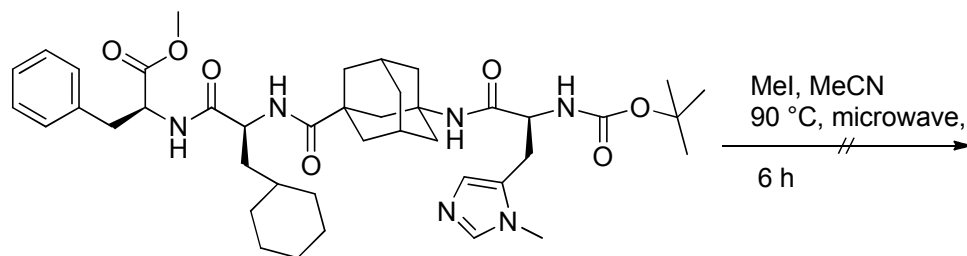


Methylation of the peptides

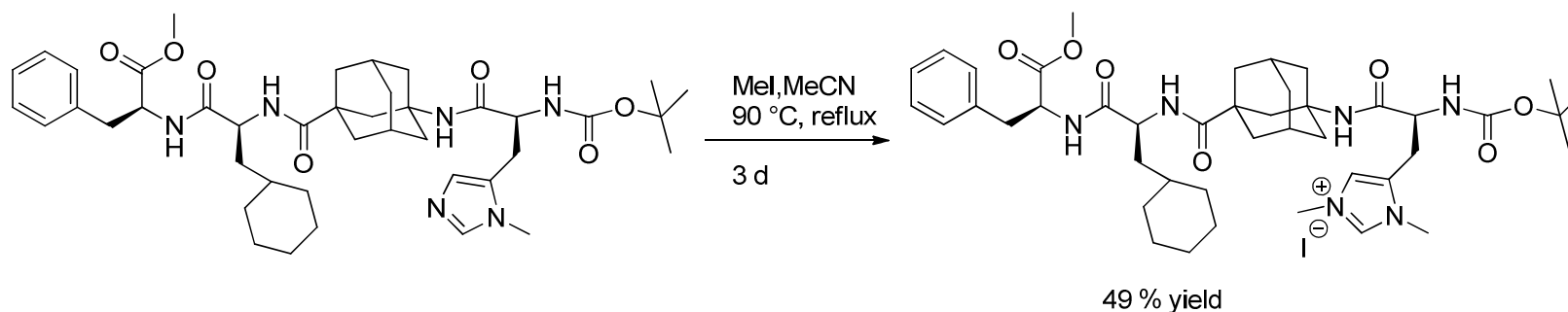
Meerwein's reagent $[(\text{CH}_3)_3\text{O}]\text{BF}_4$:



Microwave assisted:



General method:

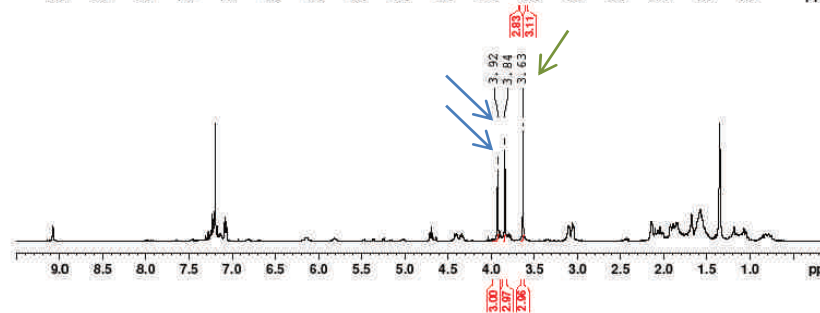
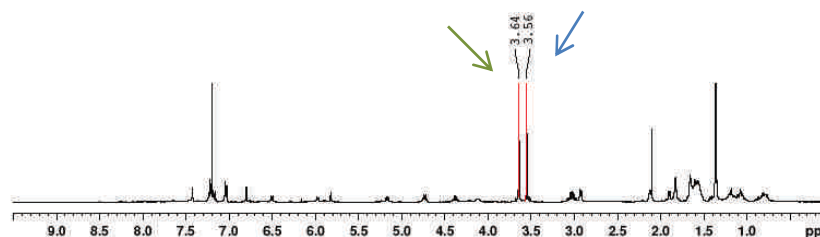
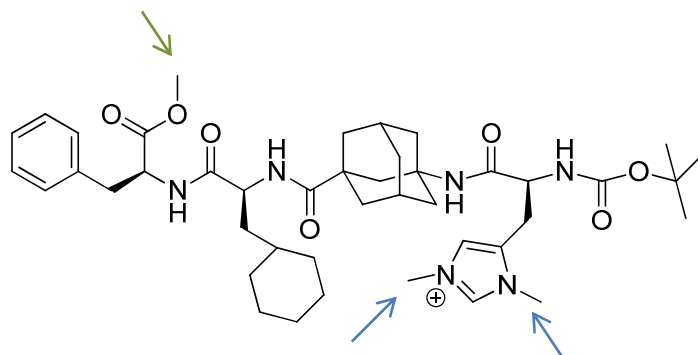


Also for Boc-L-Taz-^AGly-L-Cha-L-Phe-OMe (59 % yield)

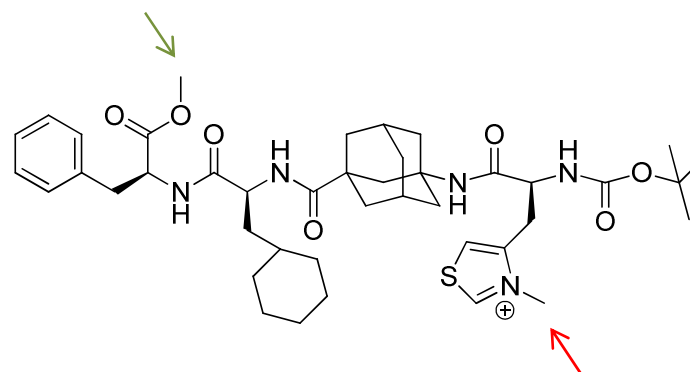
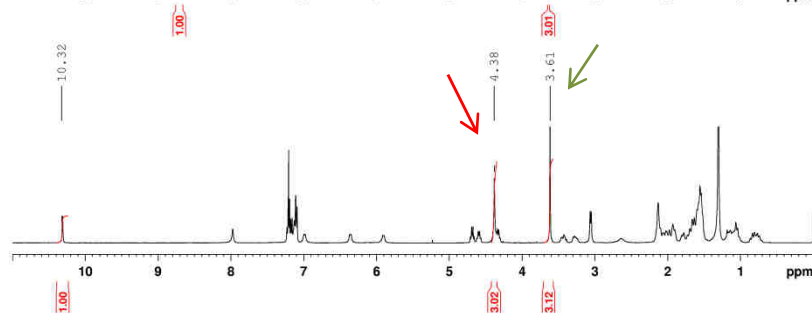
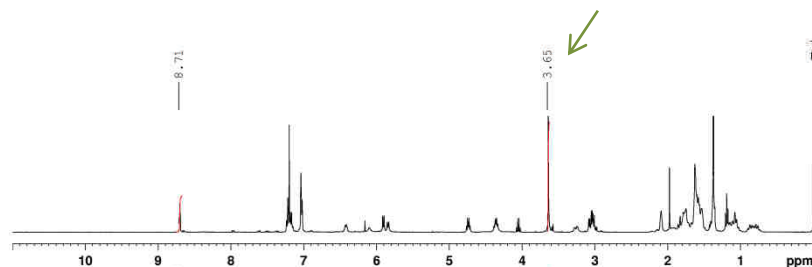


Methylation of the peptides

NMR (CDCl_3 , 400 MHz):



ESI-MS: $m/z = 776.4$

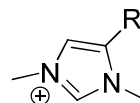
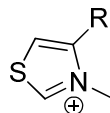


ESI-MS: $m/z = 779.3$

Deprotonation



Base-screening for deprotonation and *in situ* generation of the NHC



pK_a (DMSO) =

14.5

R = H

22.0

Bases:

DIPEA¹ (1 eq.)

i-Pr₂NEt² (2 eq.)

DBU² (2 eq.)

Et₃N² (2 eq.)

K₂CO₃³ (2 eq.)

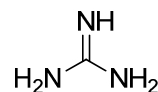
NaH (1 eq.)

KO^tBu (2 eq.)

~~DBU (2 eq.)~~

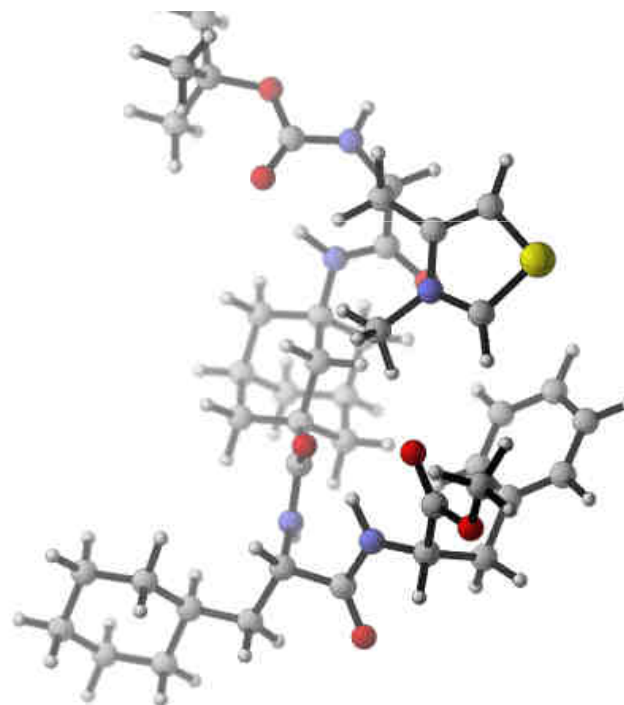
~~NEt₃ (2 eq.)~~

Testing: other organic bases like guanidine (pK_a = 28.5)





- Reaction optimization for the *in situ* generation of the NHC
- Asymmetric catalysis using peptide-catalyst:
 - Benzoin condensation
 - Stetter reaction
- Catalyst-Screening:
 - change amino acid sequence
 - synthesis of tripeptides





Thanks to

- Prof. Dr. Peter R. Schreiner
- Daniela Zell
- Lab in the 5th floor
- The whole research group