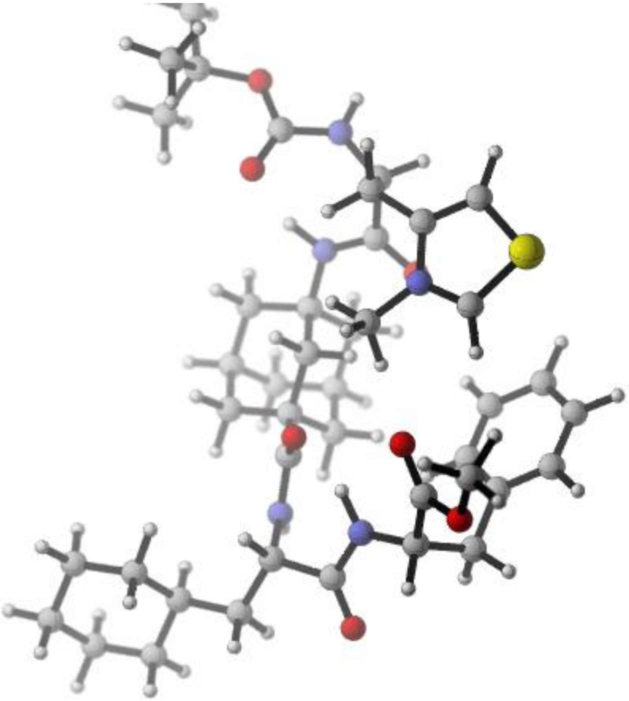
Towards Organocatalysis Mediated by NHC-Containing Peptides



Seminar talk presented by
Friederike Gasiorek

October 26th, 2012

Institute of Organic Chemistry
Justus-Liebig University Giessen

Introduction

Organocatalysis – why?

“Organocatalysis combines the concepts of molecular recognition as well as supramolecular chemistry with enzyme-like catalytic activity.”

- Chemical answer to nature as archetype
- Many enzymes act metal-free

Advantages:

low costs, broad spectrum of reactions, easy handling and stability against air and moisture, green chemistry

In this group:

oxidations
epoxidations
multi-catalysis
thiourea organocatalysis
…

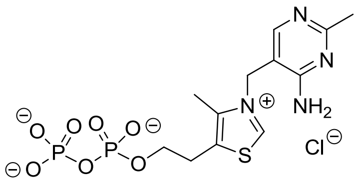
NHCs as organocatalysts: Formation of new carbon–carbon bonds

http://www.uni-giessen.de/cms/fbz/fb08/Inst/organische-chemie/agschreiner/research/nikoorgano/index_html

Carbenes in Nature

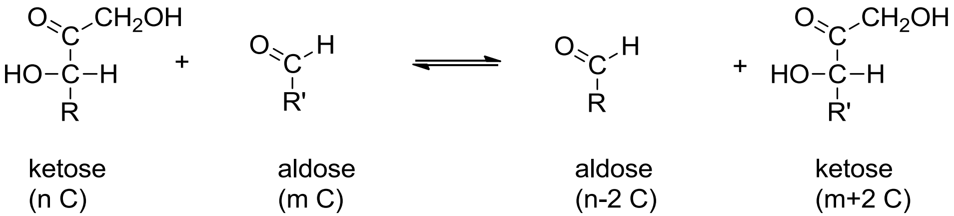
Coenzyme thiamine (vitamine B_1):

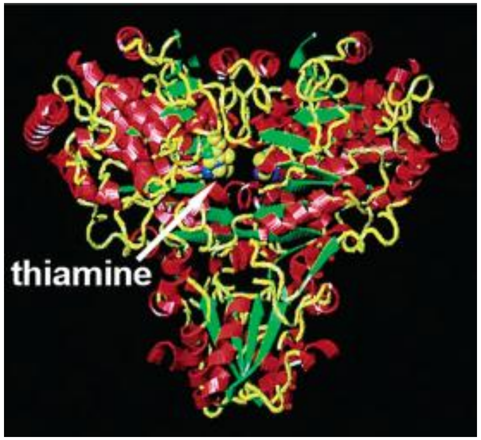
- natural thiazolium salt, which forms *in situ* a nucleophilic carbene
- involved in many transformations as TPP:
  cofactor of pyruvate-dehydrogenase,
  α-ketoglutarate-dehydrogenase and transketolase



thiaminepyrophosphate (TPP)

Activated glycolaldehyde reacts as acyl anion equivalent
with a ketose (*Umpolung*)



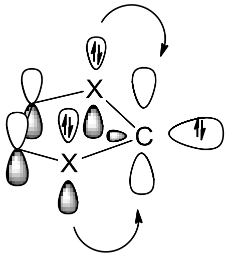


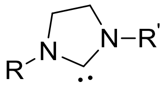
- Deprotonation by pyrimidine-unit
- Coupling process is reversible
- Ring opening at physiological pH for easier transport through the lipophilic double layer

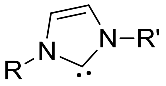
D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534 – 541; M. Sunstrom, Y. Lindqvist, G. Schneider, U. Hellmann, H. Ronne, *J. Biol. Chem.* **1993**, *268*, 24346 – 24352; U. Nilsson, L. Meshalkina, Y. Lindqvist, G. Schneider, *J. Biol. Chem.* **1997**, *272*, 1864 – 1869; J. M. Berg, J. L. Tymoczlo, *Stryer Biochemie,* Spektrum Akademischer Verlag, 6. Auflage, **2007**

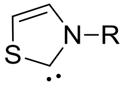
N-Heterocyclic Carbenes

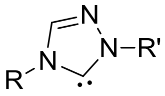
- Carbene: neutral, bivalent carbon atom with electron sextett
- NHC: most important singlet carbenes
- Stabilized by two π-donors


X = CR_2, NR, S, O, PR


imidazolinylidene


imidazolylidene


thiazolylidene


triazolylidene

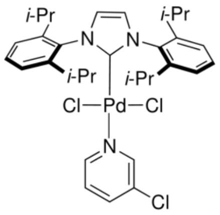
- Highly nucleophilic
- Basicity of five-membered carbenes:

  N>S

  double bond decreases proton affinity

  extra ring nitrogen electron has a electron withdrawing effect
- Substitution patterns have significant effects on catalytic activities
- Numerous stable carbenes have been synthesized as ligands for transition-metal catalysis (e.g. PEPPSI-^{i}Pr) and

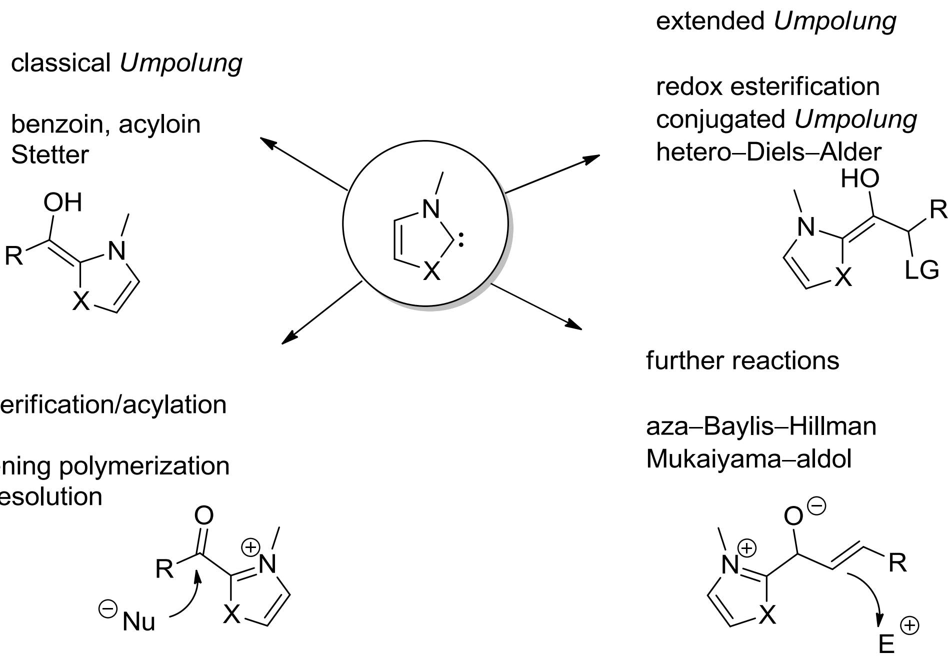
  as nucleophiles for organocatalysis



D. Martin, M. Melaimi, M. Soleilhavoup, G. Bertrand, *Organometallics* **2011***, 30*, 5304 – 5313; J. Mahatthananchai, J. W. Bode, *Chem. Sci.* **2012***, 3,* 192 – 197; D. Bourissou, O. Guerret, F. P. Gabbaï, G. Bertrand, *Chem. Rev.* **2000***, 100*, 39 – 91;

NHCs as Organocatalysts

Different modes of action in NHC organocatalysis:



classical *Umpolung*

benzoin, acyloin
Stetter

extended *Umpolung*

redox esterification
conjugated *Umpolung*
hetero–Diels–Alder

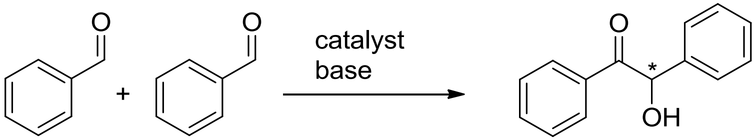
transesterification/acylation

ring opening polymerization
kinetic resolution

further reactions

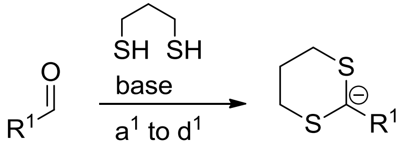
aza–Baylis–Hillman
Mukaiyama–aldol

Benzoin condensation:



Umpolung:

First described by Seebach for the access to synthetic acyl anion equivalents *via* reaction of aldehydes with dithianes

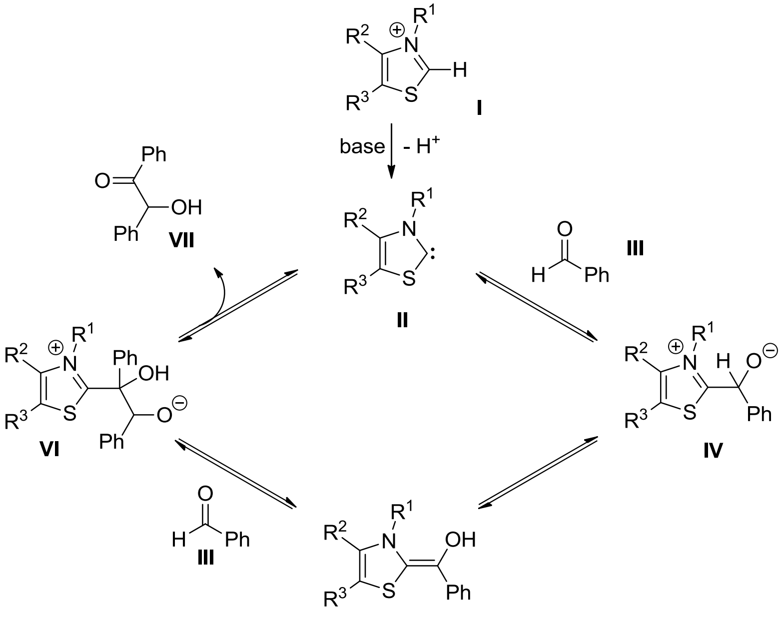


X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511 – 3522; A. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Rev.* **2011**, *44*, 1182 – 1195; D. Seebach, *Angew. Chem.* **1979**, *79*, 239 – 258; B.-T. Göbel, D. Seebach, *Synthesis*, **1977**, 357 – 402;

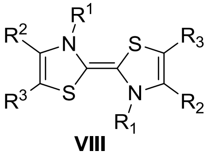
The Breslow Mechanism

Benzoin condensation: Cyanide- or NHC-catalyzed carbon – carbon bond formation

- 1832: Discovered by J. Liebig and F. Wöhler in the reaction of bitter almond oil with potash
- 1943: Ugai *et al.* recognized that thiazolium salts are also suitable
- 1954: Mizuhara *et al.* reported catalytic activity of
- natural thiamine derivatives
- 1903: Lapworth reported the HCN addition process
- 1958: Breslow proposed a mechanistic model for
  the thiazolium salt catalyzed benzoin condensation
- 1964: Lemal *et al.* proposed a bis(thiazol-2-ylidene)
  as active species



V



VIII

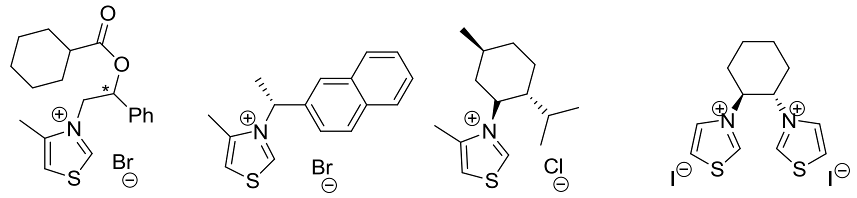
– Breslow intermediate has not yet been detected;
mechanism is still under investigation, but commonly accepted

---

F. Wöhler, J. Liebig, *Ann. Pharm.* **1832**, *3*, 249; T. Ugai, S. Tanaka, S. Dokawa, *Chem. Abstr.* **1951**, *45*, 5148; S. Mizuhara, P. Handler, *J. Am. Chem. Soc.* **1954**, *76*, 571 – 573; A. Lapworth, *J. Chem. Soc.* **1903**, *83*, 995 – 1005; A. Lapworth, J. Chem. Soc. 1903, 83, 995 – 1005; R. Breslow, *J. Am. Chem. Soc.* **1958**, *80*, 3719 – 3726; D. M. Lemal, R. A. Lovald, K. I. Kawano, *J. Am. Chem. Soc.* **1964**, *86*, 2518 – 2519

Asymmetric Benzoin Condensation

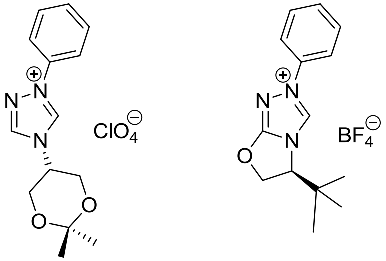
- First described by Sheehan and Hunneman using chiral thiazolium salts; other attempts have been made without better results for yield and *ee*



6% yield, 22% *ee* | 6% yield, 52% *ee* | 20% yield, 35% *ee* | 21% yield, 27% *ee*

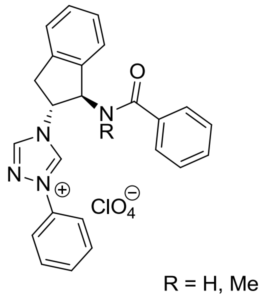
Sheehan and Hunneman | Tagaki *et al.* | López–Calahorra

- Catalysts have been modified at the nitrogen atom, which carries a modified pyrimidine unit in natural thiamine
- Triazolium-based systems turned out to be more powerful in benzoin condensations
- Enders *et al.* : bulky substituent shieds one side of the formed Breslow intermediate
- Connon *et al.* : hydrogen bond donation of the amide as a control element



Enders and Teles

22 - 72 % yield
20 - 86 % *ee*



Connon *et al.*

10 - 63% yield
31 - 62% *ee*

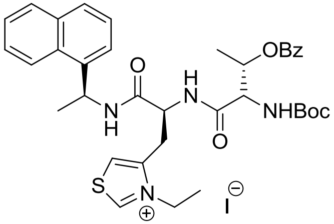
J. Sheehan, D. H. Hunneman, *J. Am . Chem. Soc.* **1966**, *88*, 3666 – 3667; J. Sheehan, T. Hara, *J. Org. Chem.* **1974**, *38*, 1196 – 1199; W. Tagaki, Y. Tamura, Y. Yano, *Bull. Chem. Soc. Jpn.* **1980**, *53*, 478 – 480; J. Martí, J. Castells, F. Lopéz Calahorra, *Tetrahedron Lett.* **1993**, *34,* 521 – 524; D. Enders, K. Breuer, J. H. Teles, *Helv Chim. Acta* **1996**, *79,* 1899 – 1902; S. E. O'Toole, S. Connon, *J. Org. Biomol. Chem.* **2009**, *7*, 3584 – 3593;

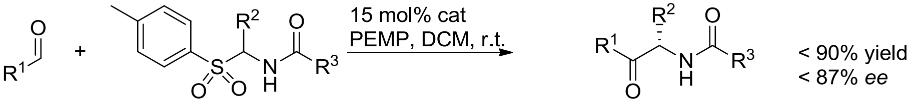
Crossed Condensations

- Benzoin condensation of different aldehydes

Not limited to aldehydes:

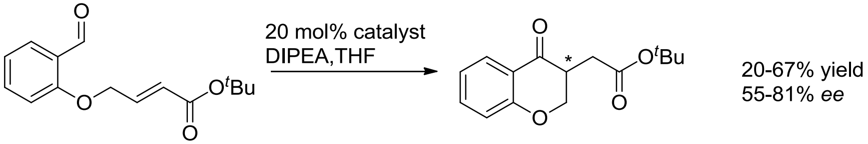
- Miller *et al.* were first to present an asymmetric aza-benzoin condensation of aromatic aldehydes with arylsulfonamides





- First peptidic catalyst with functionalized thiazolyl alanine to attain a NHC precursor

  they hypothesized a bifunctional mechanism: covalent binding of the aldehyde with chiral environment and simultaneous activation of the *N*-acylimine component by H-bonding
- The same catalyst showed catalytic activity in Stetter cyclizations



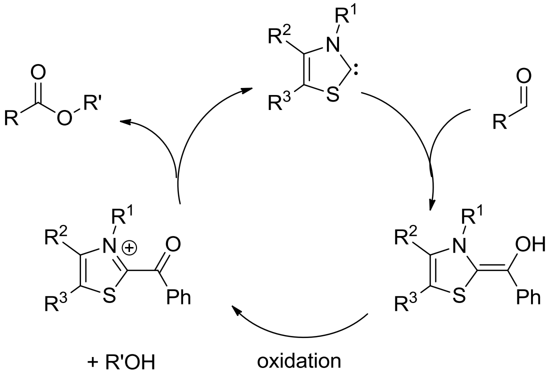
D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491 – 1495; S. M. Mennen, J. D. Gipson, Y. R. Kim, S. J. Miller, *J. Am. Chem. Soc.* **2005**, *127*, 1654 – 1655; S. M. Mennen, J. T. Blank, M. B. Tran-Dubé, J. E. Imbriglio, S. J. Miller, *Chem. Commun.* **2005**, 195 – 197;

Esterification with NHCs

- Fundamental processes in organic synthesis as well as in nature

  Most convenient method is the Steglich esterification with DMAP as a nucleophilic catalyst

- Oxidative esterification with NHCs:



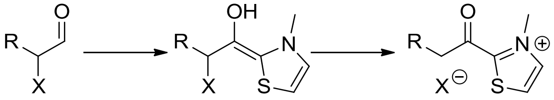
- Also thioesterification, transesterification/acylation

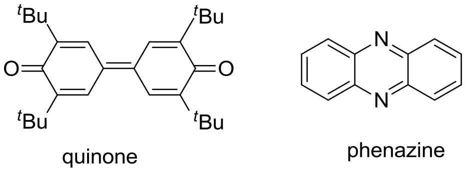
Internal redox reaction:

functionalized aldehydes, e.g. α-halogen-aldehydes

External redox reaction:

oxidant such as MnO_2 or organic heterocycles





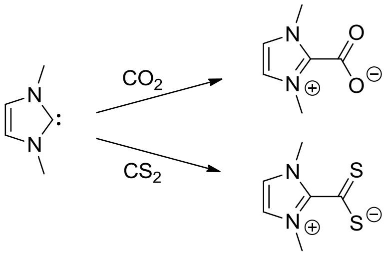
G. Höfle, W. Steglich, H. Vorbrüggen, *Angew. Chem., Int. Ed.* **1978**, *17*, 569 – 583; Y.-C. Xin, S.-H. Shi, D.-D. Xie, X.-P. Hui, P.-F. Xu, *Eur. J. Org. Chem.* **2011**, 6527 – 6531; T. Uno, T. Inokuma, Y. Takemoto, *Chem. Commun.* **2012**, *48,* 1901 – 1903; N. T. Reynolds, J. Read de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *26*, 9918-9919

NHC-CO_2 Adducts

- Most NHC-mediated organocatalytic reactions include the formation of a covalent bond with carbonyl functions

NHCs can serve as efficient organocatalysts for CO_2 fixation,

they react also with CS_2



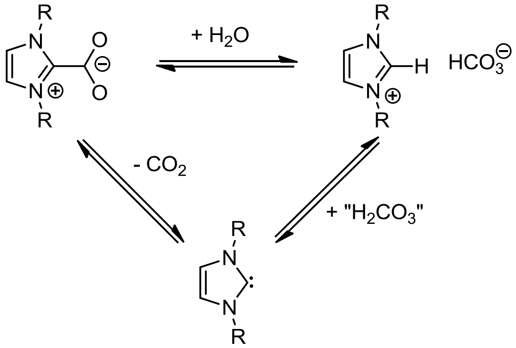
- Masking the free carbene circumvents the necessity of dry and oxygen-free conditions for NHC-catalyzed reactions
- Reversibly bound adducts are rather labile in solution

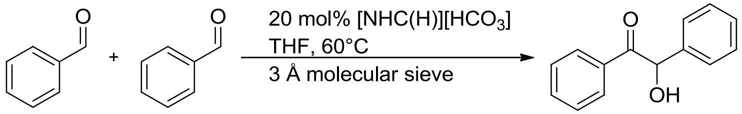
Taton *et al.* reported air-stable imidazolium hydrogen carbonates [NHC(H)][HCO_3]

equilibrium in solution between their carboxylates

and the free carbene

Benzoin condensation without base (88% yield)

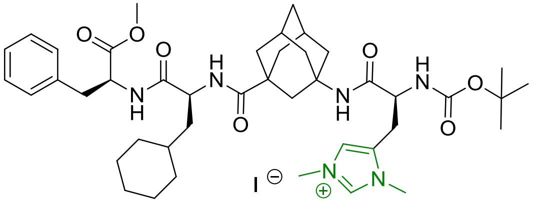




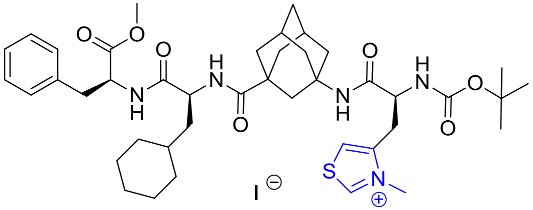
J. Pinaud, J. Vignolle, Y. Gnanou, D. Taton, *Macromolecules* **2011**, *44*, 19002 – 1908; K.-I. Iwamoto, H. Kimura, M. Oike, M. Sato, *Org. Biomol. Chem.* **2008**, *6*, 912 – 915; M. Fèvre, J. Pinaud, A. Leteneur, Y. Gnanou, J. Vignolle, D. Taton, *J. Am. Chem. Soc.* **2012**, *134*, 6776 – 6784

Motivation

- Application of peptide-based organocatalysts incorporating NHC moieties with the unnatural amino acids *N*-π-methyl histidine and thiazolyl alanine



Boc-L-(*N,N'*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe

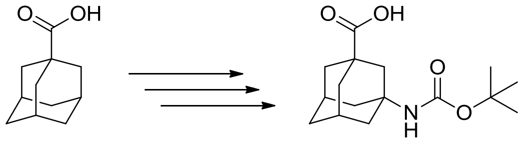


Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe

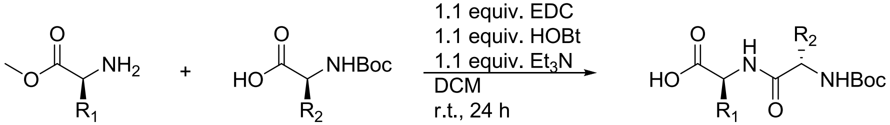
- *In situ* deprotonation for generation of the carbene
- Application in NHC-catalyzed reactions like benzoin condensations, Stetter reactions and esterifications

Synthesis of the Peptides

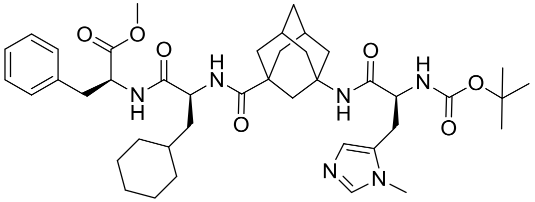
- Synthesis of Boc-^{A}Gly-OH

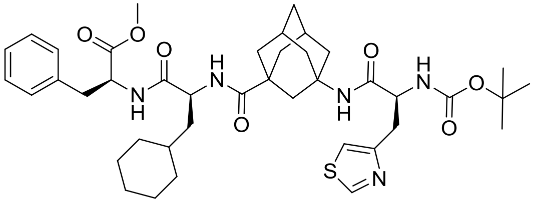

21% yield

- Peptide synthesis following the Boc-strategy


1.1 equiv. EDC
1.1 equiv. HOBt
1.1 equiv. Et_3N
DCM
r.t., 24 h

Tetrapeptides with imidazole and thiazole moiety:

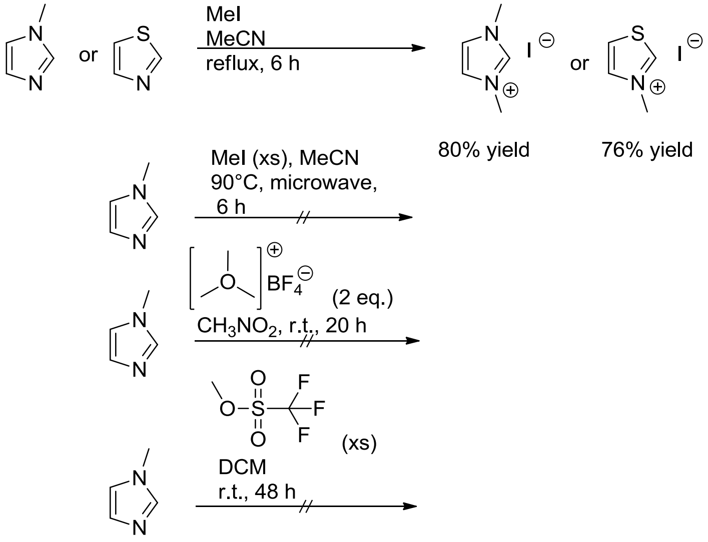




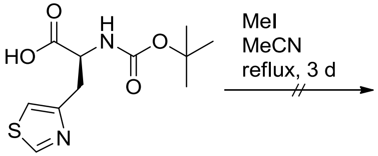
L. Wanka, C. Cabrele, M. Vanejews, P. R. Schreiner, *Eur. J. Org. Chem.* **2007***,* 1474 – 1490;

Methylation

Methylation of *N*-methyl imidazole and thiazole :



- Iodomethane, reflux:
- Microwave-assited
- Meerwein`s salt
- Methyl trifluorosulfonate

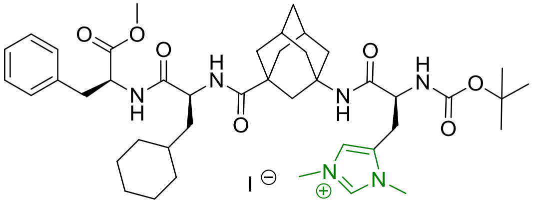


– Methylation of the single amino acid Boc-L-Taz-OH failed due to problematic work up

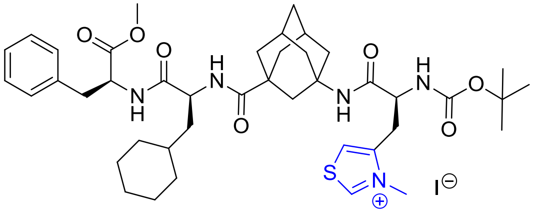
– Methylated tetrapeptides could be purified by flash column chromatography yields between 40-55%

Synthesized NHC-Precursor Peptides

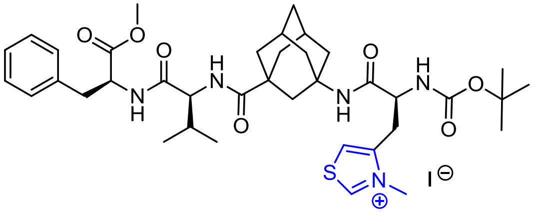
- Six tetrapeptides have been synthesized
  thiazole-moiety was prefered due to better deprotonation and higher coupling yields



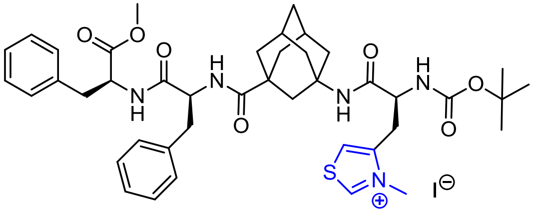
Boc-L-(*N,N'*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe



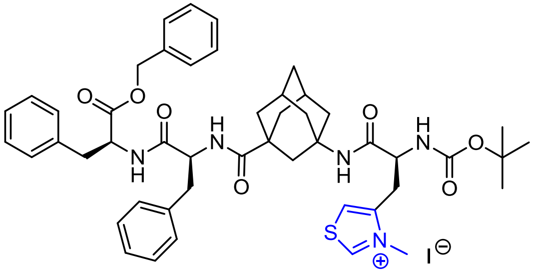
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe



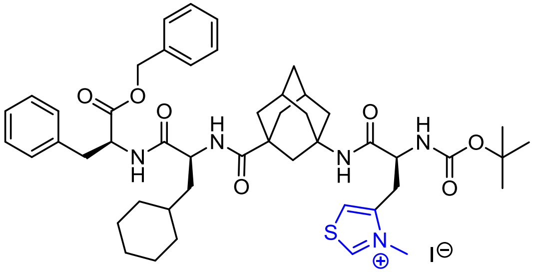
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Val-L-Phe-OMe



Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OMe

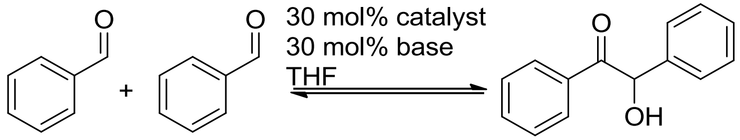


Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OBzl

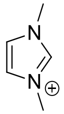
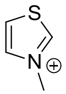


Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OBzl

Deprotonation



- Several bases have been tested:

Base		
NaH	Yes	Yes
KO^{t}Bu	Yes	Yes
K_2CO_3	No	No
Et_3N	No	No
DBU	No	Yes
^{i}Pr$_2$NEt	No	No
TMG	No	Yes

pKa values in DMSO: 21.4 14.5

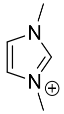
formation of benzoin detected *via GC*-FID

- Base of choice: KO^{t}Bu (and DBU)

A. M. Magill, K. J. Cavell, B. F. Yates, *J. Am. Chem. Soc.* **2004**, *126*, 8717 – 8724

Variation of Solvent and Temperature

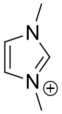
- Solvents need to be dry



Solvent	Yield
THF	40%
toluene	3%
DCM	<1%
1,4-dioxane	0%

Peptide-catalyst	Solvent	Base	Yield
	THF	KO^{t}Bu	40%
	THF	DBU	8%
	toluene	KO^{t}Bu	20%
	toluene	DBU	1%

- Fluorinated solvent showed no improvements
- Solvent of choice: THF (and toluene)
- Temperature:

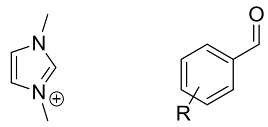


Temperature / °C	Yield
5	--
27	20%
50	65%

- 20 h of reaction time
- Yields determined by GC-FID

Substrate Scope for Benzoin Condensation

Several aromatic aldehydes have been tested:



	Catalytic Loading	Yield
H	30 mol%	20%[a)]
p-F	30 mol%	40%[a)]
p-CF_3	30 mol%	--
p-MeO	30 mol%	4%[b)]
p-NO_2	30 mol%	--
o-Cl	30 mol%	15%[b)]
o-CH_3	30 mol%	23%[b)]

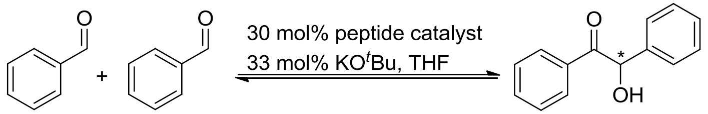
a) yield of isolated product

b) yield determined by GC-FID

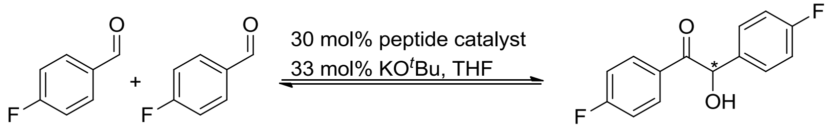
- Catalytic loading of >20 mol% necessary, 1.2 equiv. base
- Determination of benzoin *via* GC-FID

- Benzaldehyde and *p*-fluorobenzaldehyde

Catalytic Experiments



Catalyst	Yield	*ee*
Boc-L-(*N,N′*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe	5%	5%
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe	20%	5%

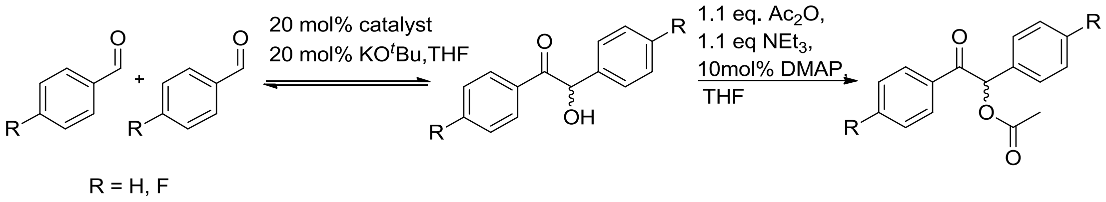


Catalyst	Yield	*ee*
Boc-L-(*N,N′*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe	1%	n.d
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe	10%	n.d.

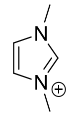
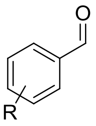
- Yields only moderate, *ee* not noteworthy
- *ee* determination with chiral HPLC
- Repeating the reactions did not yield better results
- Reaction conditions affect back and side reactions (retro-benzoin reaction)
- Capping *in situ*-formed benzoin might increase yields of products

Catalytic Experiments

Benzoin condensation followed by acylation:

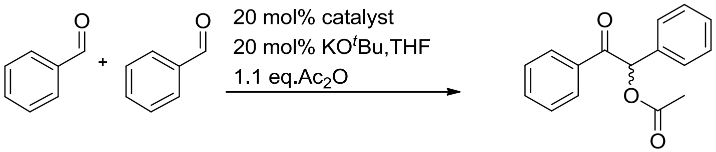


DMAP as co-catalyst:

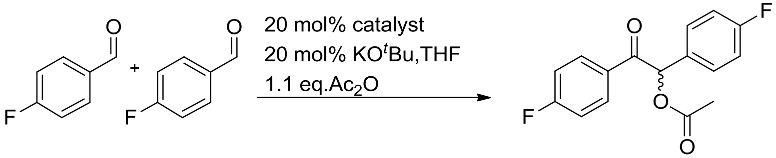
		DMAP	Yield
	H	10 mol%	33%
	H	--	70%
	p-F	10 mol%	17%
	p-F	--	47%

- DMAP is not required as the carbene is capable of acylating the benzoin on its own
- No further base

Catalytic Experiments



Catalyst	Yield	*ee*
Boc-L-(*N,N′*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe	0%	--
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Val-L-Phe-OMe	4%	n.d.
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OMe	0%	--
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OBzl	0%	--
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OBzl	0%	--



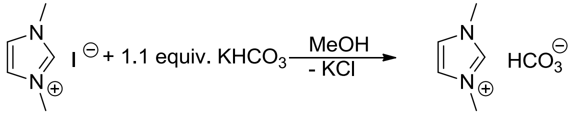
Catalyst	Yield	*ee*
Boc-L-(*N,N′*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe	0%	--
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe	0%	--.
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Val-L-Phe-OMe	2%	n.d.
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OMe	1%	n.d.
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OBzl	1%	n.d.

Yields determined by GC-FID, *ee* determined by chiral HPLC

NHC-CO_2 Adducts for Benzoin Condensation

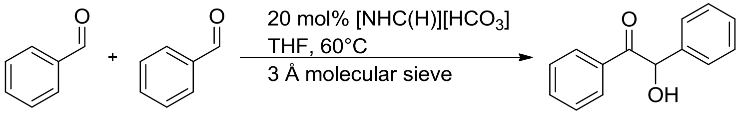
- Dry and inert conditions could be avoided by encapsuling the carbene

Anion metathesis of *N*-*N*‘-Dimethylimidazolium iodide with $KHCO_3$:



- ^1H and ^{13}C NMR spectra in methanol-d_4 and DMSO-d_6 were recorded, but unlike reported in literature no signals of the free carbene were observed

- Benzoin condensation showed no results

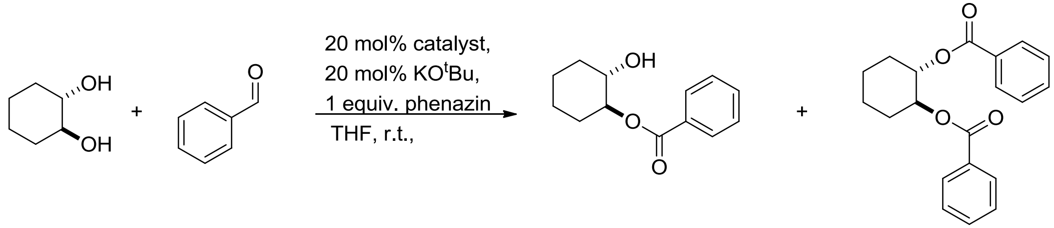


- Molecular sieve to capture traces of water

M. Fèvre, J. Pinaud, A. Leteneur, Y. Gnanou, J. Vignolle, D. Taton, *J. Am. Chem. Soc.* **2012***, 134*, 6776 – 6784

Esterifications

- Esterification of aldehydes with alcohols by external oxidation
- MnO_2 showed only racemic di-esterified product
- Phenazine showed mono-esterified product
- Kinetic resolution of *trans*-1,2-cyclohexanediol with several aldehydes by Schreiner and co-workers



Catalyst	Yield	*ee*
Boc-L-(*N,N'*-Dime-His)I-^{A}Gly-L-Cha-L-Phe-OMe	0%	--
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Cha-L-Phe-OMe	0%	--
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Val-L-Phe-OMe	4%	n.d.
Boc-L-(*N*-Me-Taz)I-^{A}Gly-L-Phe-L-Phe-OMe	0%	--

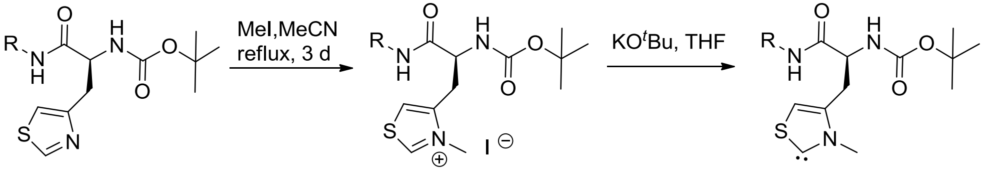
- Non-optimized reaction conditions
- Method not applicable for kinetic resolution

C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 6180 – 6183

Summary

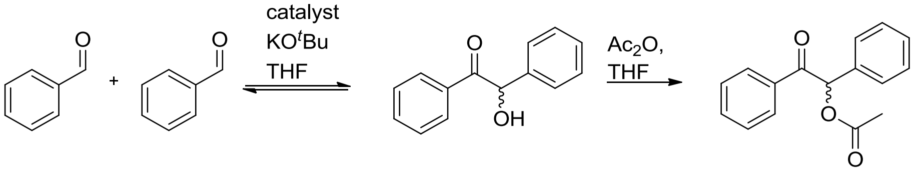
I. Deveploment of a *N*-methylation protocol for peptides

II. Generation of a free carbene *in situ*, which is stable enough to catalyze reactions

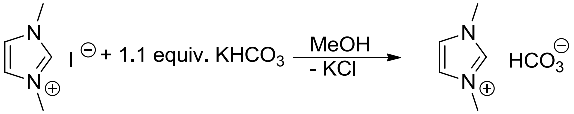


III. Peptide-catalyzed benzoin condensations of several aldehydes under optimized reaction conditions gave only moderate yields, due to small amounts of benzoin only two *ee* values could be determined

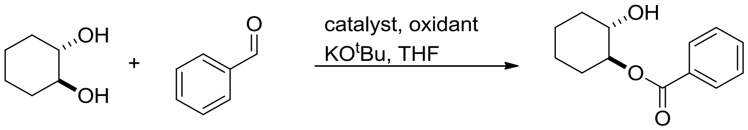
IV. Strategy-development for trapping the just-formed benzoin to prevent a possible retro-reaction



V. Anion-metathesis for NHC-CO$_2$ catalysis without addition of base



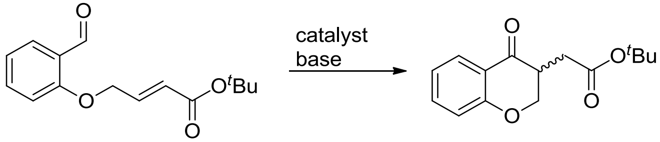
VI. Esterification with NHCs and application as kinetic resolution of meso-diols



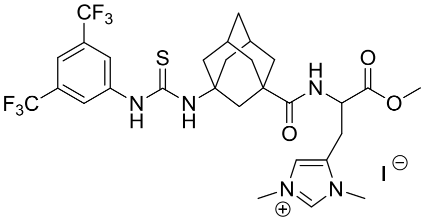
Outlook

- Synthesis of smaller peptides as catalysts for benzoin condensation

- Other NHC-catalyzed reactions like Stetter cyclizations



- Development of small peptidic catalysts incorporating ^{A}Gly, *N*-π-Me-His and thiourea for hydrogen bond donation as a control element



Many thanks to…

- Prof. Dr. Peter. R. Schreiner for the opportunity to complete my studies in his research group
- Daniela Zell for her guidance during my master thesis
- Dr. Dennis Gerbig for always having an open ear and enough coffee
- 7th floor
- Anika Bernhardt and Dr. Erwin Röcker for helping me with analytical problems
- The whole research group
- My fellow students Michael, Stefanie and Philipp for five wonderful years of studies at the JLU