Bachelor-Thesis:

Studies on the Enantioselektive Dakin-West-Reaction

Lindsay Coby
Institute of Organic Chemistry
Justus-Liebig University
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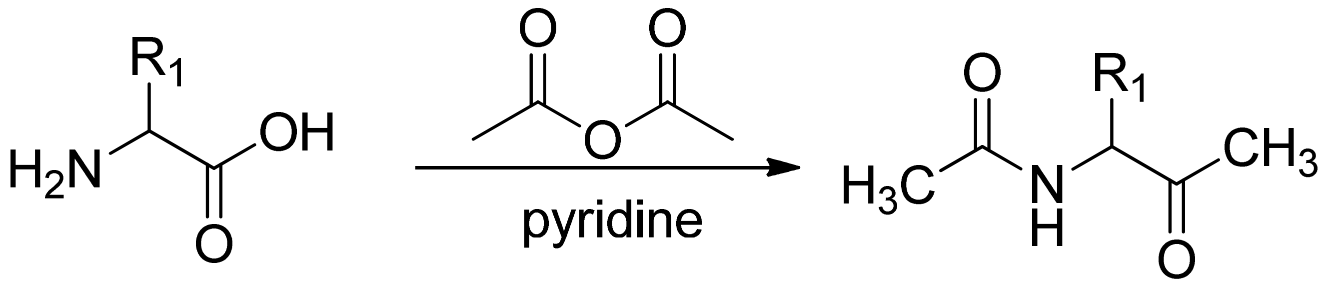
Outline

- Dakin-West-Reaction
  - Mechanism
- Acylation
- Enantioselective Dakin-West-Reaction
  - Goal and idea
  - Reproducing previous results
  - Optimizing the reaction conditions
  - Catalyst screening
- Conclusion
- Outlook

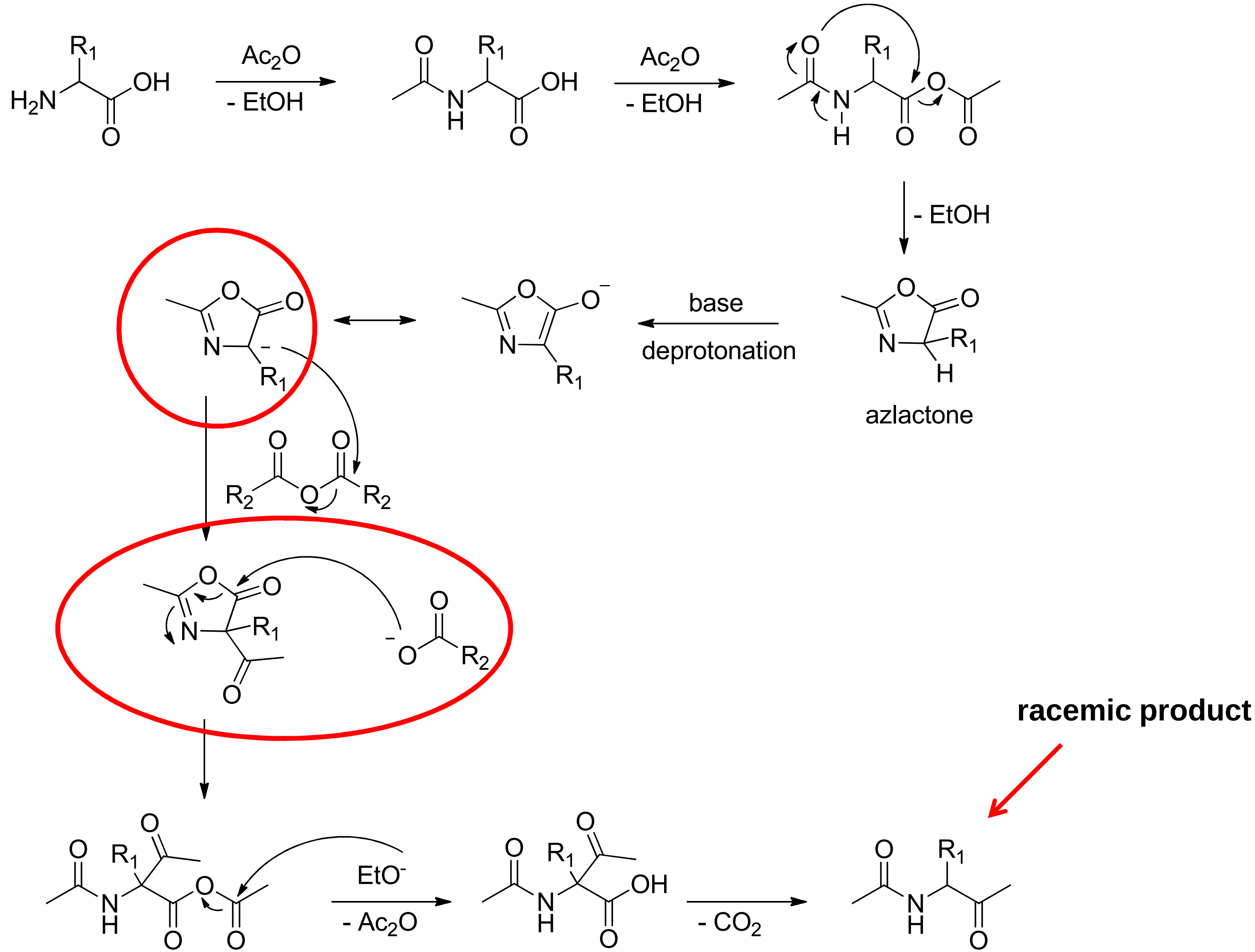
- The reaction was discovered by Dakin and West in 1928:



→ transformation of amino acids into α-acetamino ketones

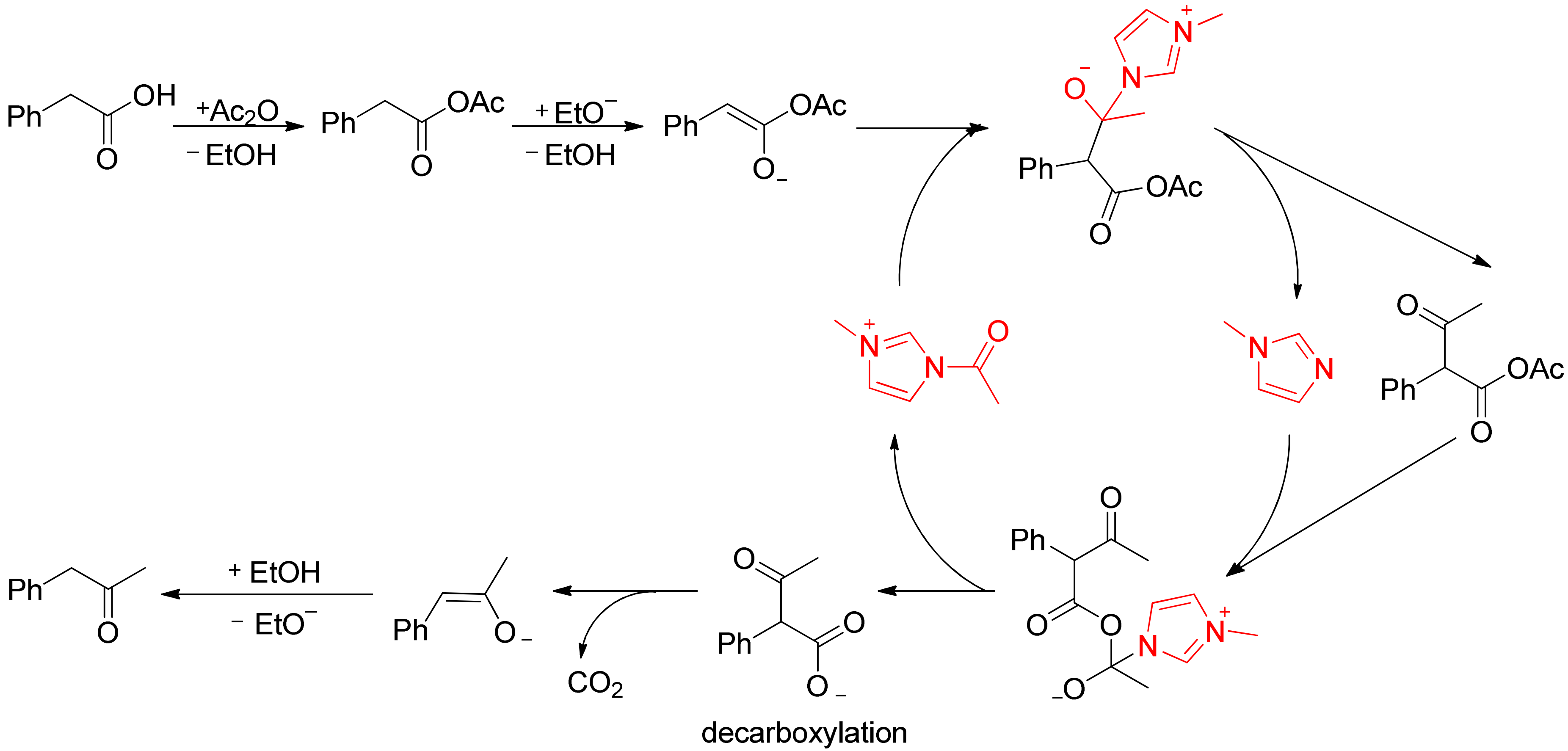
H. D. Dakin, R. West, *J. Biol. Chem.* **1928**, *78*, 91–105.

Dakin-West-Reaction: Mechanism of amino acids



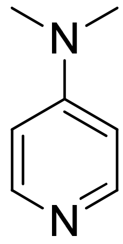
G. H. Cleland, C. Niemann, *J. Am. Chem. Soc.* **1949**, *71*, 841–843.
G. L. Buchanan, *Chem. Soc. Rev.* **1988**, *17*, 91–109.

Dakin-West-Reaction: Mechanism of carboxylic acids



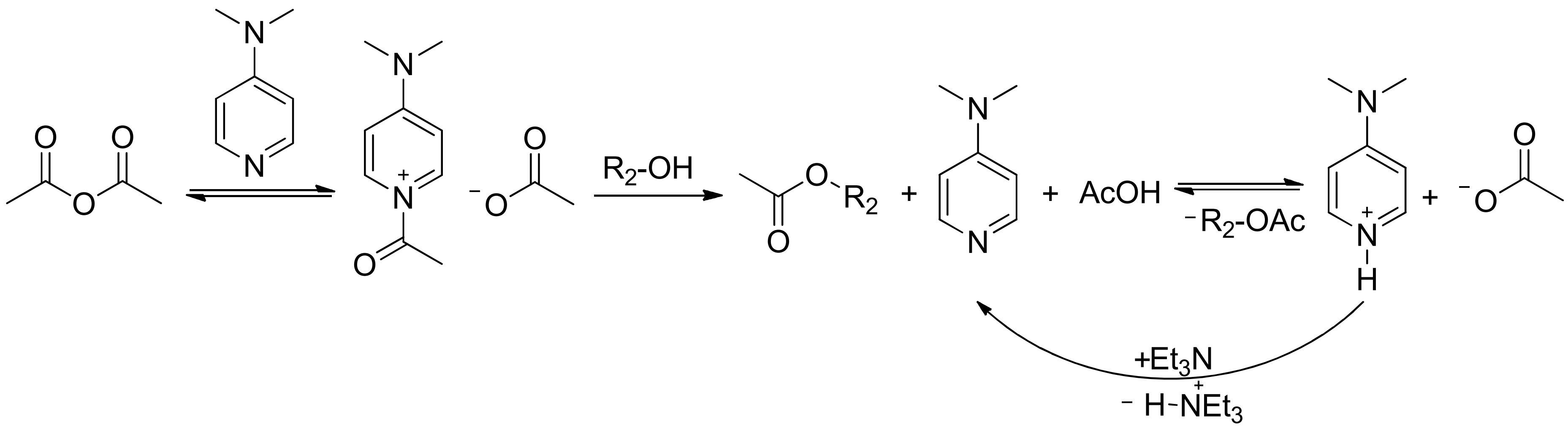
K. V. Tran, D. Bickar, *J. Org. Chem.* **2006**, *71*, 6640–6643.

- Nucleophilic achiral catalyst:



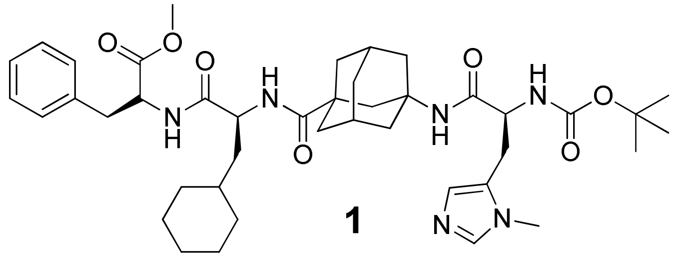
DMAP

- Acylation mechanism:



W. Steglich, G. Hofle, *Angew. Chem. Int. Ed.* **1969**, *8*, 981.
L. M. Litvinenko, A. I. Kirichenko, *Dokl. Akad. Nauk SSSR* **1967**, *176*, 197 – 200.
C. E. Mueller, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2011**, *50*, 6012–6042.

- Nucleophilic chiral catalyst:



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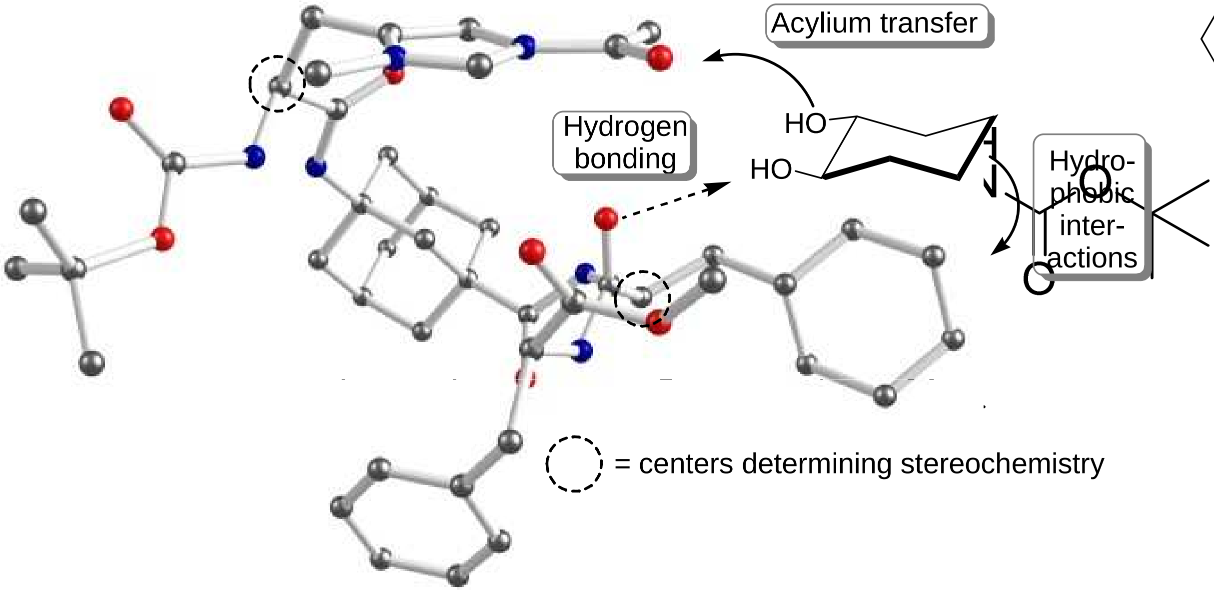
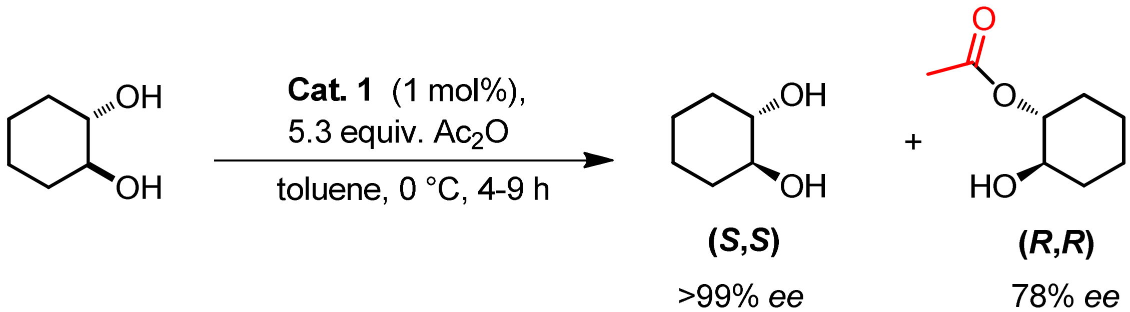


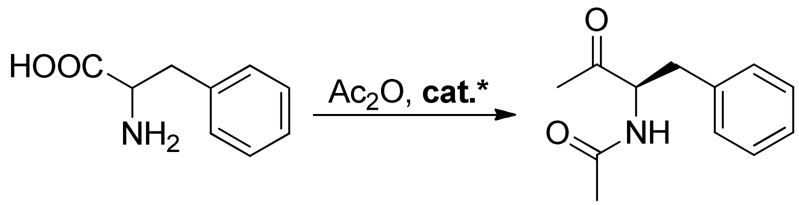


C. E. Müller, L. Wanka, K. Jewell, P. R. Schreiner, *Angew. Chem. Int. Ed.* **2008**, *47*, 6180.
C. B. Shinisha, R. B. Sunoj, *Org. Lett.* **2009**, *11*, 3242.

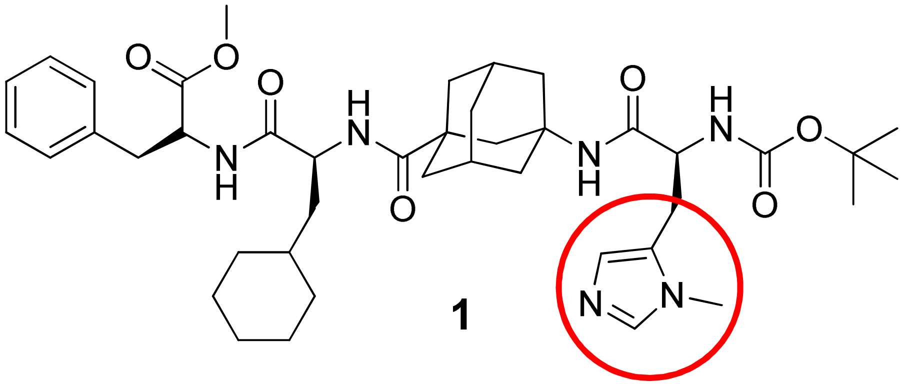
JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

- Dakin-West-Mechanism for amino acids yields racemic products

- Goal of this work:



- Enantiomeric excess (*ee*) can be received by using a chiral acylation catalyst such as:



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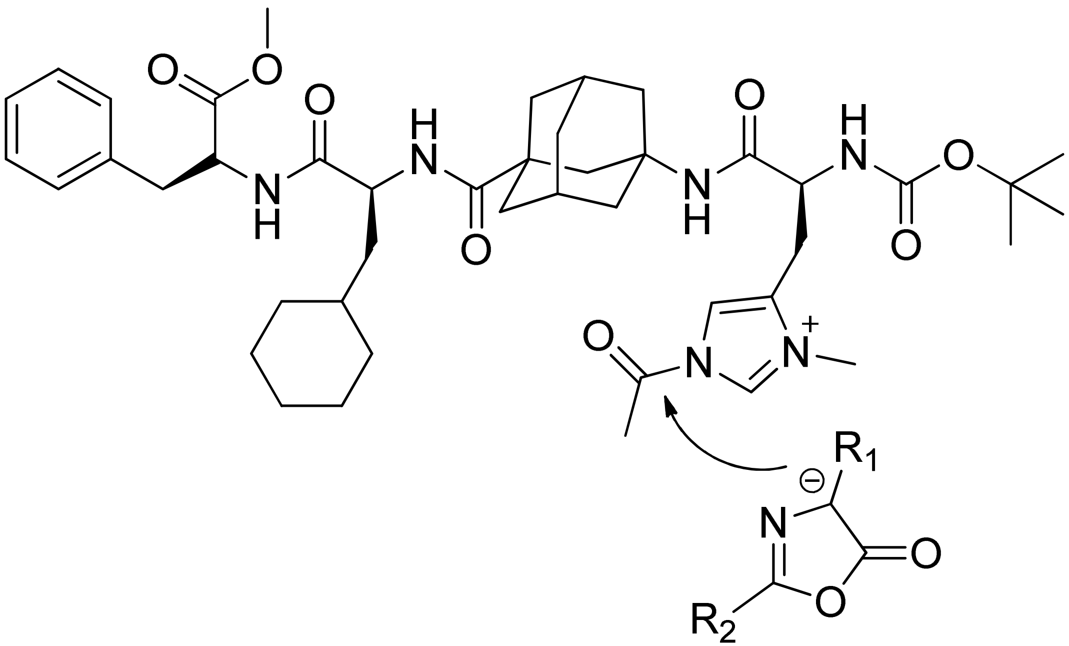
- Enantioselective acyl transfer onto the azlactone by the chiral catalyst



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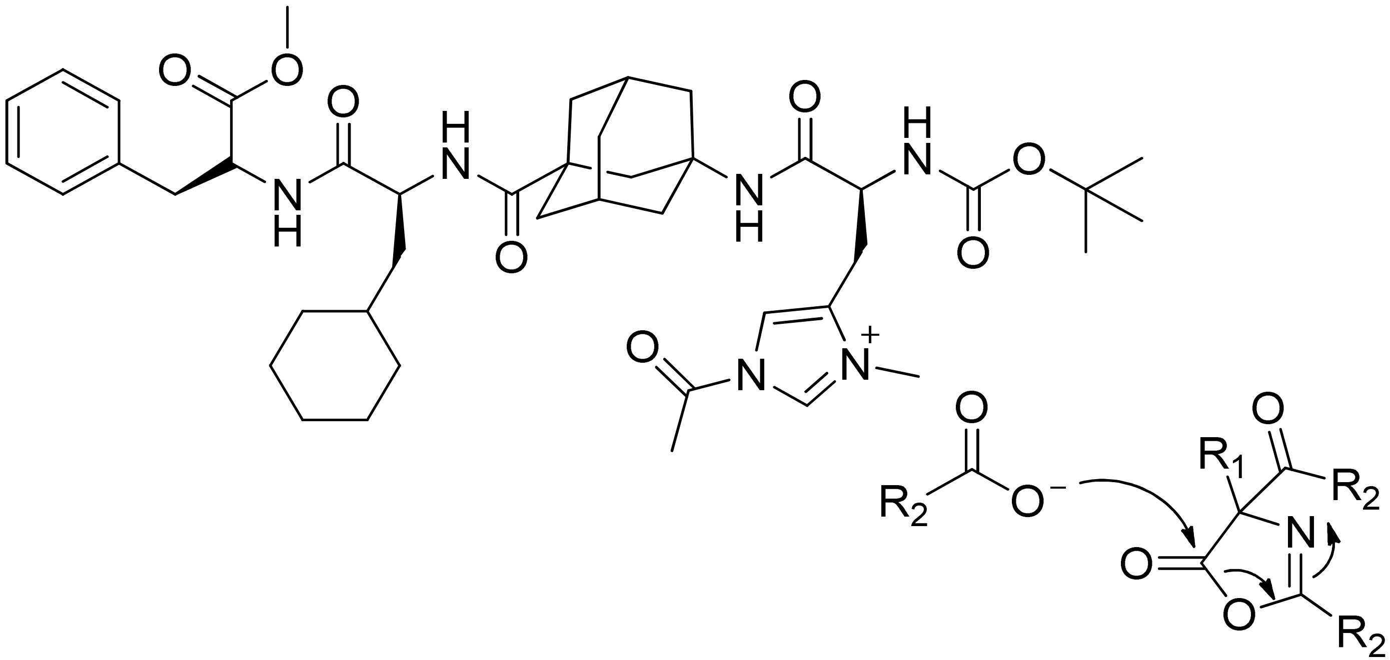
- Chiral catalyst has an enantioselective influence on the ring opening step



- Catalytic experiment:

  producing an *ee* of 16% was possible by using the previous shown catalyst **1**

- Preparative experiment:

  loss of *ee* was observed (16% → 6% *ee*)

➡ Both results were reproducible using the same reaction conditions

Enantioselective DKW: Loss of enantiomeric excess

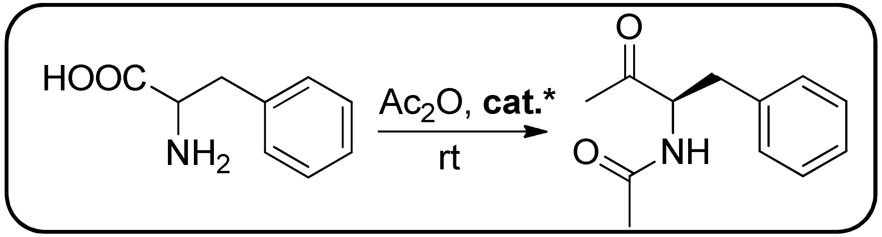
- Enantiomeric excess reduces while working up the preparative experiment
  → 16% to 6%

- Key to the problem:
  → Immediate removal of the catalyst after the end of the reaction

Entry	Time of the analysis	*ee*
1	End of the reaction[a]	16.8%
2	After removing the catalyst	17.1%
3	After column chromatography	17.8%

[a] reaction time: 24 h

- The reaction conditions were optimized by variation of:

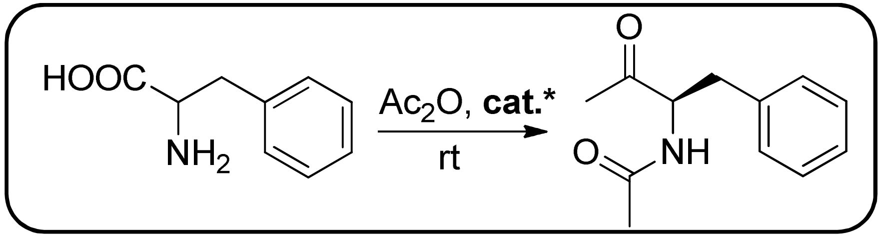


1. Solvent
2. Solvent volume
3. Amount of acetic anhydride
4. Catalyst loading

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

- The reaction conditions were optimized by variation of:

1. Solvent



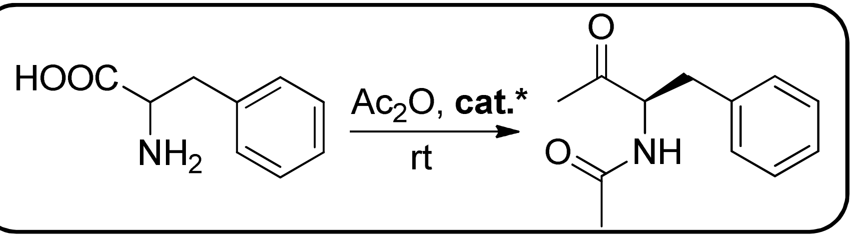
Entry	Solvent[a]	*ee*[b]
1	Dichloromethane	17.5%
2	Toluene	22.5%
3	Tetrahydrofuran	6.2%
4	Diethyl ether	4.0%
5	*n*-Hexane	9.7%
6	Ethyl acetate	–[c]

[a] dry solvent [b] reaction time: 4 days [c] no product could be identified by gas chromatography

JUSTUS-LIEBIG-UNIVERSITÄT GIESSEN

- The reaction conditions were optimized by variation of:

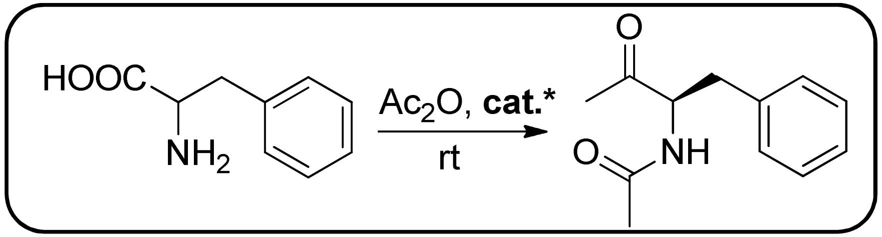
1. Solvent
2. Solvent volume



Entry	Solvent volume[a]	*ee*[b]
1	30 µL	12.8%
2	62 µL	17.6%
3	125 µL	23.7%
4	250 µL	31.0%
5	500 µL	28.0%
6	1000 µL	–[c]
7	2000 µL	–[c]

[a] dry solvent (toluene) [b] reaction time: 24 h [c] no product could be identified by gas chromatography

- The reaction conditions were optimized by variation of:

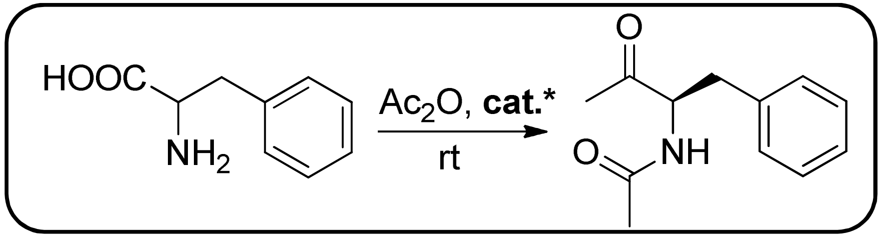


1. Solvent
2. Solvent volume
3. Amount of acetic anhydride

Entry	Acetic anhydride	*ee*[a]
1	9.44 µL (10 eq.)	34.9%
2	18.87 µL (20 eq.)	31.0%
3	28.31 µL (30 eq.)	23.8%
4	37.74 µL (40 eq.)	26.6%
5	56.62 µL (60 eq.)	19.8%
6	75.48 µL (80 eq.)	19.1%

[a] reaction time: 24 h

- The reaction conditions were optimized by variation of:

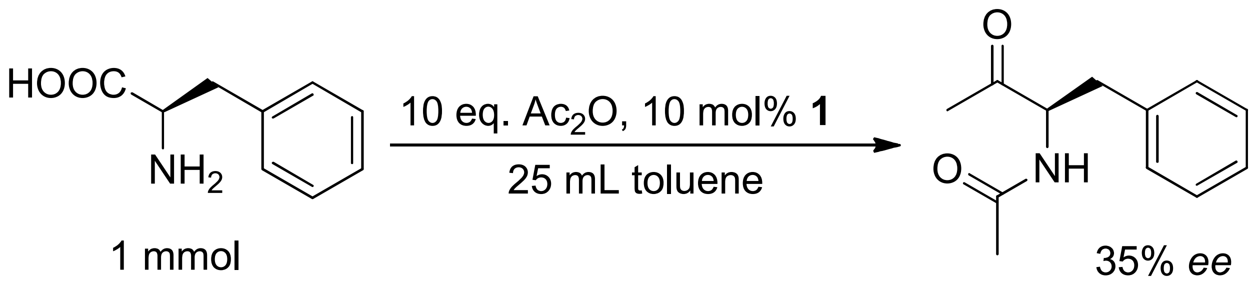


1. Solvent
2. Solvent volume
3. Amount of acetic anhydride
4. Catalyst loading

Entry	Catalyst loading	*ee*[a]
1	5 mol%	24.4%
2	10 mol%	31.0%
3	20 mol%	31.1%
4	30 mol%	28.9%

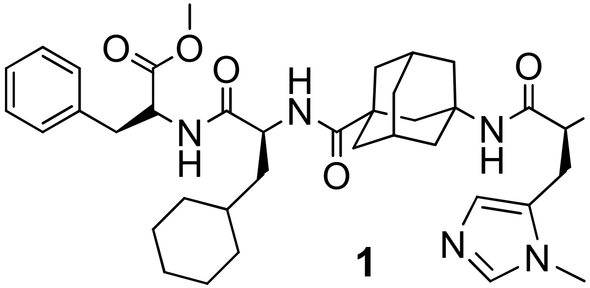
[a] reaction time: 24 h

- Optimized reaction conditions:
  - 1 mmol L-Phenylalanin
  - 10 eq. acetic anhydride
  - 10 mol% catalyst **1**
  - 25 mL toluene



Enantioselective DKW: Catalyst screening

- Catalysts are homoconfigured and differ only in their stereochemistry



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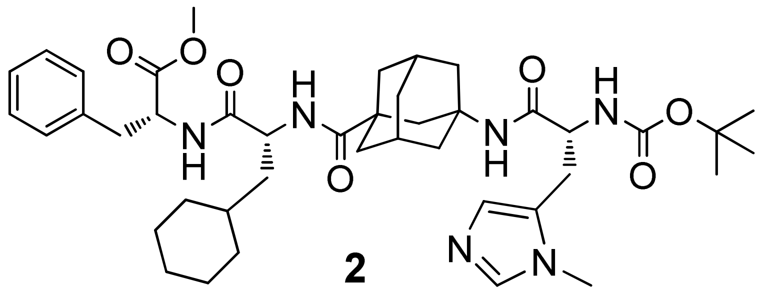

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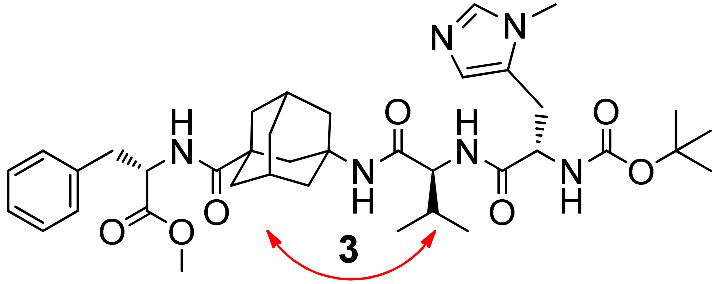
Entry	Catalyst	*ee*[a]
1	**1**	31.0%
2	**2**	– 29.8%[b]

[a] reaction time 24 h [b] The negative sign indicates the formation of the opposite enantiomer

Enantioselective DKW: Catalyst screening

- Catalysts contain the same four amino acid but they differ in position (**3**) or stereochemistry (**4 – 7**)



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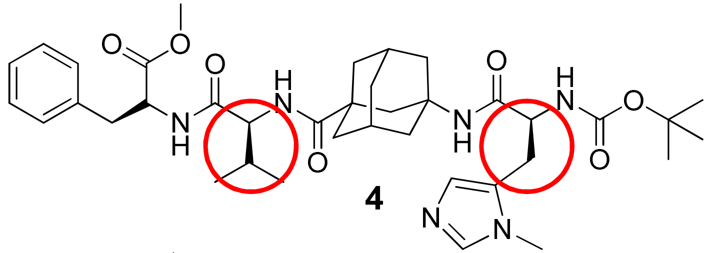
Entry	Catalyst	*ee*[a]
1	**3**	0.3%[b]
2	**4**	24.1%
3	**5**	– 23.1%
4	**6**	3.3%
5	**7**	– 4.4%[c]

[a] reaction time 24 h h [b] peptides were used after solid phase synthesis without any work up [c] The negative sign indicates the formation of the opposite enantiomer



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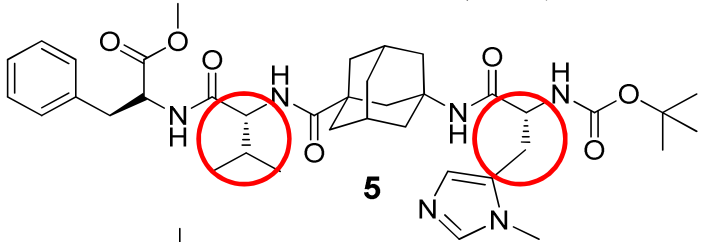

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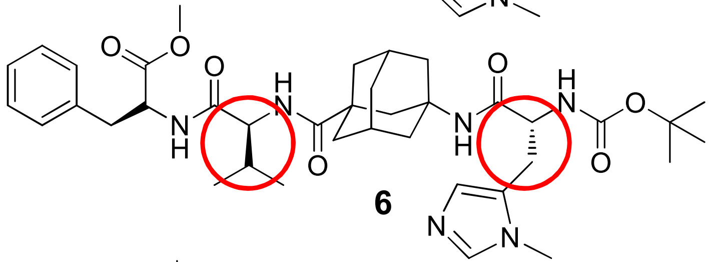

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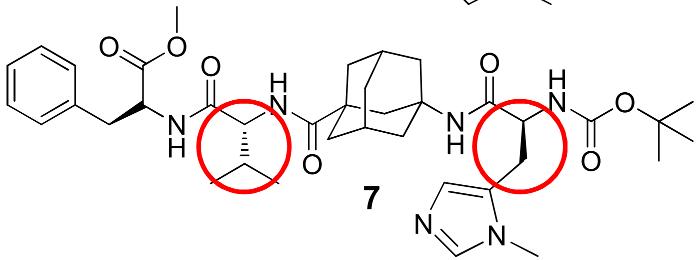

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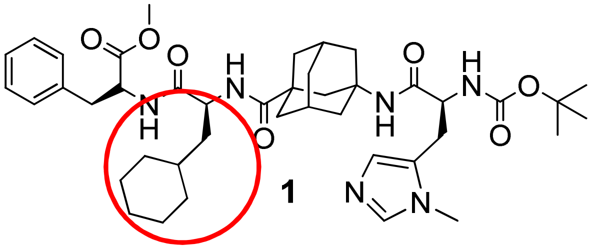
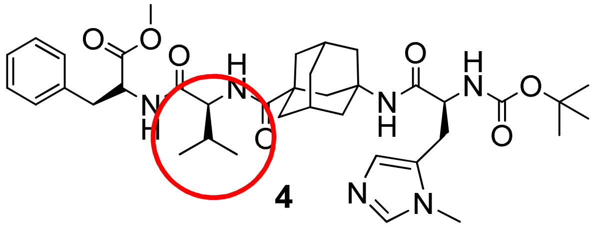
- These catalysts differ in the amino acid next to phenylalanine



1



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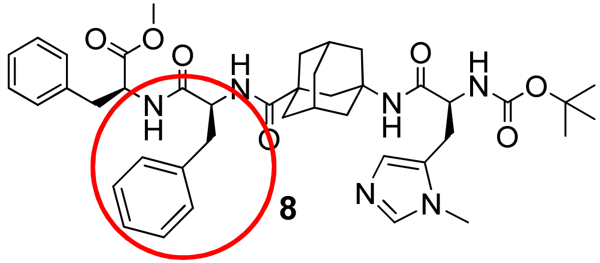

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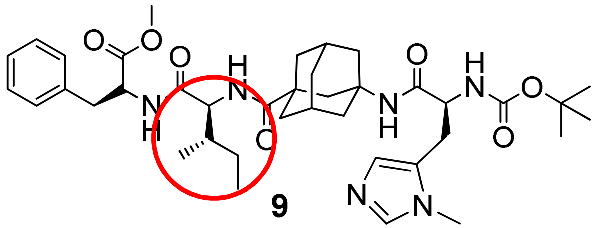
Entry	Catalyst	*ee*[a]
1	**1**	31.0%
2	**4**	24.1%
3	**8**	–[b, c]
4	**9**	18.5%
5	**10**	17.0%[c]

[a] reaction time 24 h [b] no product could be identified by gas chromatography [c] peptide catalysts were used after solid phase synthesis without any work up



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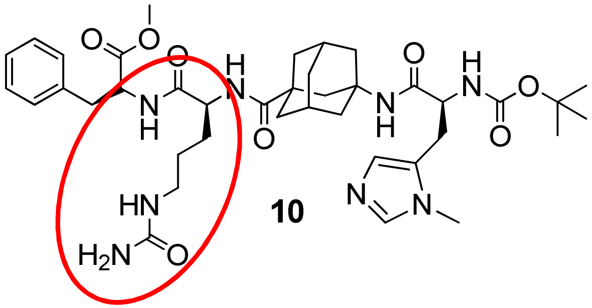

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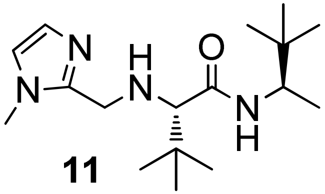
Enantioselective DKW: Catalyst screening

- Various catalysts: Hoveyda‘s catalyst (**11**), Miller‘s catalyst (**12**, **13**), DMAP derivatives (**14**, **15**)



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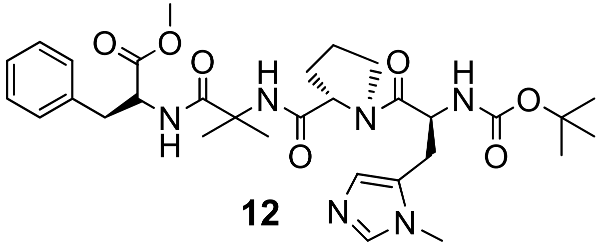

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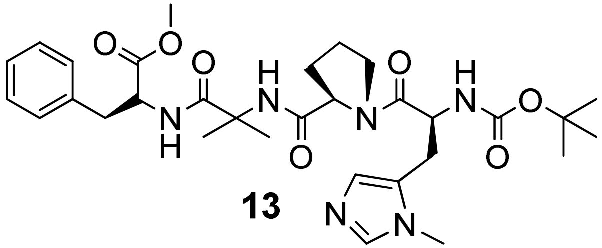

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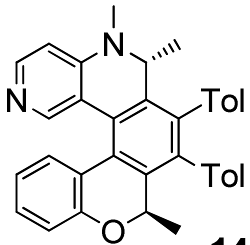
Entry	Catalyst	*ee*[a]
2	**11**	–[d]
3	**12**	0.2%[b]
4	**13**	–5.3%[b, c]
5	**14**	1.6%
6	**15**	–[d]

[a] reaction time: 24 h [b] peptides were used after solid phase synthesis without any work up [c] negative sign indicates the formation of the opposite enantiomer [d] no product could be identified by gas chromatography



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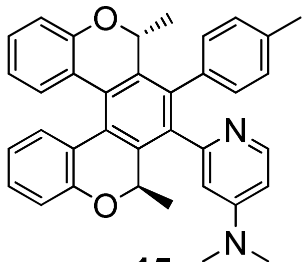

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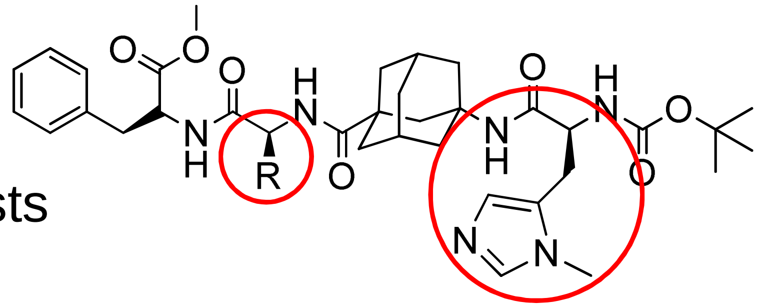
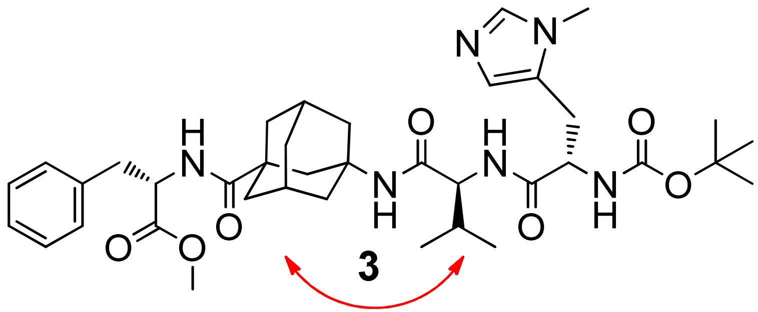
Y. Zhao, J. Rodrigo, A. H. Hoveyda, M. L. Snapper, *Nature* **2006**, *443*, 67–70.
E. R. Jarvo, G. T. Copeland, N. Papaioannou, P. J. Bonitatebus, S. J. Miller, *J. Am. Chem. Soc*. **1999**, *121*, 11638–11643.
M. R. Crittall, H. S. Rzepa, D. R. Carbery, *Org. Lett.* **2011**, *5*, 1250–1253.

- Important structural features:



  - Best *ee* with homoconfigured catalysts
  - The amino acids left and right of adamantyl gycine muss have the same stereochemistry to gain a good *ee*
  - The opposite enantiomer can be obtained by changing the stereochemistry of either all or only the two amino acids left and right of adamantyl glycine
  - varying the position of adamantyl glycine leads to a significant reduction of the *ee*



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- Through the different work up the ee was kept constant
- The variation of reaction conditions led to a significant improvement of the enantioselectivity (16% → 35%)
- No enhancement of the *ee* was achieved by using one of the previous shown catalysts
- The catalyst screening pointed out some catalytic relevant structural features
- Even after a reaction time of 4 days the yield is moderate which is a problem that can not be ignored

Outlook

- Identification of side products
- Synthesize the azlactone
- Finding or synthesizing a new catalyst
- Variation of substrates
- Investigate the decarboxylation step

Thank you:

Prof. Dr. Peter R. Schreiner

Dr. Christian E. Müller

The complete 5th floor

The Schreiner group

Stefanie Pleik

The analytics on the 8th floor