Diploma thesis – Peptide catalysts for the Morita-Baylis-Hillman-reaction

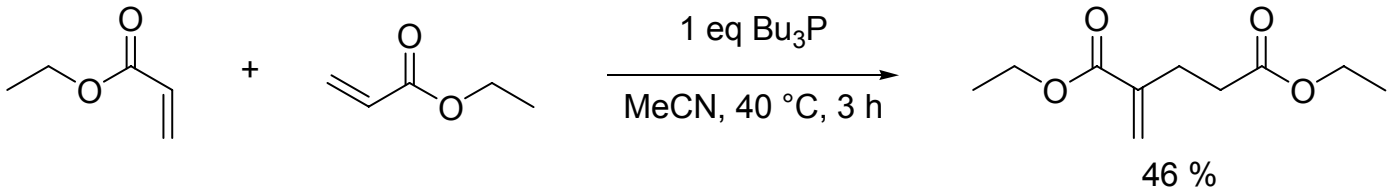
by Katharina Maria Lippert

Index

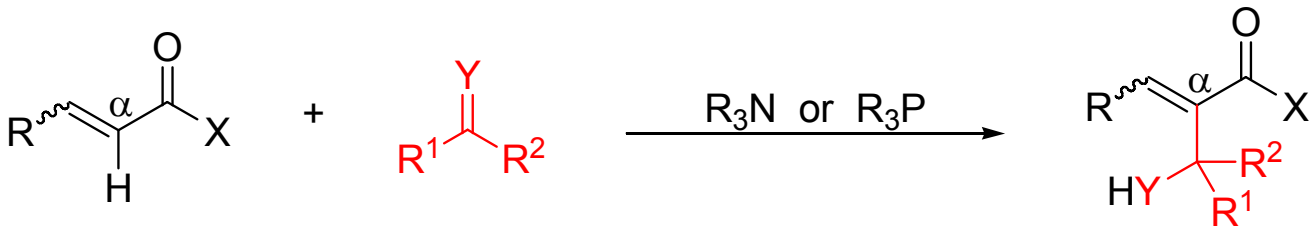
- historical review
- mechanism
- catalyst and base requirement
- applied catalysts
- tested MBH-Systems, tandem reaction
- peptide coupling
- synthesis of a 3D-catalyst
- examination peptide catalysts
- outlook

Introduction

- 1963: first phosphine catalyzed dimerization of activated alkenes by Rauhut and Currier



- 1968: methyl-acrylate oder acrylnitril with aldehydes in presence of a phosphine

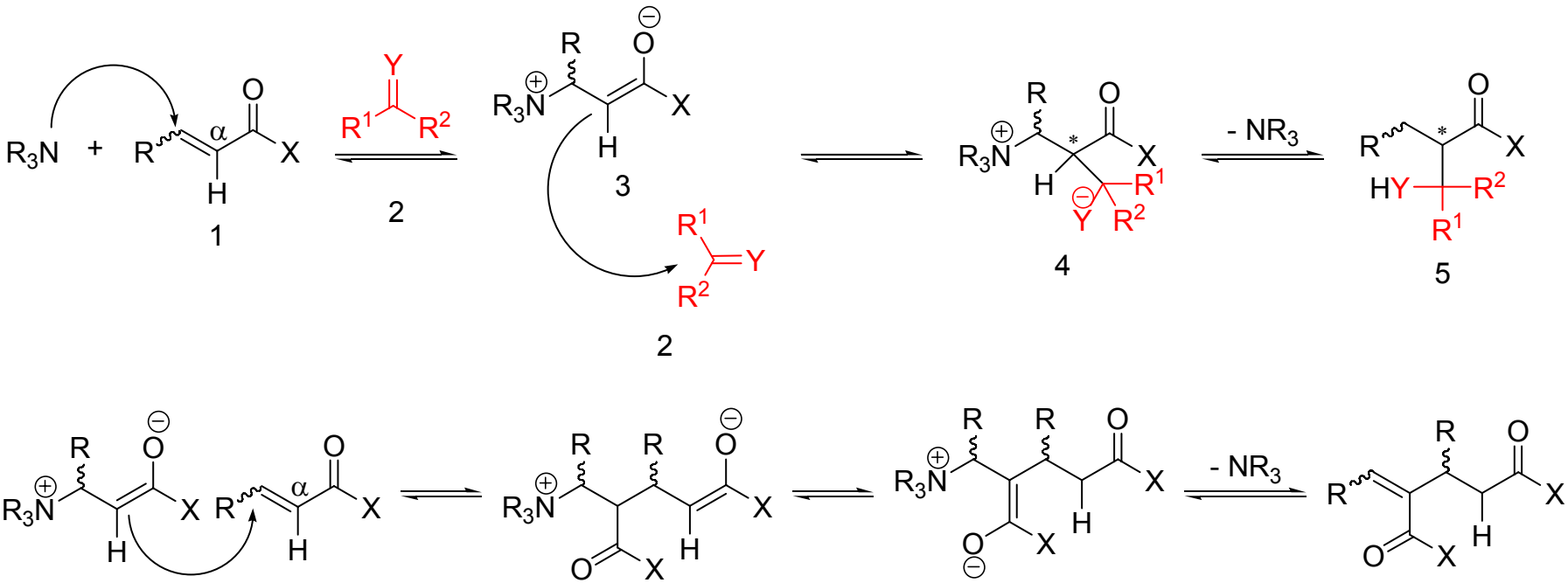


;

X = NH_2, NR_2, OR; Y = O, NTs, NCO_2R, NSO_2Ar; R^1, R^2 = alkyl, aryl, H

Rauhut, M. M.; Currier, H. U.S. Patent 3074999 1963 January 22, American Cyanamid Co., **1963;** Morita, K.; Suzuki, Z.; Hirose, H. *B. Chem. Soc. Jpn.* **1968**, *41*, 2815 ; Baylis, A. B., Hillman, M. E. D., DE-B2155113, 1972

Mechanism

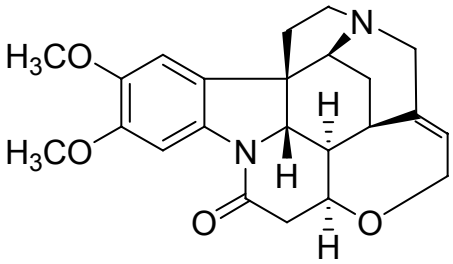


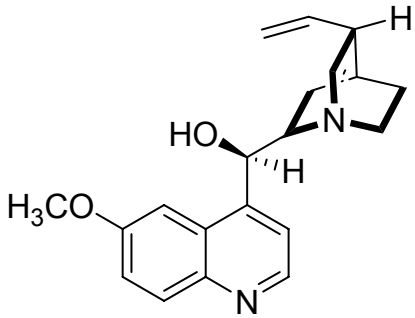
X = NH_2, NR_2, OR; Y = O, NTs, NCO_2R, NSO_2Ar; R^1, R^2 = alkyl, aryl, H

Morita, K.; Suzuki, Z.; Hirose, H. *B. Chem. Soc. Jpn.* **1968**, *41*, 2815 , Baylis, A. B., Hillman, M. E. D., DE-B2155113, 1972

Base requirement

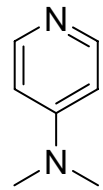
- Nucleophilic
- metal-free
- particularly tertiary amine-bases
- release the MBH-adduct after reaction
- carry a stereogenic unit for enantioselectivity



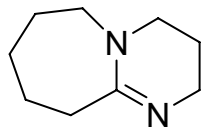


quinine

quinuclidine



DMAP



DBU

Morita, K.; Suzuki, Z.; Hirose, H. *B. Chem. Soc. Jpn.* **1968**, *41*, 2815 , Baylis, A. B., Hillman, M. E. D., DE-B2155113, 1972

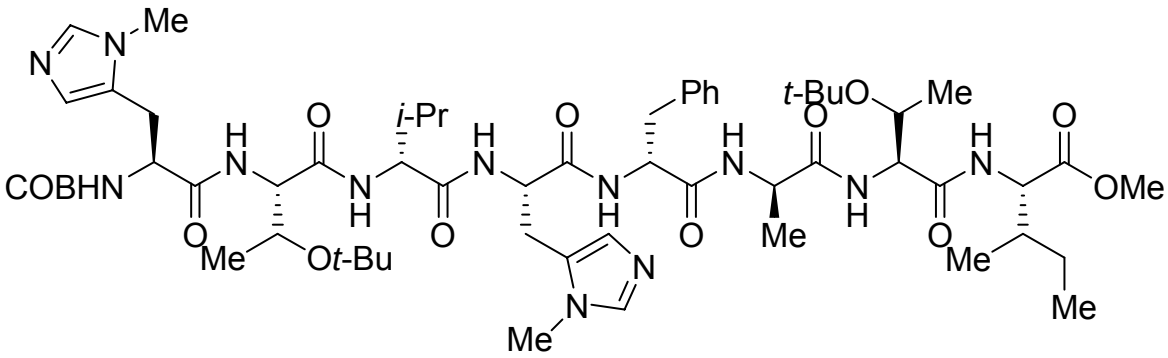
Catalyst requirement

- Synergistic activation by functionalities for high enantioselectivity
- using organic materials
- using natural amino acids
- Lewis-base- and Brœnsted-acid units

⇒ Activation of α,β-unsaturated carbonyl-compounds via acid and activation of β-Position via base

Matsui, K. Takizawa, S., Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681, Berkessel, A., Roland, K., Neudörfl, J. M. *Org. Lett.* **2006**, *8(9)*, 4195-4198, Imbriglio, J. E., Vasbinder, M. M., Miller, S. J. *Org. Lett.* **2003**, *5(20)*, 3741-3743

Catalyst requirement



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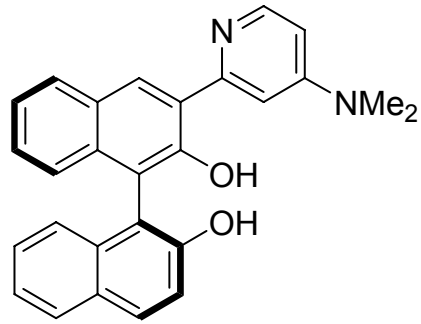

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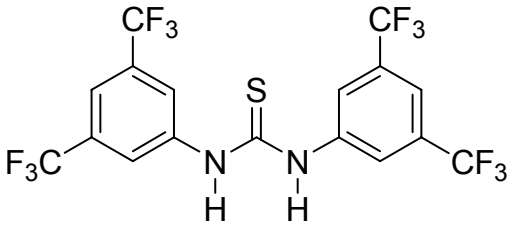

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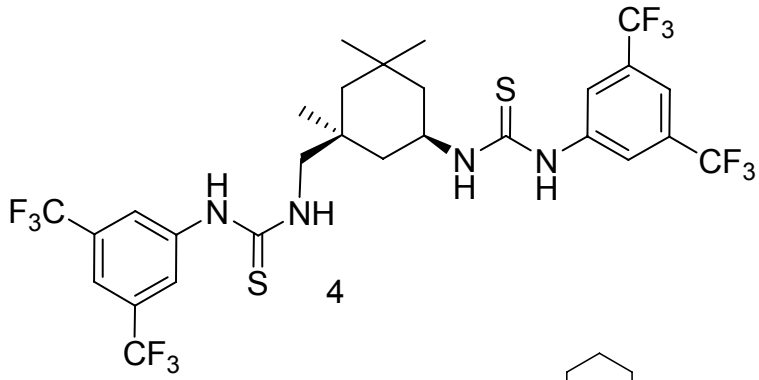

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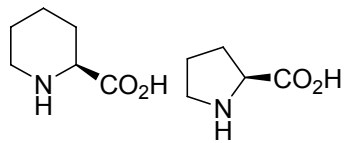
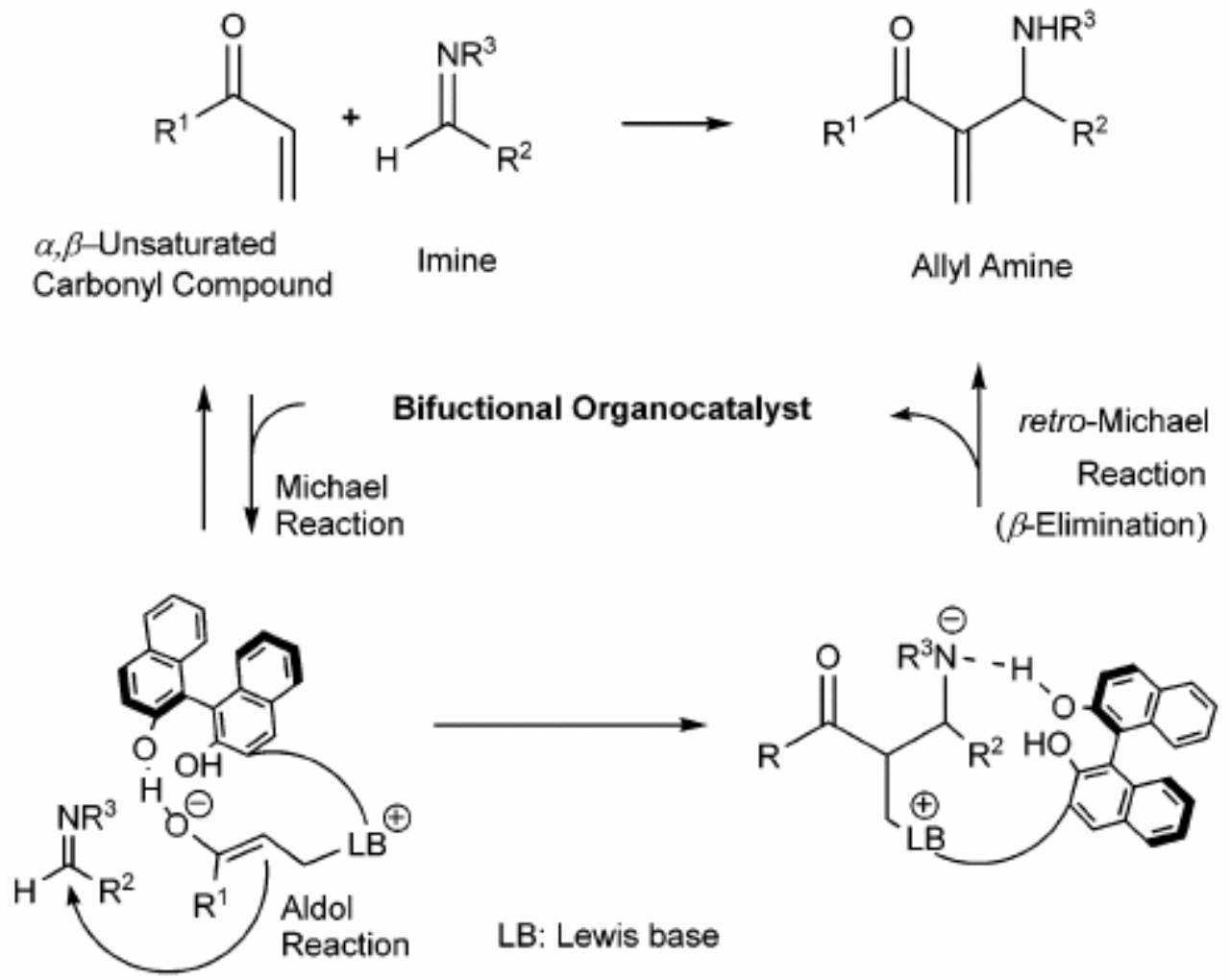


catalyst-system 5

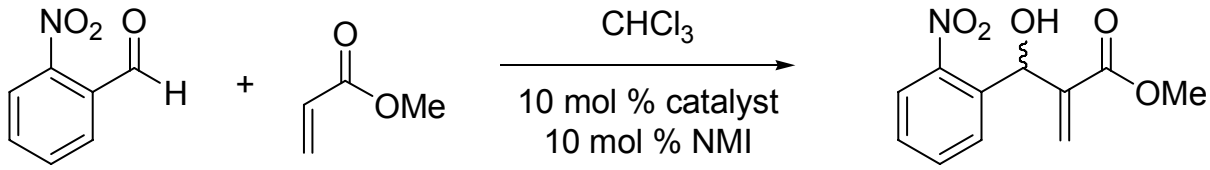
Matsui, K. Takizawa, S., Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681, Berkessel, A., Roland, K., Neudörfl, J. M. *Org. Lett.* **2006**, *8(9)*, 4195-4198, Imbriglio, J. E., Vasbinder, M. M., Miller, S. J. *Org. Lett.* **2003**, *5(20)*, 3741-3743

Aza-MBH

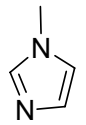


Matsui, K. Takizawa, S., Sasai, H. *J. Am. Chem. Soc.* **2005**, *127*, 3680-3681

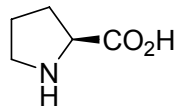
Amino-acid-peptid-catalyst



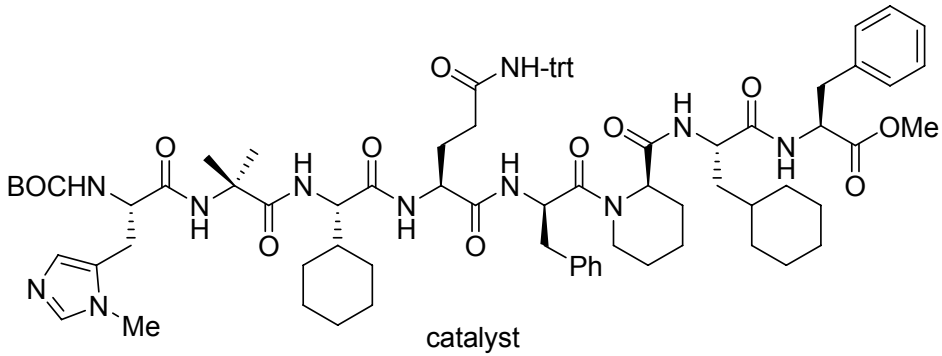
with NMI as catalyst <10 % ee
with octamer peptide as catalyst 78 % ee



NMI



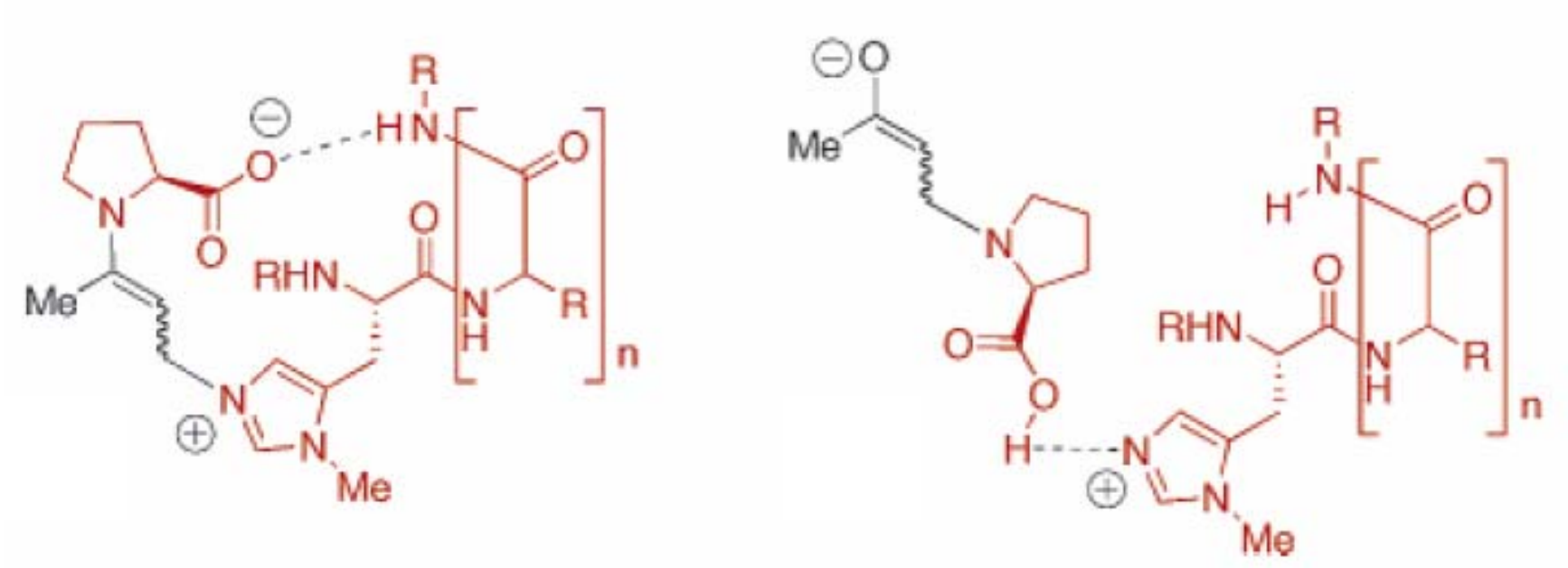
proline



catalyst

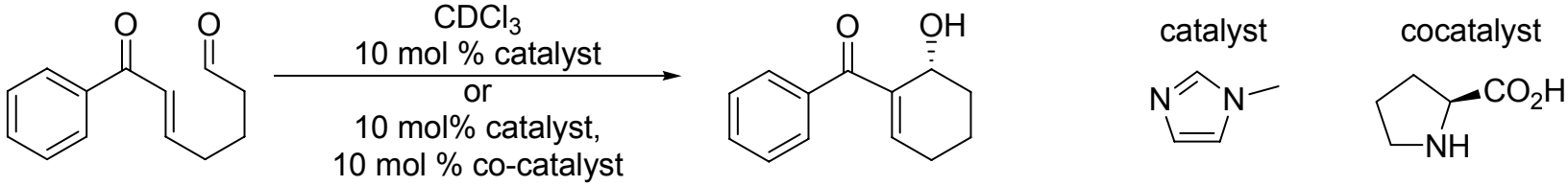
Imbriglio, J. E., Vasbinder, M. M., Miller, S. J. *Org. Lett.* **2003**, *5(20)*, 3741-3743

Purposed transition state



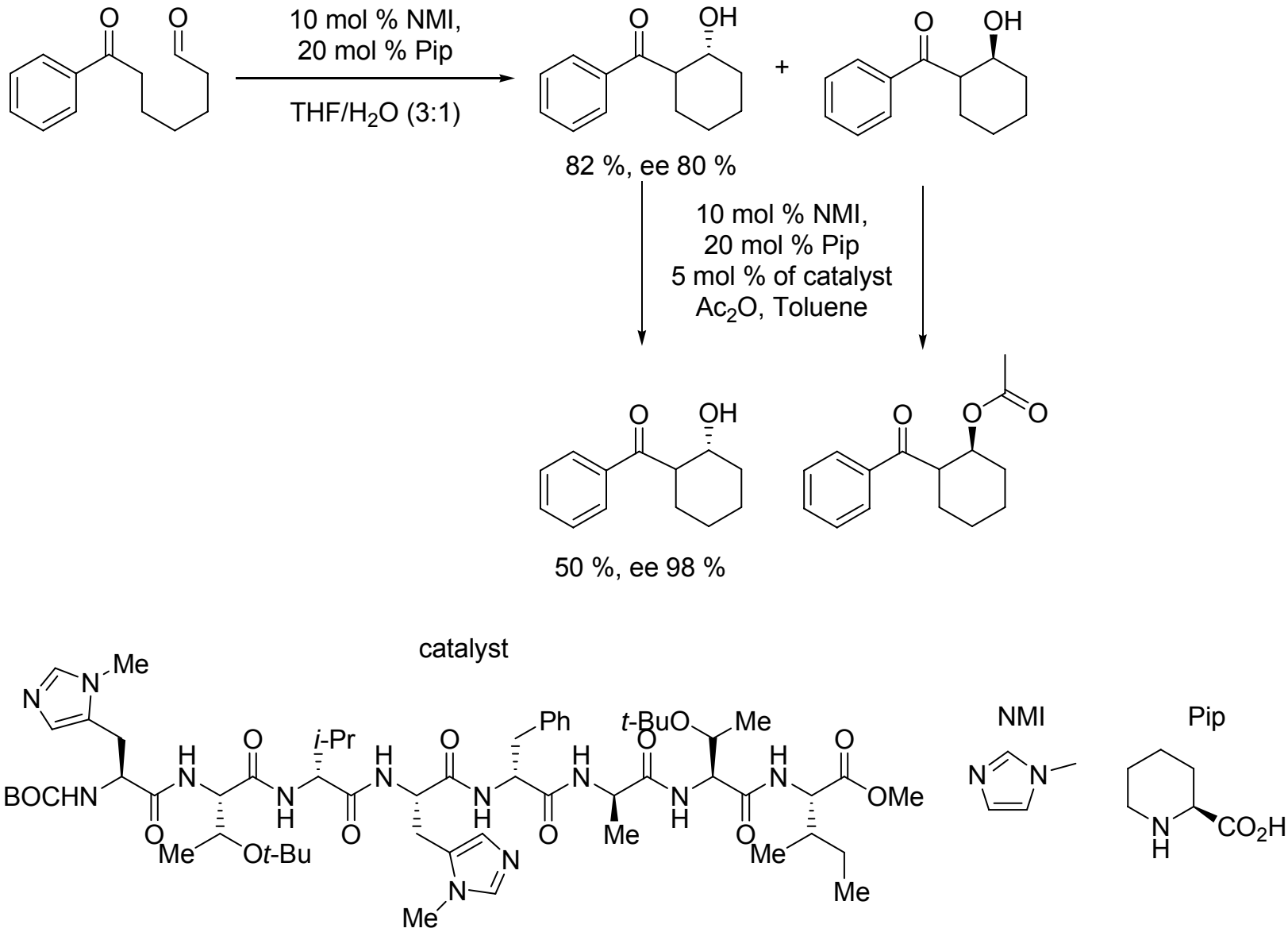
Imbriglio, J. E., Vasbinder, M. M., Miller, S. J. *Org. Lett.* **2003**, *5(20)*, 3741-3743

Intramolecular MBH-reaction



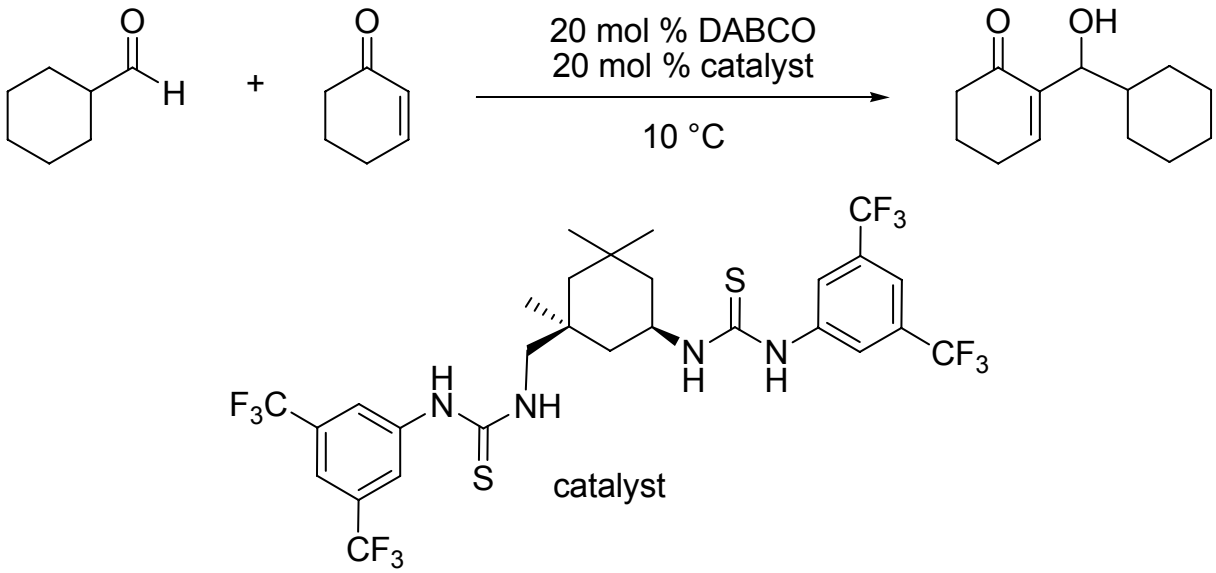
- catalyst: conversion to intermolecular and intramolecular product
- catalyst + co-catalyst: 100 % conversion to intramolecular product with 60 % ee
- no catalyst: no reaction

Miller, S. J., Aroyan, C. E., Vasbinder, M. M. *Org. Lett.* **2005**, *71*, 3849



Miller, S. J., Aroyan, C. E., Vasbinder, M. M. *Org. Lett.* **2005**, *71*, 3849

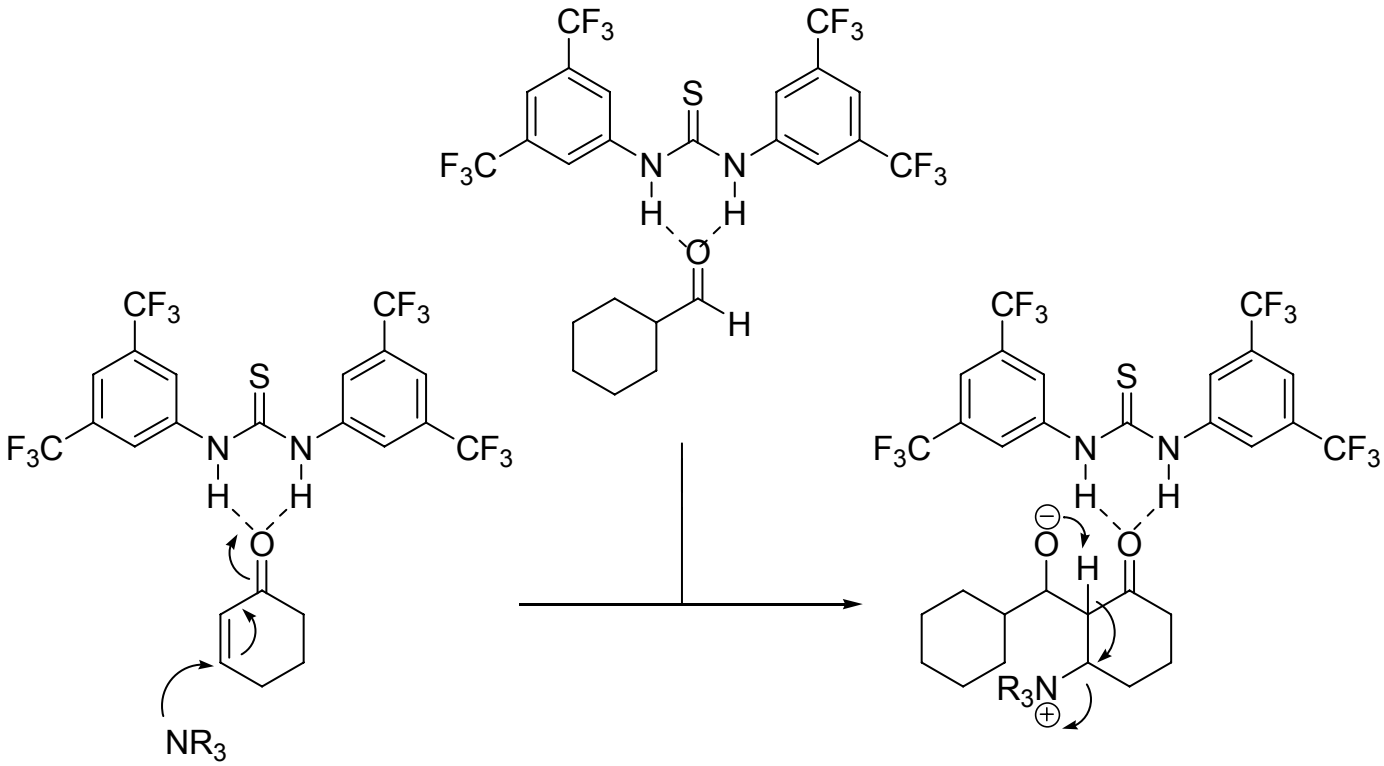
Thiourea-catalyst



- Yield: 81 % and ee of 90 %

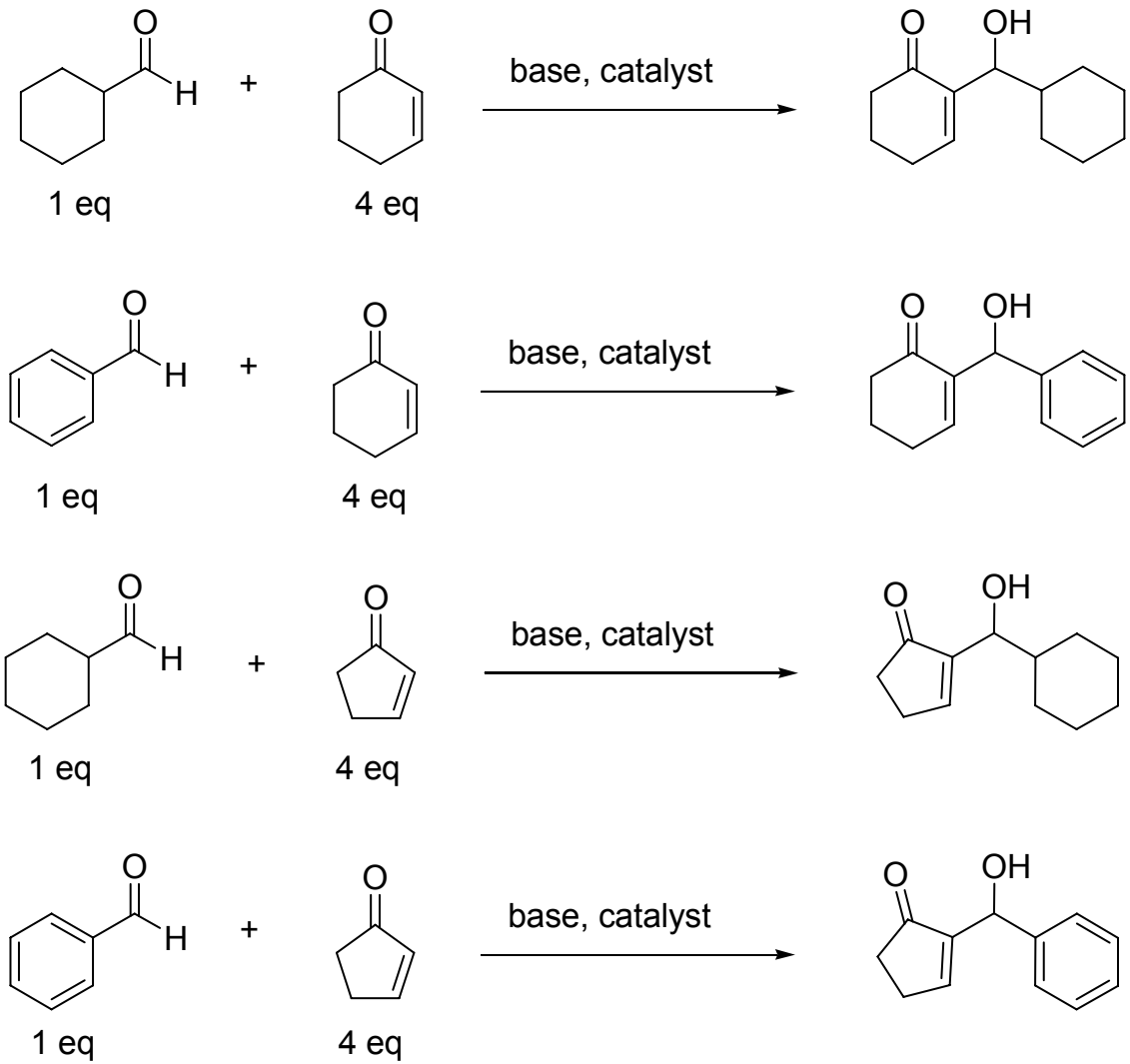
Berkessel, A., Roland, K.,Neudörfl, J. M. *Org. Lett.* **2006**, *8(9)*, 4195-4198

Thiourea-catalyst

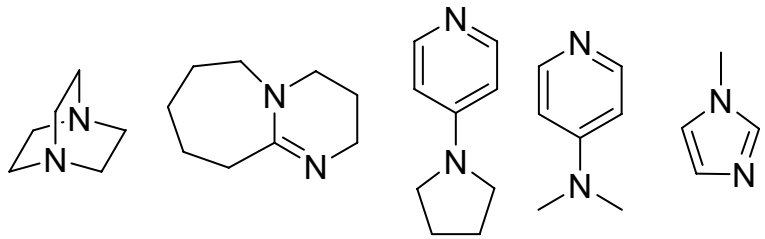


Sohtome, Y., Tanatani, A., Hashimoto, Y. Nagasawa, K. *Tetrahedron Lett.* **2004**, *40*, 5589-5592

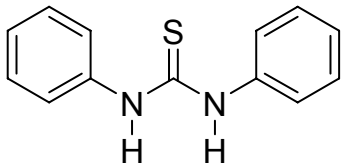
Tested MBH-Systems



Used catalysts and bases



- Thiourea units



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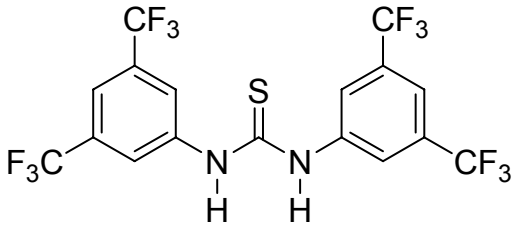
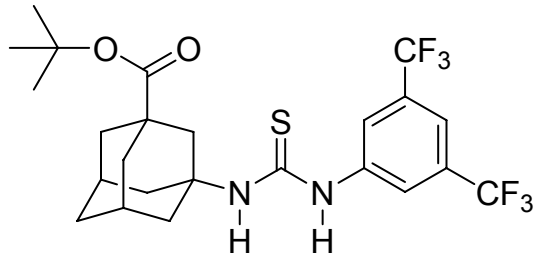
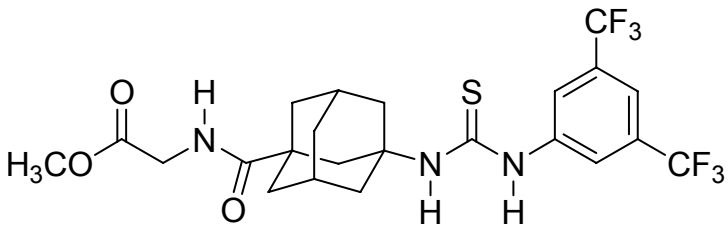


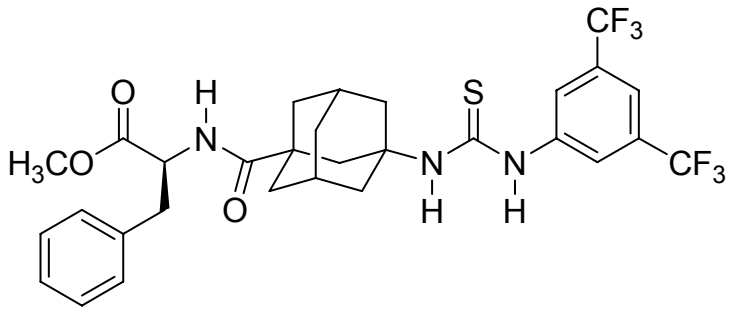
T1



Iso-^{A}Gly-O^{t}Bu



Iso-^{A}Gly-Gly-OMe

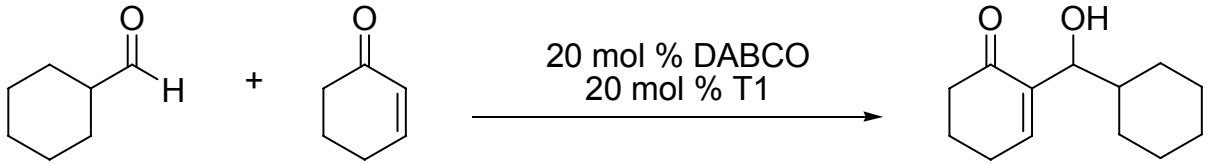


Iso-^{A}Gly-Phe-OMe

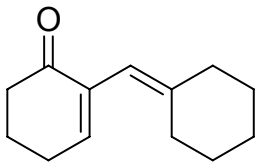
Wanka, L., Cabrele, C., *Vanejews, M., Schreiner, Eu. J. Org. Chem.* In print

Conclusion of tested reaction systems

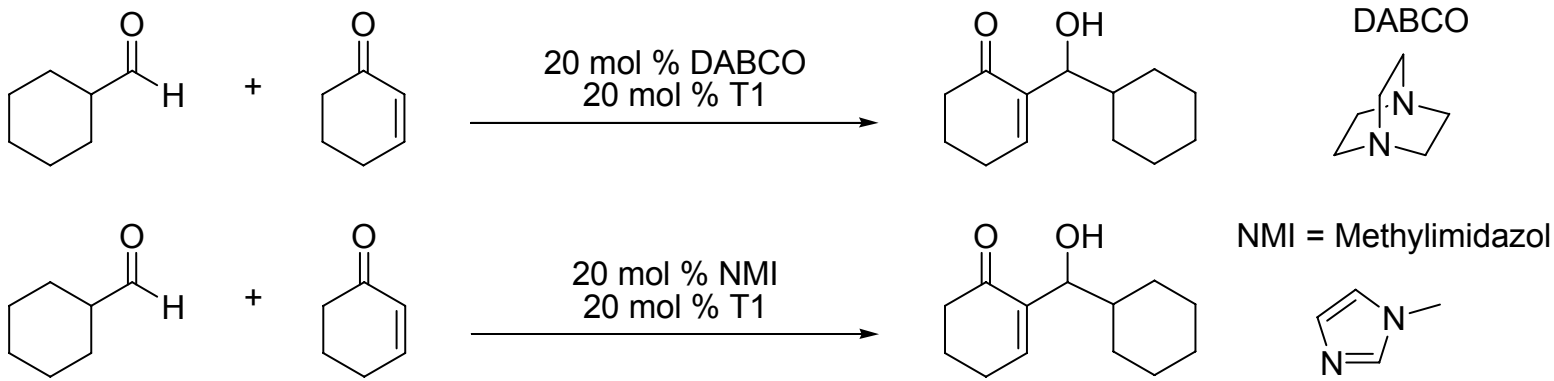
- System



- In comparison to the other reactions:
  - formation of target-product is preferred
  - less by-product after condensation

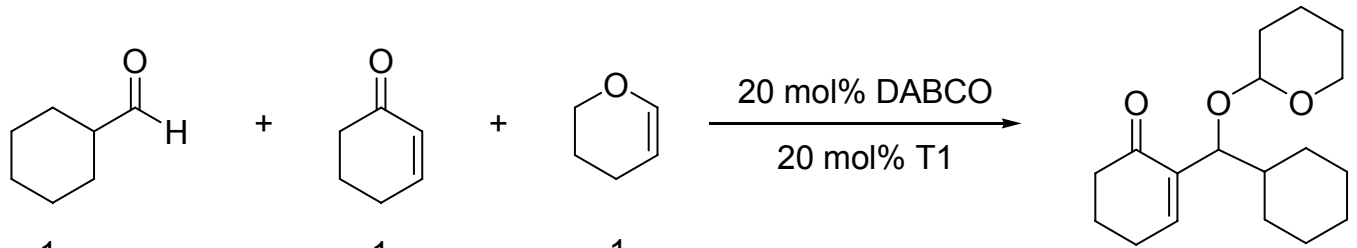


Examination of two systems

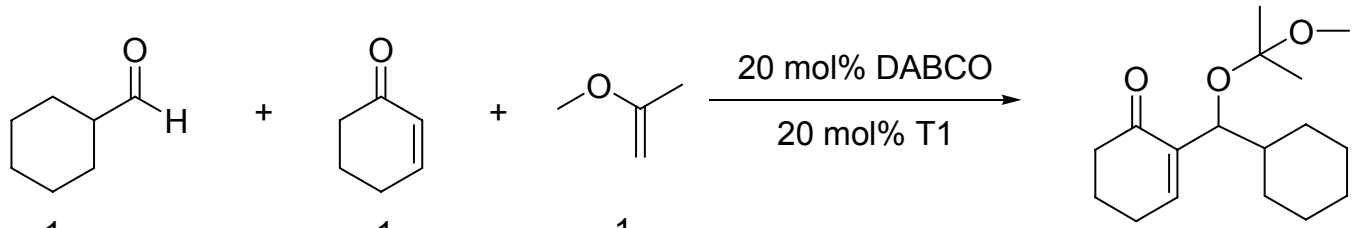


- result: long reaction times
  low yield
  by-products
- **Working hypothesis:**
  trapping the MBH-adduct through ether protection

Tandem-reaction



experiment 1	1	1	1
experiment 2	1	4	1



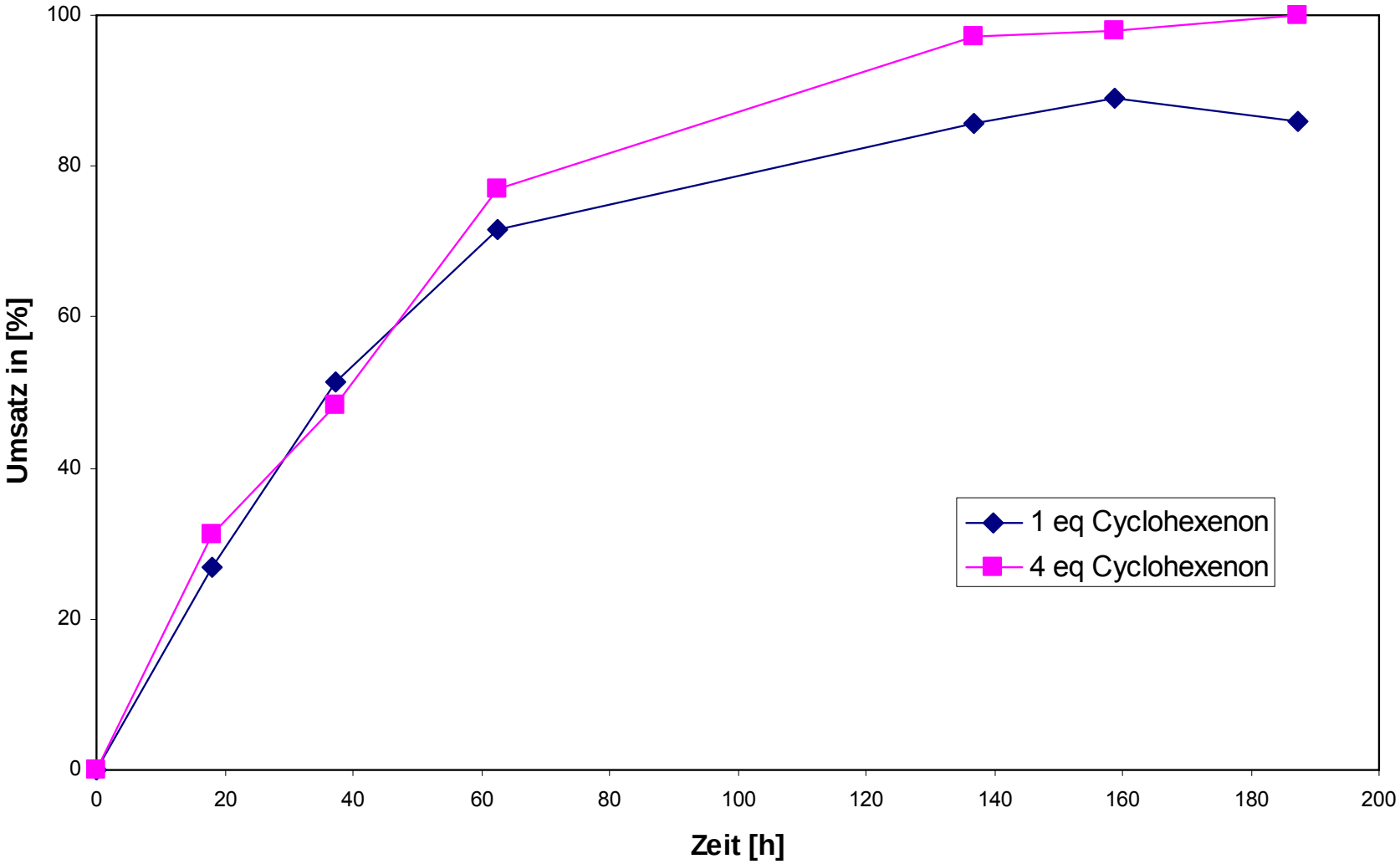
experiment 3	1	1	1
experiment 4	1	4	1

- System 1:4 ($C_7H_{12}O/C_6H_8$) seems to be the best
  ➡ low amount of by-products

Kotke, M., Schreiner, P. R. *Tetrahedron* **2006**, *62,* 434-439,

Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779-790

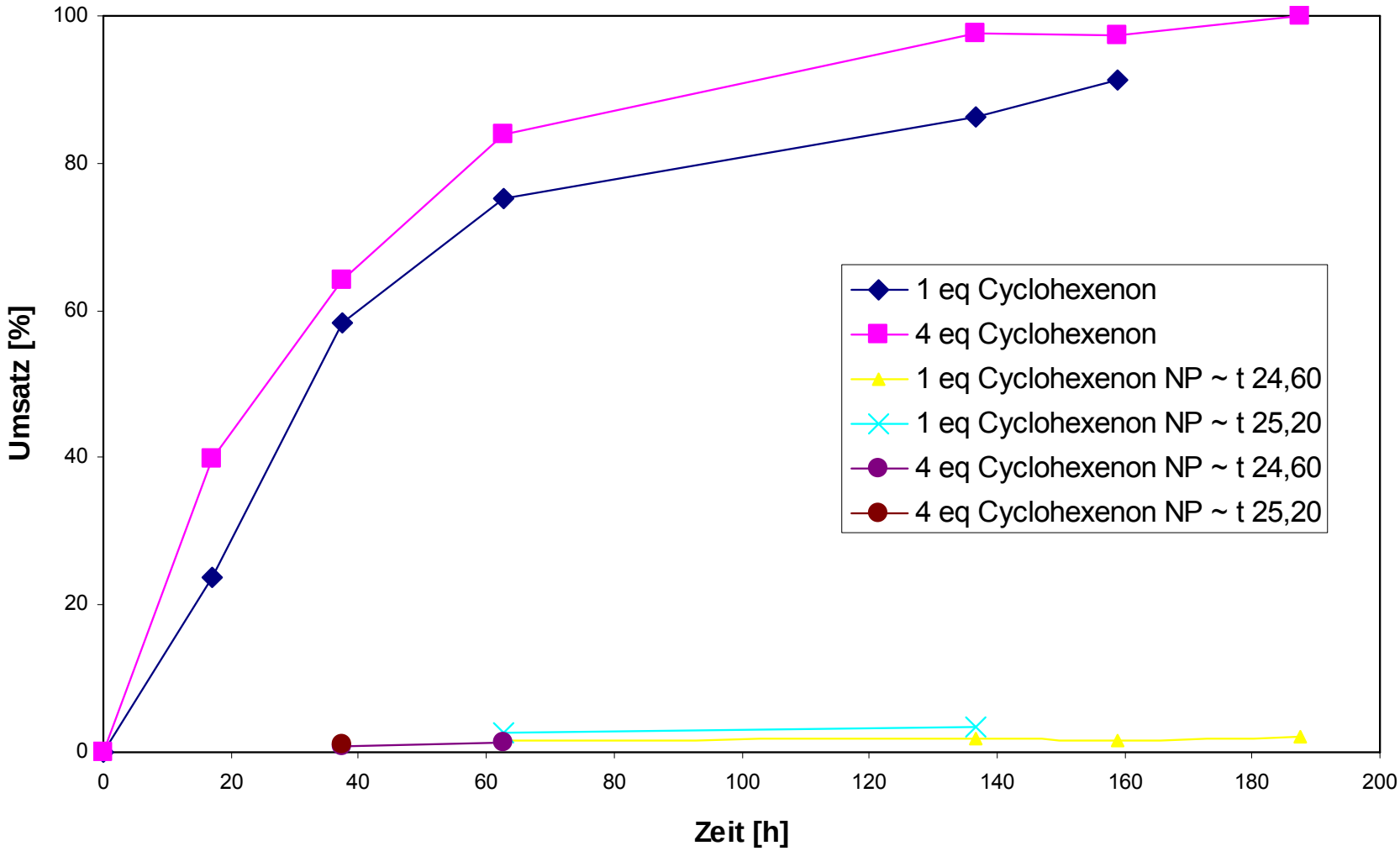
MBH - Cyclohexenon + 1 eq Cyclohexylcarbaldehyd + 1 eq DHP



Kotke, M., Schreiner, P. R. *Tetrahedron* **2006**, *62,* 434-439,

Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779-790

MBH - Cyclohexenon + 1 eq Cyclohexylcarbaldehyd + 1 eq MOP

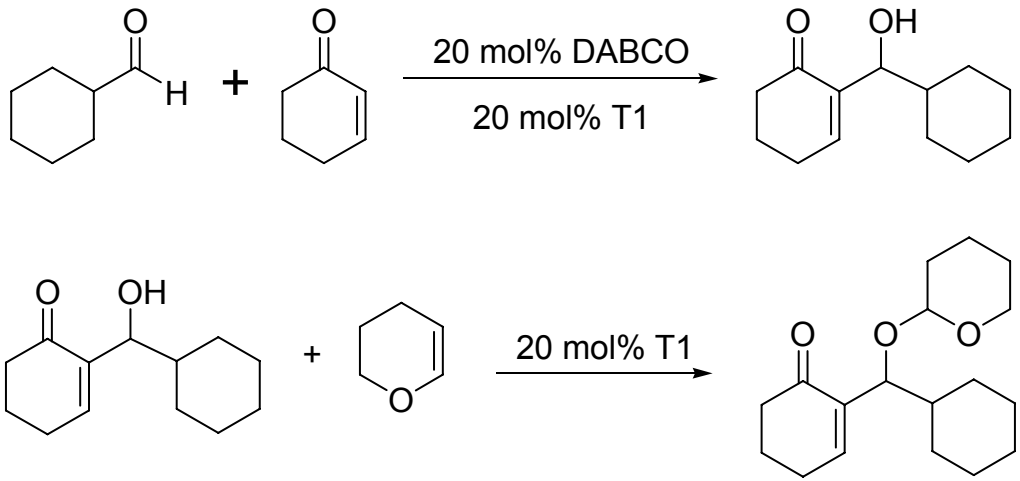


Kotke, M., Schreiner, P. R. *Tetrahedron* **2006**, *62,* 434-439,

Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779-790

Result

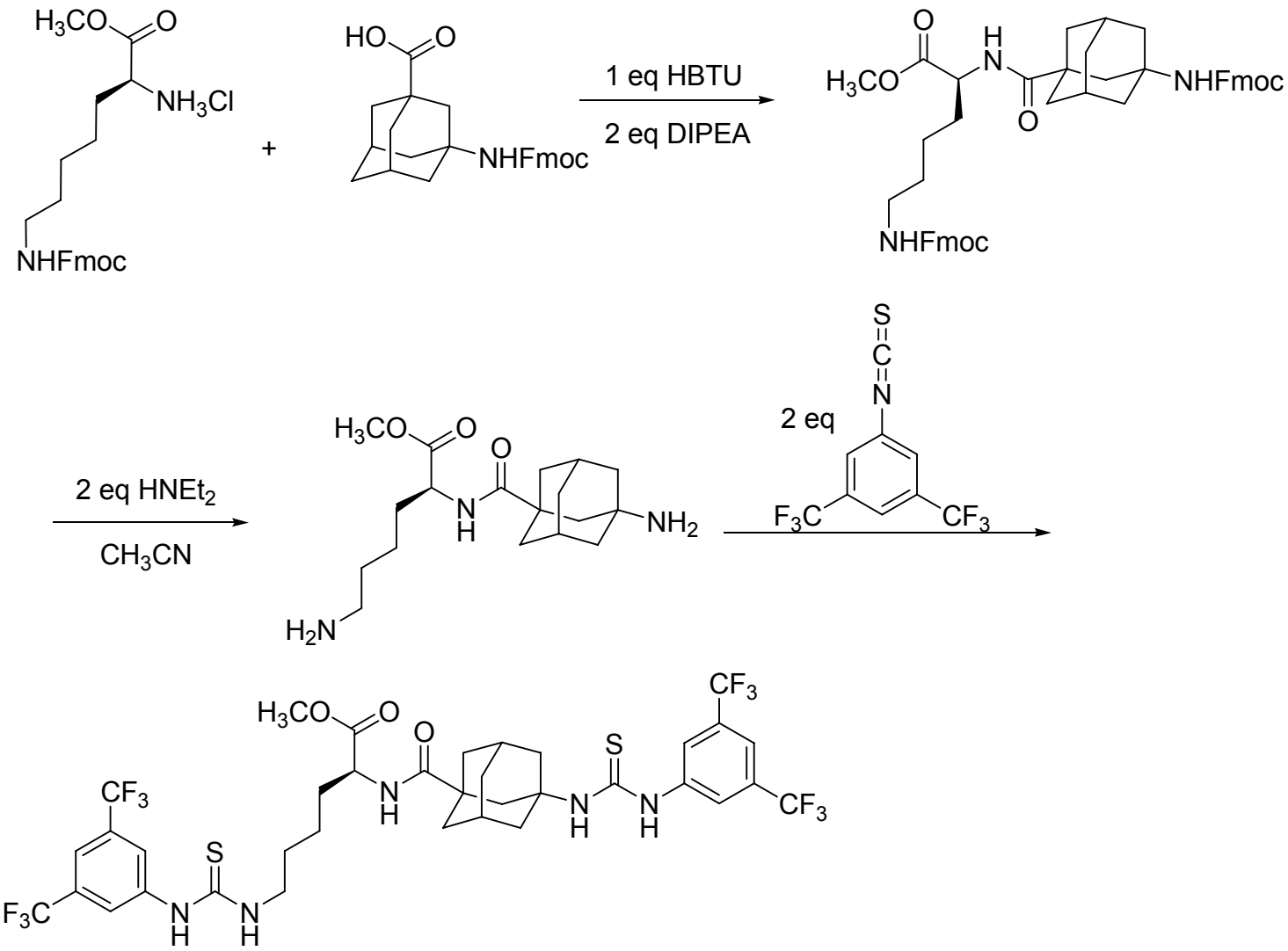
- GC/MS-chromatogram reveals product signal, but retention time is identical as MBH-product
- ESI: $[MBH\text{-}adduct+H]^+$ but no $[MBH\text{-}adduct\text{-}ether+H]^+$,
- Next step: produce the MBH-adduct and isolate
  direct conversion of the MBH-adduct into the ether



Kotke, M., Schreiner, P. R. *Tetrahedron* **2006**, *62,* 434-439,

Kotke, M.; Schreiner, P. R. *Synthesis* **2007**, 779-790

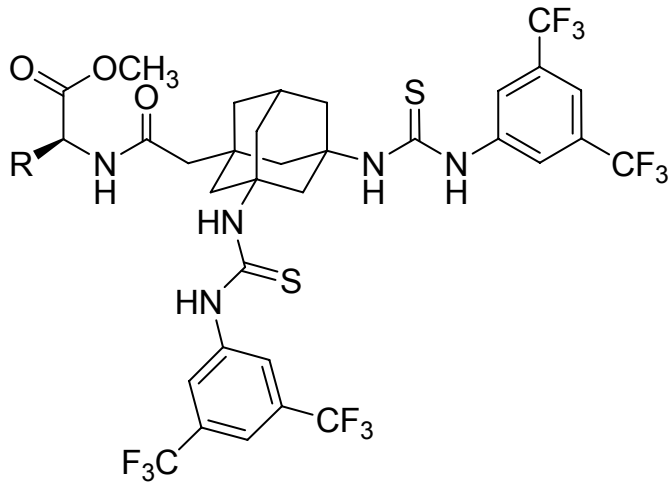
Example of coupling a peptide



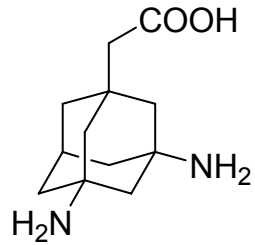
Wanka, L., Cabrele, C., *Vanejews, M., Schreiner, Eu. J. Org. Chem.* In print

Synthesis of a 3D-catalyst

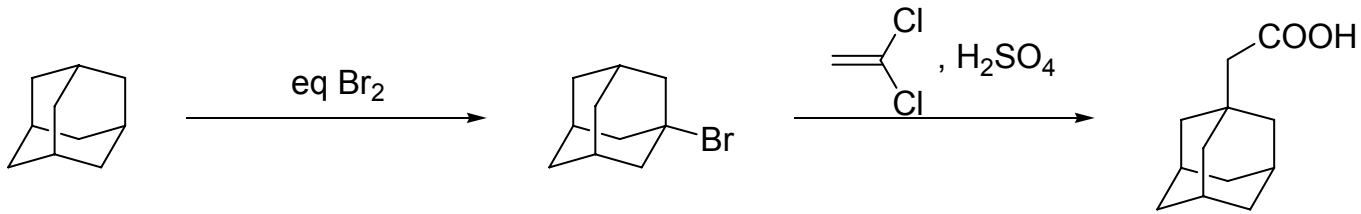
- 3D-structure



- building block:

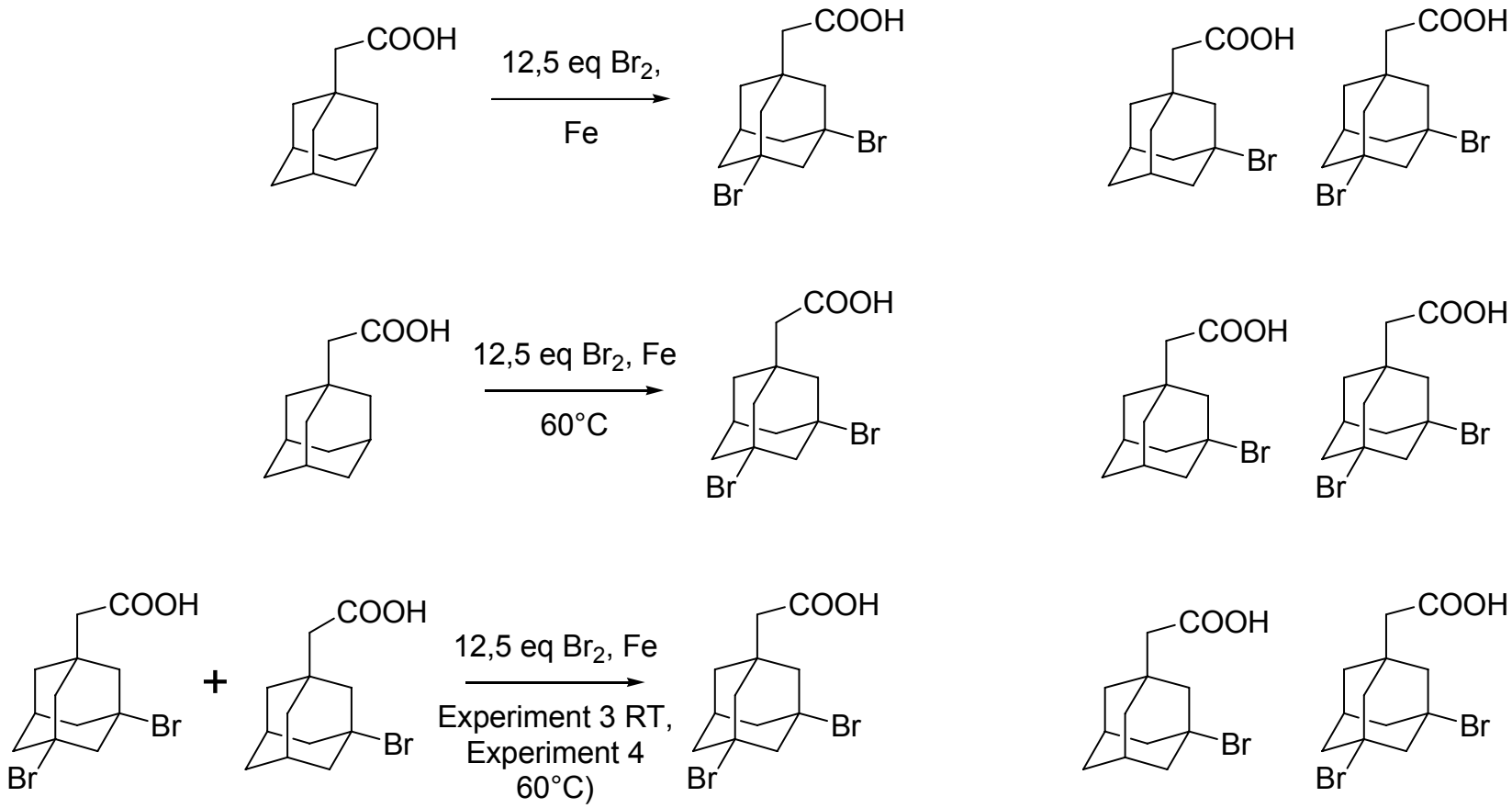


- Synthesis started from



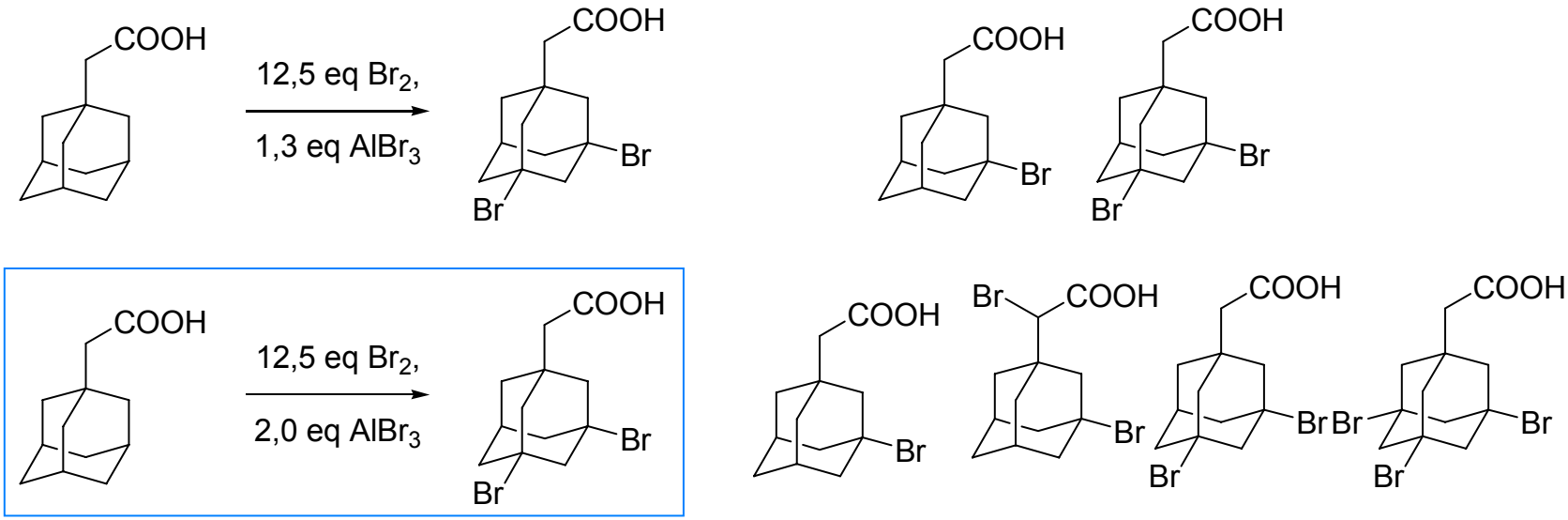
Bott, K. *Chem. Ber.* **1968**, *101*, 564-573

result



Product distribution analyzed via GC/MS after esterfication with Diazomethan

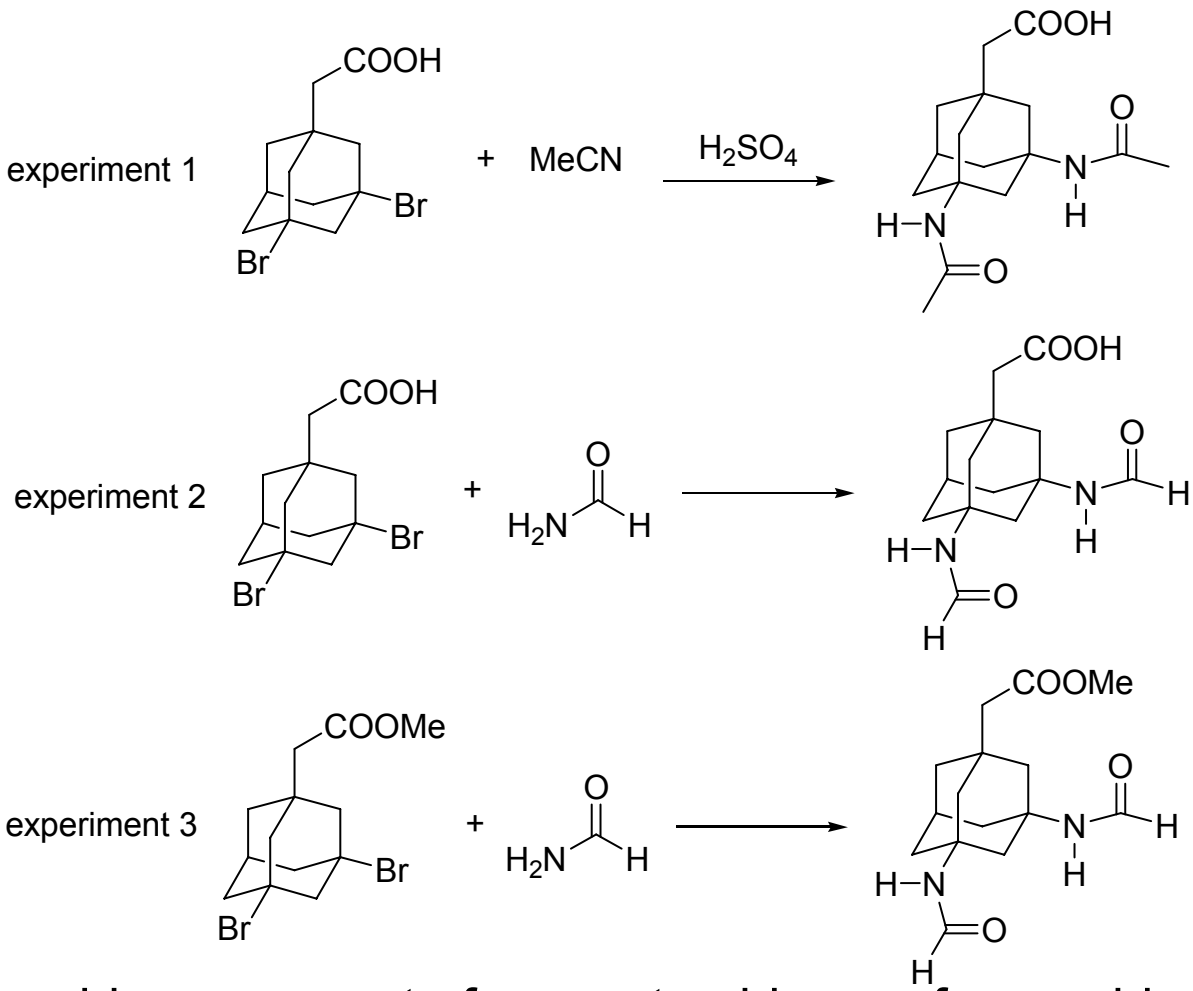
result



- Purification?
  - methylester seperation through chromatography
  - distillation under reduced pressure (Kugelrohr oven and short Vigreux column)
  - Re-precipitation

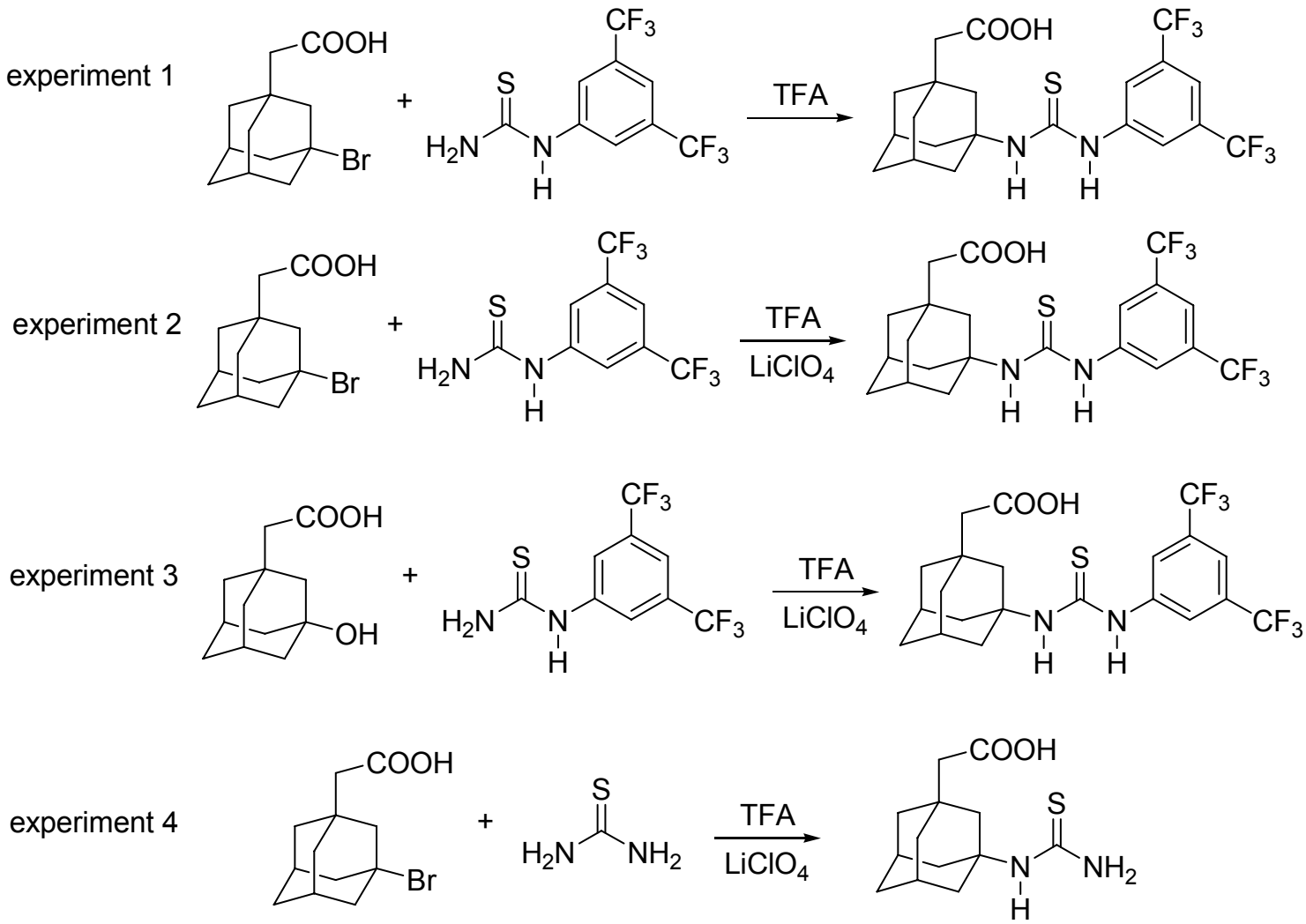
⇨ But: To date purification-methods failed

Next step: Substi-tution of the bromide



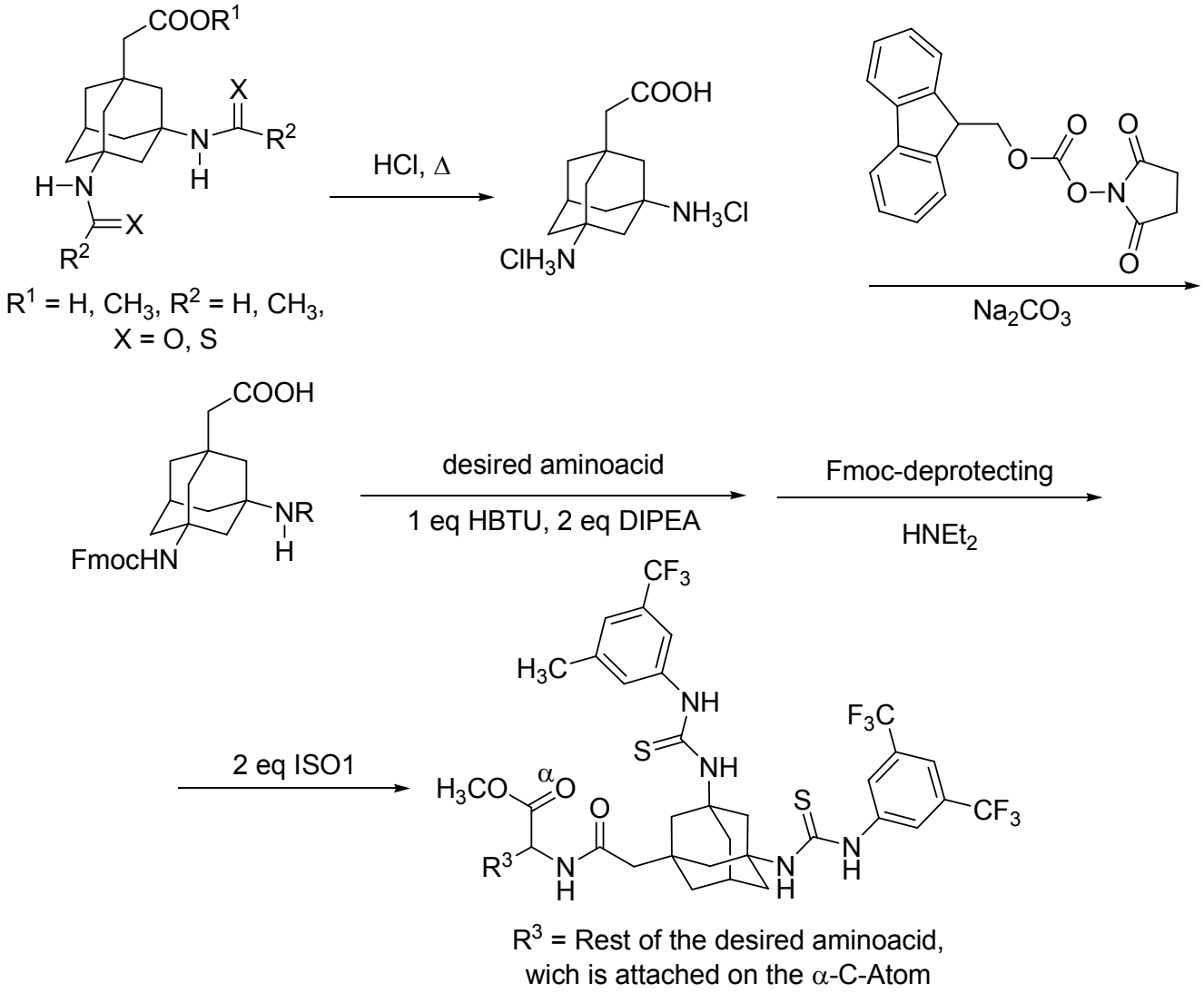
- no reaction provide an amount of an acetamide or a formamide
- nearly 90 % of the crude reaction product was soluble in water, so it hydrolyzed obviously to ammonium-salts (^{1}H-NMR: ^{15}N-quadropol-peaks as seen in ^{A}Gly·HCl

Seino, A. Mochizuki, A. Ueda, M. *J. Pol. Sci. Pol. Chem.* **1999**, *37*, 3584-3590,
Wanka, L., Cabrele, C., *Vanejews, M., Schreiner, Eu. J. Org. Chem.* In print



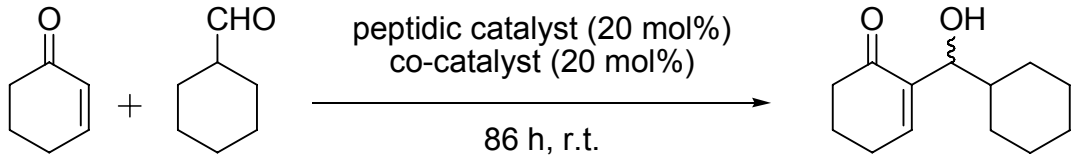
Shokova, E., Mousoulou, T., Luzikov, Y. Kovalev, V. *Synthesis* **1997**, 1034

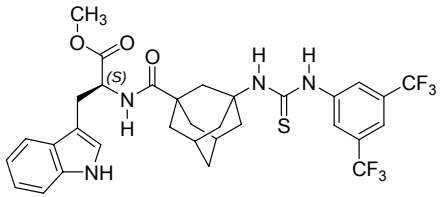
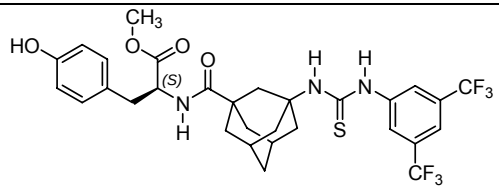
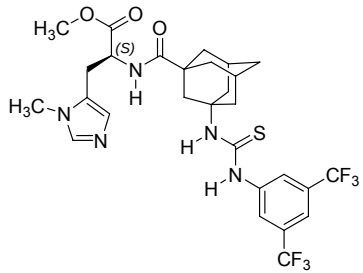
Next steps



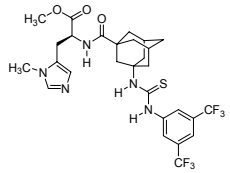
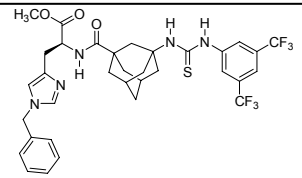
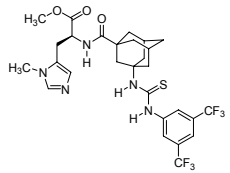
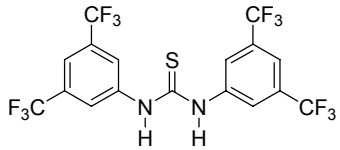
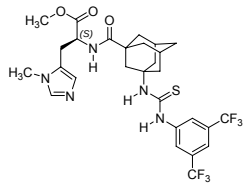
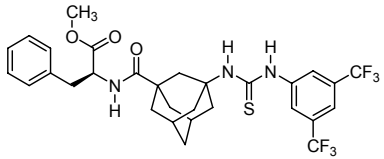
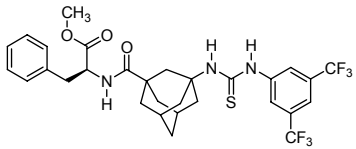
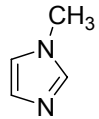
Wanka, L., Cabrele, C., *Vanejews, M., Schreiner, Eu. J. Org. Chem.* In print

Lukas petides



entry	peptidic catalyst	co-catalyst	yield [%][a]	er
1	none	none	-[b]	-
2	none	DABCO	-[b]	-
3		DABCO	52	?[c]
4		DABCO	20.4	?[c]
5		none	5.4	?[c]

Wanka, L., Cabrele, C., *Vanejews, M., Schreiner, Eu. J. Org. Chem.* In print,
Lukas Labor-Journal

entry	peptidic catalyst	co-catalyst	yield [%][a]	er
5		none	5.4	?[c]
6		none	9.8	?[c]
7[d]			8.4	?[c]
8[d]		DABCO	69.5	?[c]
9		DABCO	19.9	?[c]
10			traces?[b]	?[c]

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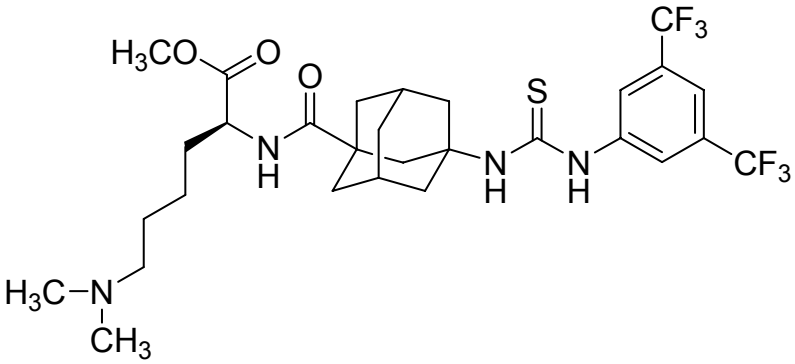
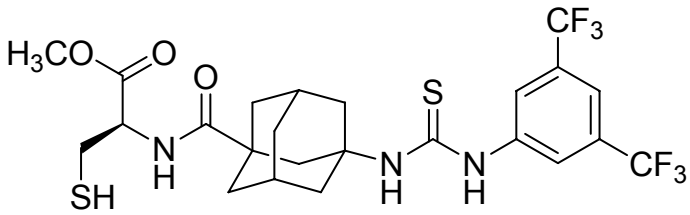
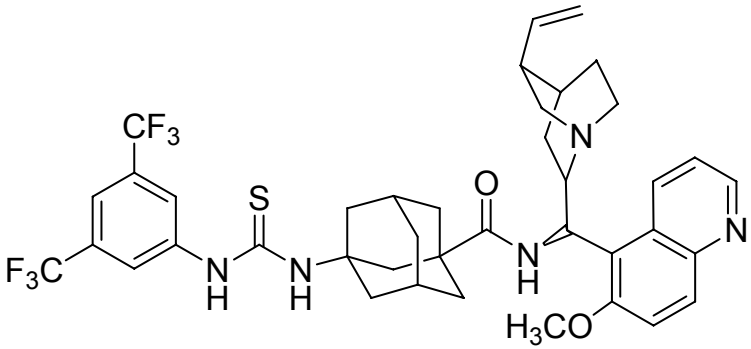
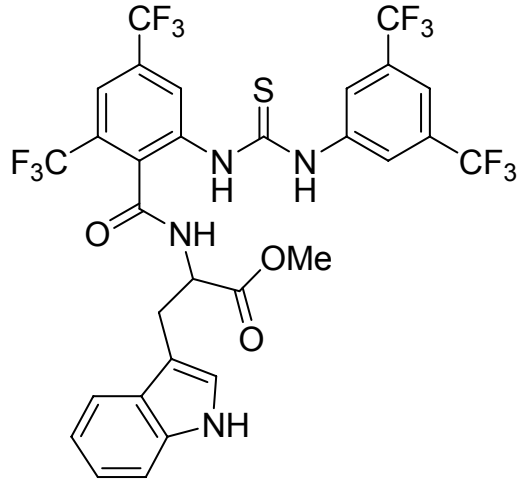
Lukas Labor-Journal

Outlook


H3CO
O
O
N
H
S
N
H
N
H
CF3
CF3
H3C–N
CH3

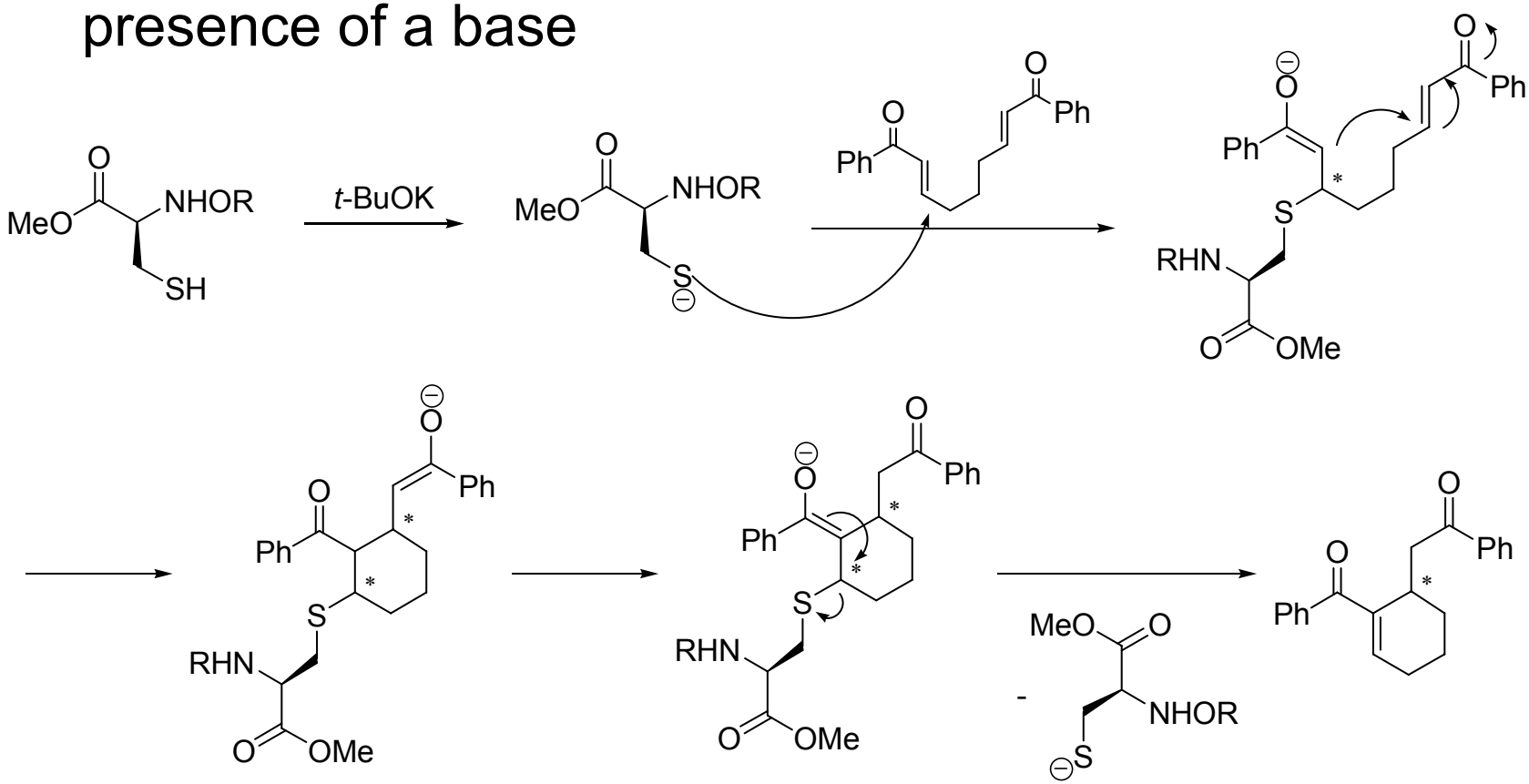

H3CO
O
O
N
H
S
N
H
N
H
CF3
CF3
SH


CF3
F3C
S
N
H
N
H
O
N
H
O
H3CO
N
CF3


CF3
CF3
F3C
S
N
H
N
H
CF3
O
NH
OMe
O
NH

Why cysteine-peptide?

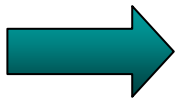
- Miller et al. investigated an enantioselective Rauhut-Currier reaction with protected cysteine derivates in presence of a base



Aroyan, C. E., Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129(2),* 256 - 257

Conclusion

- MBH-reaction takes long reaction times, low yielding and provides by-products
- bifunctional catalysts with thiourea units show reactivity and enantioselectivity (Berkessel)
- peptide catalysts with co-catalysts show reactivity and enantioselectivity (Miller)
- peptide catalysts show catalytic effect;
- ee-values will be determined



adamantyl peptides with thiourea units work

Acknowledgment

Thanks to…

- Professor Schreiner for the interesting thesis
- Lukas for discussions and inspiration
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- Edgar Reitz for rescue my computer
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- and all the others, who were available for discussions