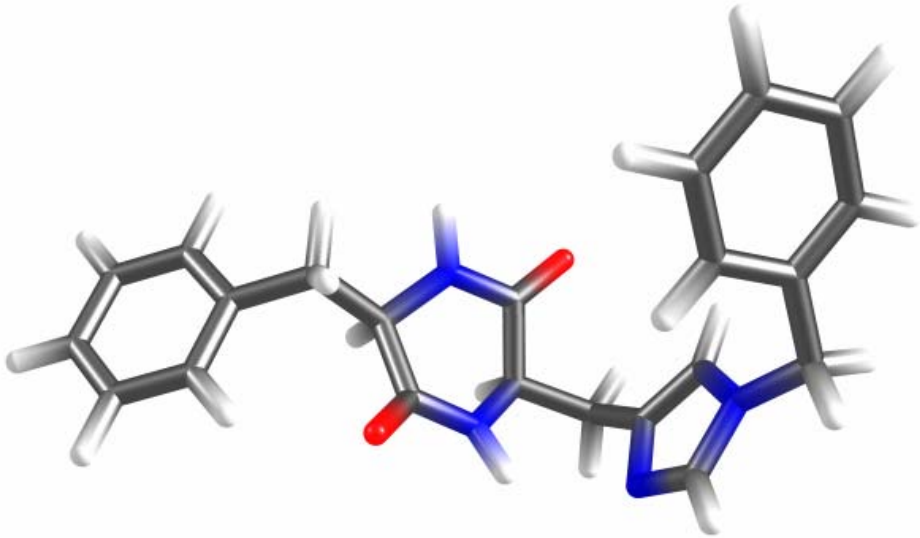
Diketopiperazines –

Troublesome By-products During Peptide Assembly or Powerful Organocatalysts?



Christian Müller

Justus-Liebig University Giessen

23.2.2007

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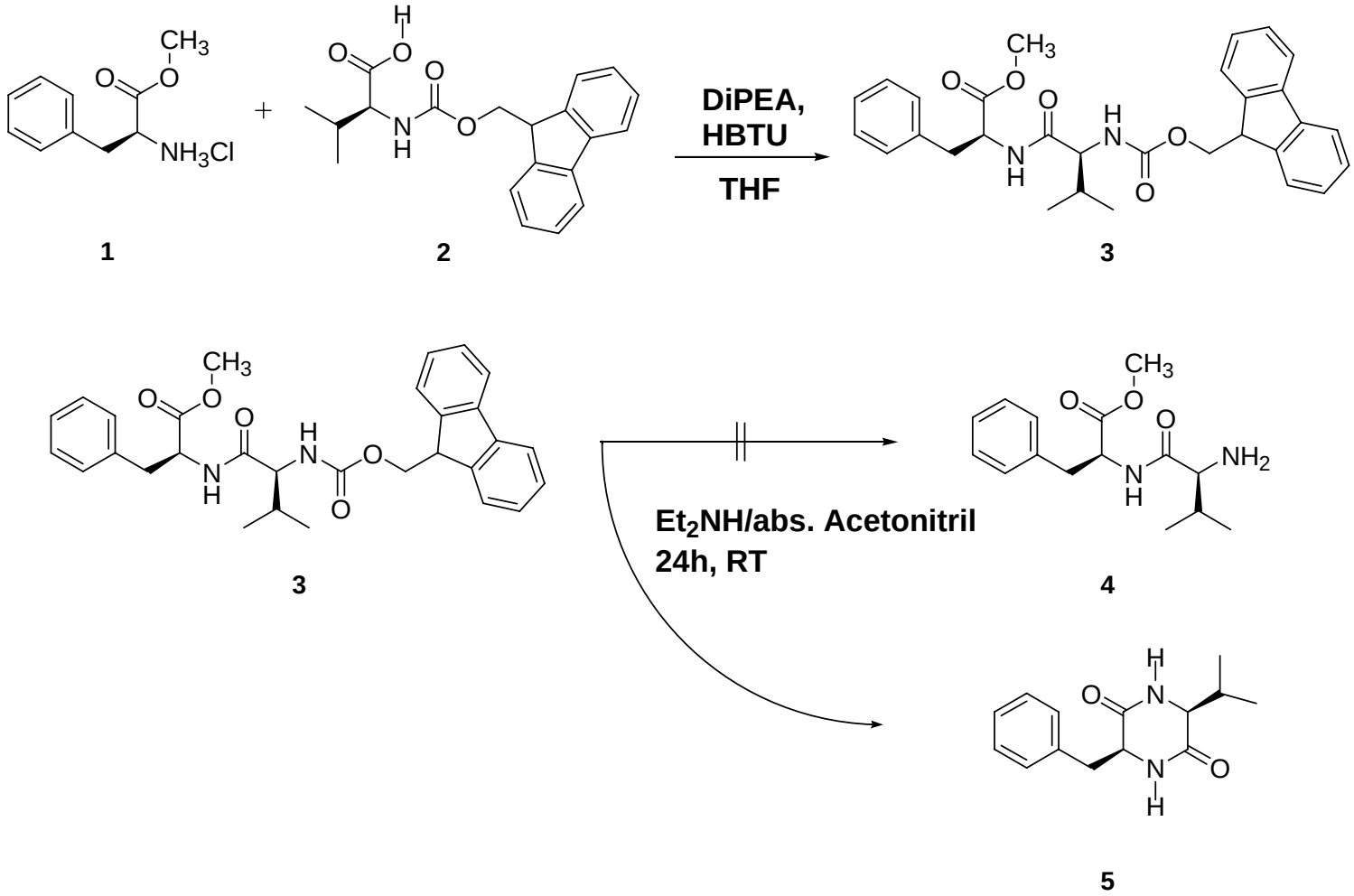
My First Diketopiperazine Synthesis



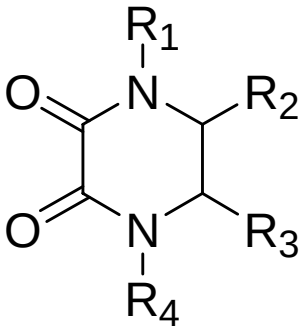
History

- Earliest report of what was later found to be a Diketo-piperazine (DKP), leucinimide (*cyclo*-[Leu-Leu]), was published by Bopp[1] in 1849.
- In 1865 Kohler[2] realized the synthesis of *cyclo*-[Gly-Gly] by heating glycine in a stream of CO_2 or HCl gas.
- In the literature of the late 19th century it was realized that DKPs could be synthesized efficiently from amino acid esters.[3,4]
- Ironically the first well defined synthetic peptide was obtained from *cyclo*-[Gly-Gly] by Fischer[5] in 1901: Warming it in aq. HCl, it underwent partial hydrolysis and provided crystalline H-Gly-Gly-OH*HCl.

1) Bopp, F., *Liebigs Ann. Chem.* ***1849***; 69, 16-17.
2) Kohler, A., *Liebigs Ann. Chem.* ***1865***; 134, 367-372.
3) Curtius, T., *Chem. Ber.* **1883**; 16, 753-757.
4) Curtius, T., *J. Prakt. Chem. Ber.* **1888**; 37, 173-181.
5) Fischer, E., Forneau, E., *Chem. Ber.* **1901**; 2868-2877.

Family of DKPs

2,3-Diketopiperazines

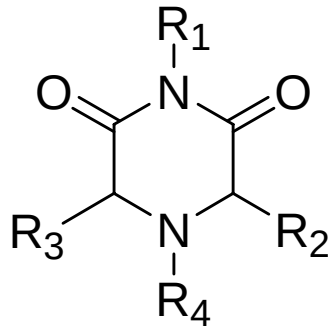


- Medicinal applications
- Natural products: antibiotics piperacillin, cefoperazone, bicyclomycin

2,5-Diketopiperazines

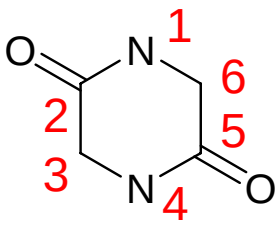
- **head-to-tail dipetide dimers**
- **common naturally occurring structural motif**

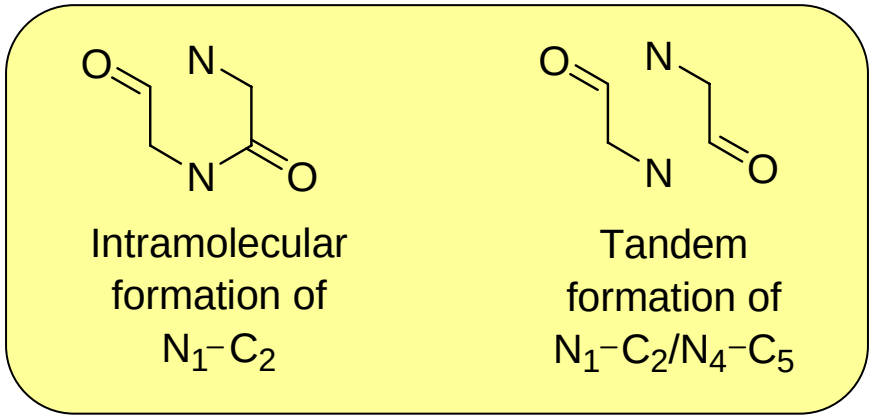
2,6-Diketopiperazines



- Investigations as antiproliferative agents through the inhibition of DNA topoisomerase II

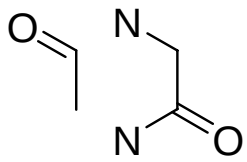
Synthesis of 2,5-DKPs



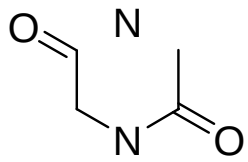


Enantiopure starting materials:

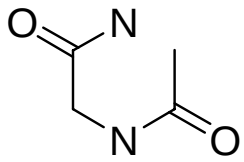
Large pool of available natural and unnatural amino acids.



Tandem formation of N_1–C_2/C_3–N_4



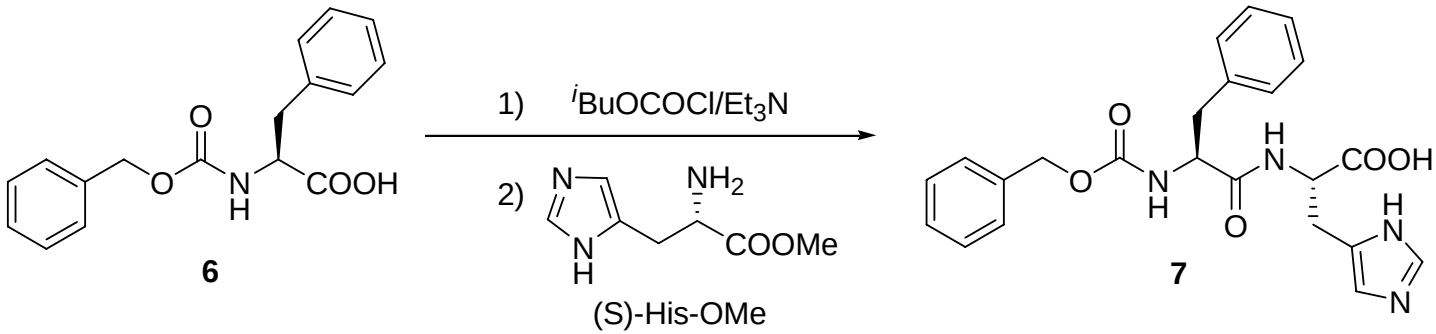
Tandem formation of C_2–N_1–C_6

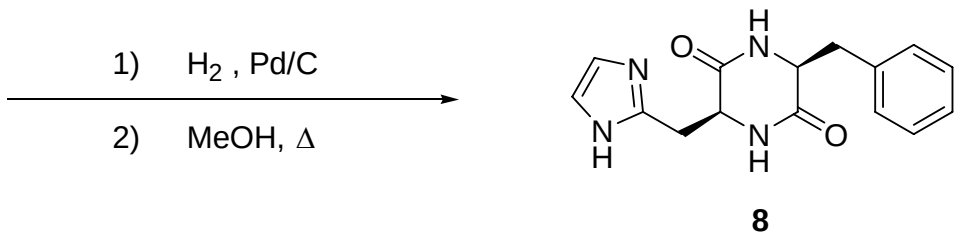


Intramolecular formation of N_1–C_6

Intramolecular Formation of N_1–C_2

2,5-DKP formation via intramolecular cyclization of the N_1–C_2 is the most efficient route to ring closure.

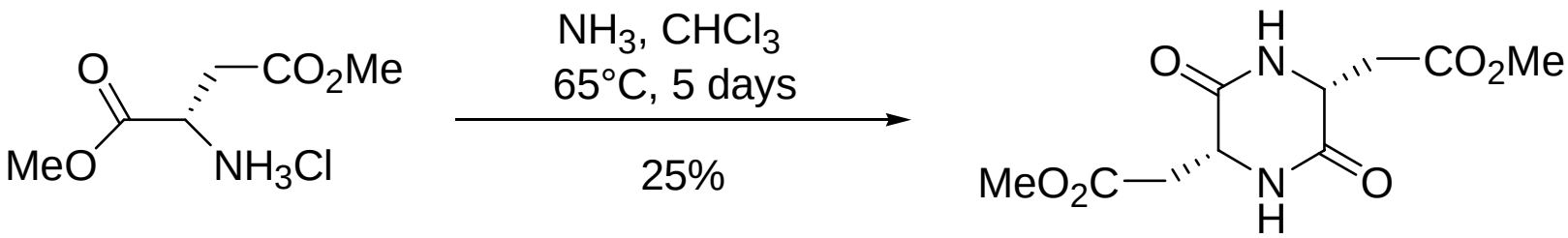




6.) Inoue, S.; Mori, A.; Tanaka, K., *J. Org. Chem.* **1990**, 55, 181-185.

Tandem Formation of $N_1–C_2/N_4–C_5$

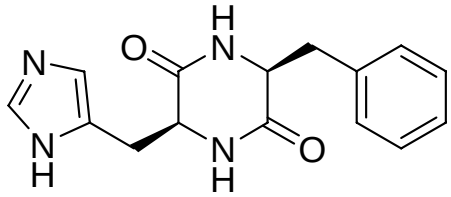
2,5-DKP formation via tandem formation of the $N_1–C_2/N_4–C_5$ often suffers from low yields.



9 **10**

7.) Taddei, M.; Porcheddu, A.; Giacomelli, G.; Falorni, M., *J. Org. Chem.* **2000**, 1669.

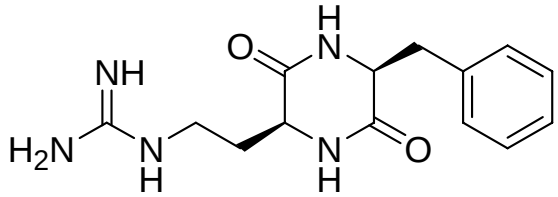
DKPs as Powerful Organocatalysts



8

cyclo[(S)-phenylalanine-(S)-histidine]

Inoue´s catalyst



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cyclo[(S)-phenylalanine-(S)-α-amino-γ-guanidinobutyric acid]

Lipton´s catalyst

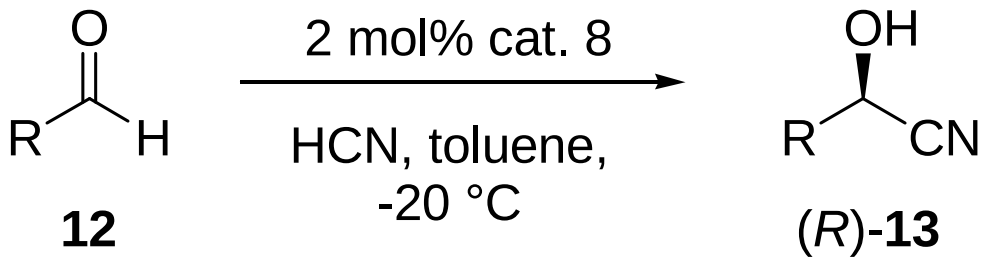
8.) Inoue, S.; Oku, J., *J. Chem. Soc., Chem. Commun.* **1981**, 229.

9.) Inoue, S.; Mori, A.; Tanaka, *J. Org. Chem.* **1990**, 55, 181.

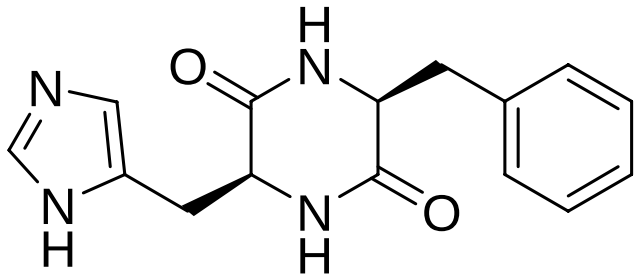
10.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *J. Am. Chem. Soc.* **1996**, 118, 4910.

11.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *Amino Acids* **1996**, 11, 259.

Organocatalytic Hydrocyanation of Aldehydes



12 (*R*)-**13**



8

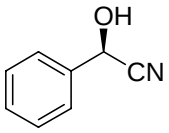
8.) Inoue, S.; Oku, J., *J. Chem. Soc., Chem. Commun.* **1981**, 229.

9.) Inoue, S.; Mori, A.; Tanaka, *J. Org. Chem.* **1990**, 55, 181.

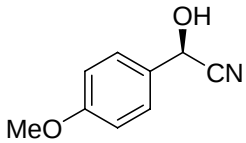
Organocatalytic Hydrocyanation of Aldehydes

Substrate range:

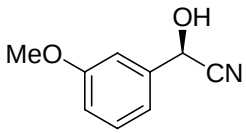
Aromatic products:



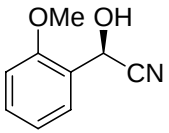
(*R*)-**13a**
97% yield
97% ee
8.0 h



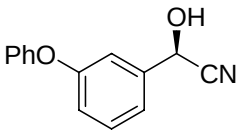
(*R*)-**13b**
57% yield
78% ee
10.0 h



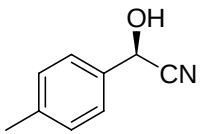
(*R*)-**13c**
83% yield
97% ee
8.0 h



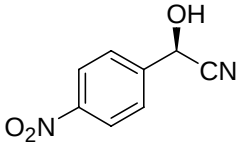
(*R*)-**13d**
45% yield
84% ee
10.0 h



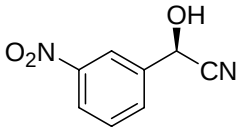
(*R*)-**13e**
97% yield
92% ee
8.0 h



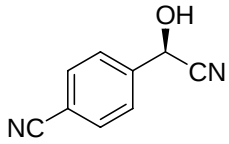
(*R*)-**13f**
78% yield
96% ee
10.0 h



(*R*)-**13g**
99% yield
53% ee
2.5 h

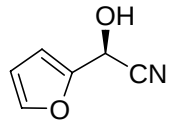


(*R*)-**13h**
100% yield
4% ee
8.0 h

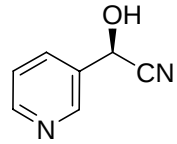


(*R*)-**13i**
100% yield
32% ee
8.0 h

Hetoaromatic products:

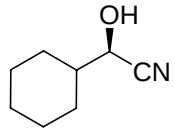


(*R*)-**13j**
60% yield
42% ee
8.0 h

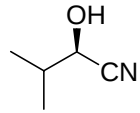


(*R*)-**13k**
73% yield
54% ee
0.5 h

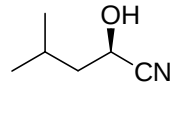
Aliphatic products:



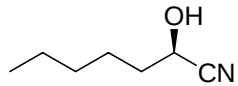
(*R*)-**13l**
96% yield
58% ee
2.5 h



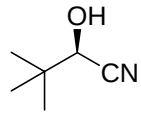
(*R*)-**13m**
79% yield
71% ee
5.0 h



(*R*)-**13n**
44% yield
18% ee
5.0 h



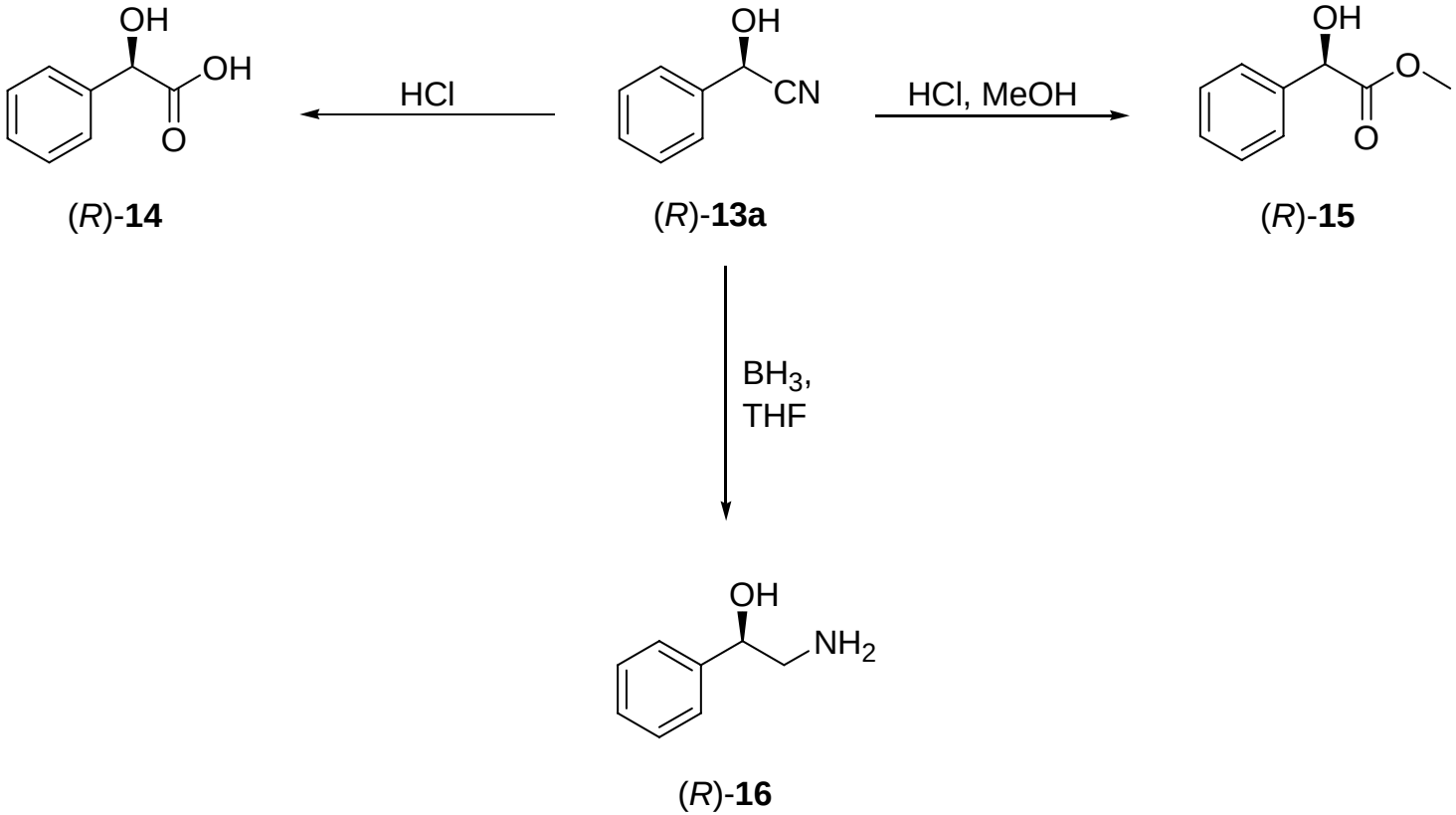
(*R*)-**13o**
90% yield
56% ee
8.0 h



(*R*)-**13p**
60% yield
58% ee
5.0 h

9.) Inoue, S.; Mori, A.; Tanaka, *J. Org. Chem.* **1990**, 55, 181.

Conversion of Mandelonitrile to Different Functional Groups

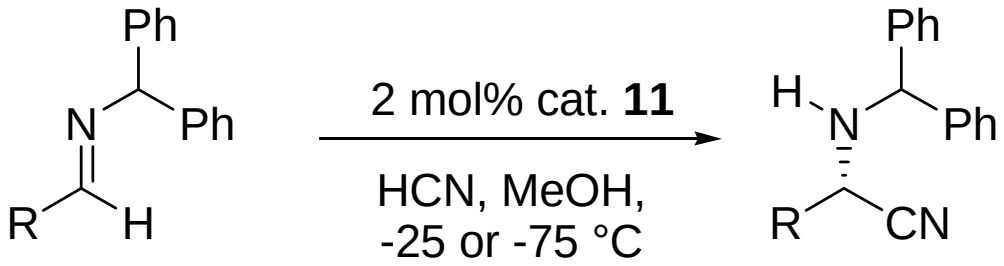


(*R*)-**14** (*R*)-**13a** (*R*)-**15**

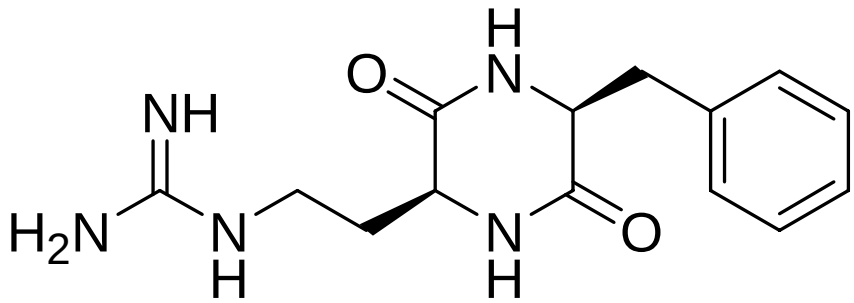
(*R*)-**16**

9.) Inoue, S.; Mori, A.; Tanaka, *J. Org. Chem.* **1990**, 55, 181.

Lipton Type Strecker Reaction



17 **18**



11

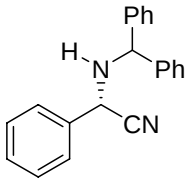
10.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *J. Am. Chem. Soc.* **1996**, 118, 4910.

11.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *Amino Acids* **1996**, 11, 259.

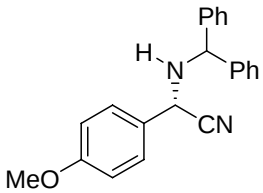
Organocatalytic Hydrocyanation of Imines

Substrate range:

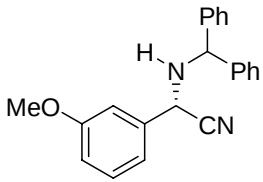
Aromatic products:



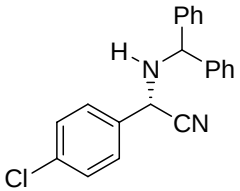
(*S*)-**18a**
97% yield
>99% ee
8.0 h



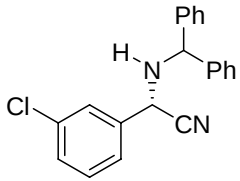
(*S*)-**18b**
90% yield
96% ee
10.0 h



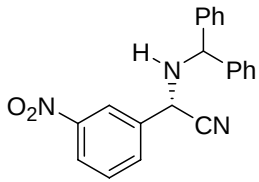
(*S*)-**18c**
82% yield
80% ee
8.0 h



(*S*)-**18d**
94% yield
>99% ee
10.0 h

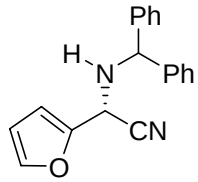


(*S*)-**18e**
80% yield
>99% ee
8.0 h

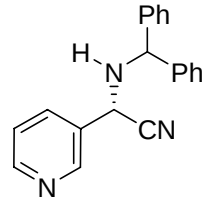


(*S*)-**18f**
71% yield
<10% ee
10.0 h

Hetoaromatic products:

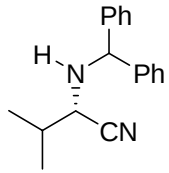


(*S*)-**18g**
94% yield
32% ee
8.0 h

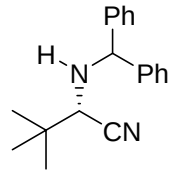


(*S*)-**18h**
86% yield
<10% ee
0.5 h

Aliphatic products:



(*S*)-**18i**
81% yield
<10% ee
5.0 h

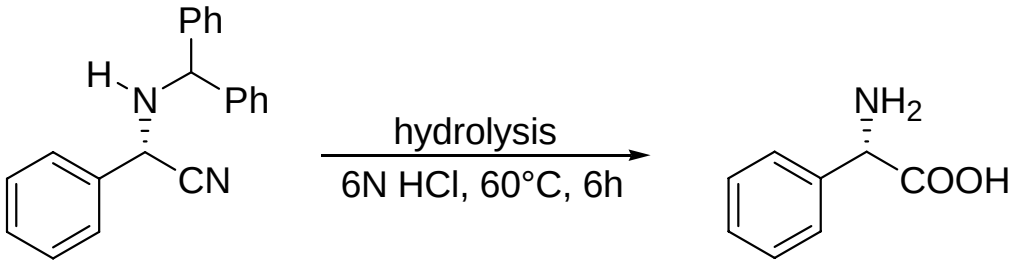


(*S*)-**18j**
80% yield
17% ee
5.0 h

10.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *J. Am. Chem. Soc.* **1996**, 118, 4910.

11.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *Amino Acids* **1996**, 11, 259.

Synthesis of (*S*)-Amino Acids



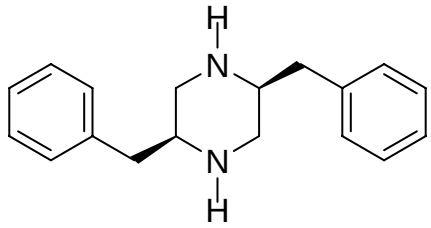
18a
>99% ee

(*S*)-19
92% overall yield
(3 steps from benzaldehyde)
>99% ee

10.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *J. Am. Chem. Soc.* **1996**, 118, 4910.

11.) Lipton, M.; Namdev, N. D.; Gigstad, K. M.; Iyer, M. S., *Amino Acids* **1996**, 11, 259.

Chiral Piperazines as Efficient Catalysts for the Asymmetric Michael Addition of Aldehydes to Nitroalkanes



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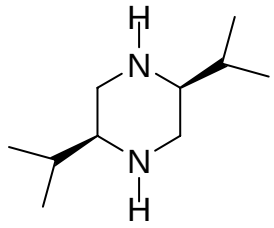

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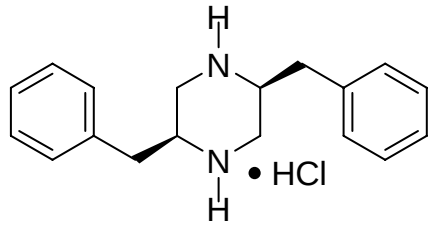

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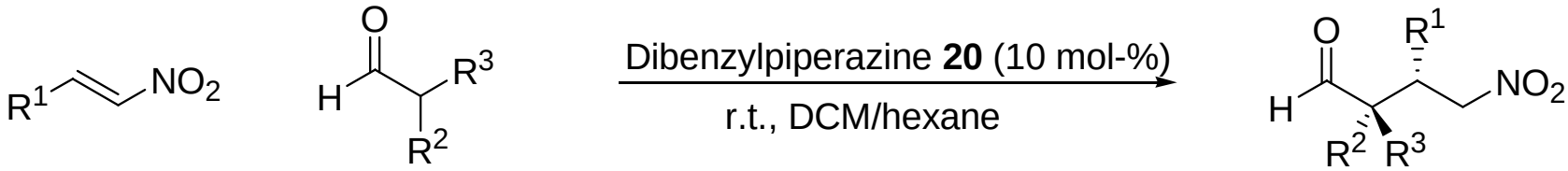
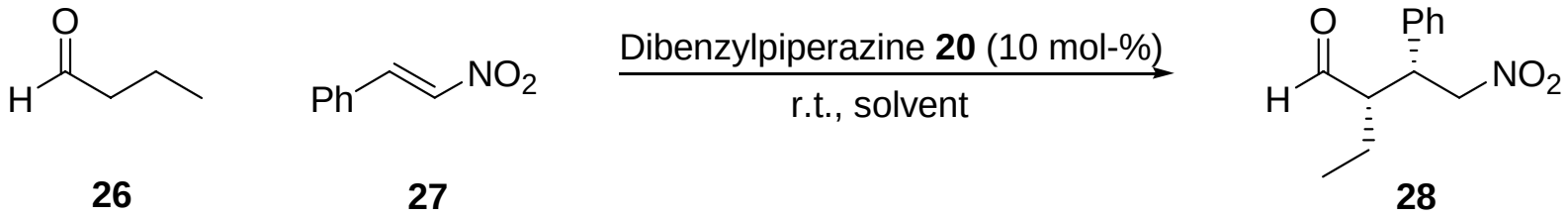


23 **24** **25**

12.) Barros, M. T.; Phillips, A. M. F., *Eur. J. Org. Chem.* **2007**, 1, 178.

Solvent Effects



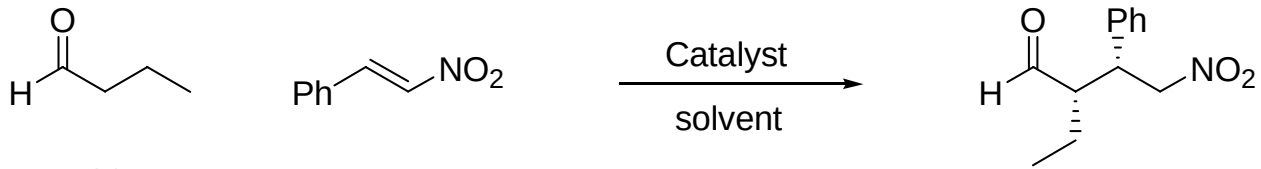
26 **27** **28**

Entry	Solvent	Time [h]	Conversion[a] [%]	Yield[b] [%]	*dr* (*syn:anti*)[c] [%]	*ee* (*syn*)[d] [%]
1	DCM/wet hexane (1:1)	17	100	54	91:9	72
2	DCM/wet hexane (1:1)	5	100	52	84:16	76
3	DCM	5	100	51	73:27	53
4	THF	5	100	80	66:34	69
5	DMF	5	64	32	62:38	59
6	DCM/hexane (1:2)	5	100	63	88:12	79
7	*i*PrOH	5	100	54	94:6	80
8	$CHCl_3$	5.5	100	90	88:12	76
9	DME	5	100	40	76:24	72

[a] Determined by ^{1}H NMR spectroscopy. [b] Yield of isolated product after chromatography. [c] Determined by ^{1}H NMR spectroscopy of unpurified products. [d] Determined by HPLC analysis on a chiral column (Chiralpak AD-H).

12.) Barros, M. T.; Phillips, A. M. F., *Eur. J. Org. Chem.* **2007**, 1, 178.

Effect of Catalyst Structure, Catalyst Loading and Temperature



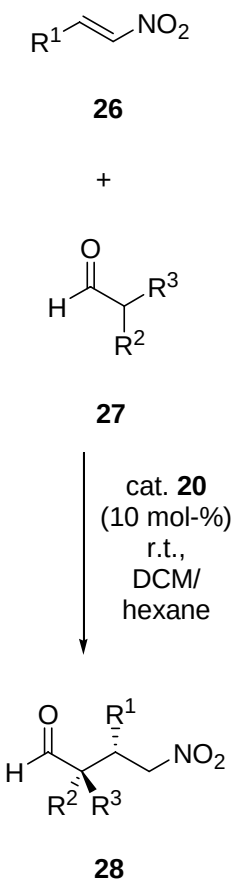
26 **27** **28**

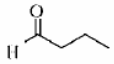
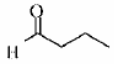
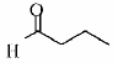
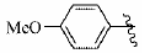
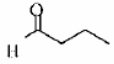
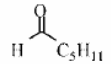
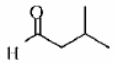
Entry	Catalyst	Catalyst load [mol-%]	Conditions (Solvent,[a] temp., time)	Conversion[b] [%]	Yield[c] [%]	*dr* [d] (*syn:anti*) [%]	*ee*[e] [%]
1	20	5	DCM, room temp., 5 h	44	14	83:17	59
2	20	10	DCM, room temp., 5 h	100	51	73:27	53
3	20	10	DCM, 0 °C, 17 h	67	56	76:24	75
4	20	5	DCM/hexane, room temp., 17 h	100	72	94:6	77
5	20	10	DCM/hexane, room temp., 5 h	100	63	88:12	79
6	20	10	DCM/hexane, 0 °C, 48 h	100	63	97:3	84
7	20	20	DCM/hexane, 0 °C, 48 h	100	80	87:13	79
8[f]	21	10	DCM/hexane, 0 °C, 48 h	100	76	87:13	41
9	22	10	DCM/hexane, room temp., 5 h	76	43	81:19	78
10	22	10	DCM/hexane, room temp., 7 h	90	55	92:8	78
11	22	10	DCM/hexane, room temp., 10 h	100	98	90:10	77
12	22	10	DCM/hexane, 0 °C, 48 h	100	ND[g]	87:13	53
13	22	10	*i*PrOH, room temp., 10 h	100	71	92:8	82

[a] DCM/hexane refers to a 1:2 solution of the two solvents. [b] Conversion determined by ^{1}H NMR spectroscopy. [c] Yield of isolated product after chromatography. [d] Determined by ^{1}H NMR spectroscopy of unpurified products. [e] Determined by HPLC analysis on a chiral column (Chiralpak AD-H). [f] Propionaldehyde was used instead of butyraldehyde. [g] ND = Not determined.

12.) Barros, M. T.; Phillips, A. M. F., *Eur. J. Org. Chem.* **2007**, 1, 178.

Catalysis with Different Substrates

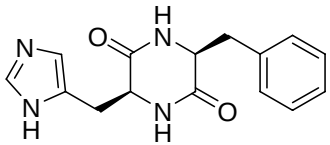


Entry	Aldehyde	R^1	T [°C]	Time	Yield [%][a]	*dr* (*syn*:*anti*)[b]	*ee* (*syn*) [%][c]	Product
1			0	17 h	78	97:3	81	**3b**
2			0	41 h	52	94:6	69[d]	**3c**
3			0	40 h	68	94:6	74[d]	**3d**
4			0	48 h	63	97:3	84	**3a**
5			0	42 h	78	95:5	77[d]	**3e**
6			0	44 h	57	97:3	84	**3f**
7			rt	68 h	67	80:20	85	**3g**
8			0	5 d	ND[e]	96:4	75	**3h**
9			0	6 d	66	89:11	68	**3i**
10			rt	11 d	36[f] + SM	–	75	**3j**

[a] Yield of isolated product after chromatography. [b] Calculated from the ^{1}H NMR spectrum of the crude product. [c] Determined by HPLC analysis (Chiralpak AD-H column). [d] Determined by ^{1}H NMR *ee* assay after reaction with L-Val-OMe.[17] [e] ND = Not determined. [f] SM = starting material; only 60% conversion.

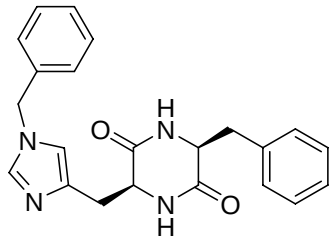
12.) Barros, M. T.; Phillips, A. M. F., *Eur. J. Org. Chem.* **2007**, 1, 178.

DKP Catalysts For Acylation Reactions



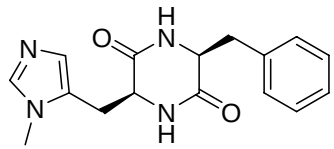
8

cyclo[(S)-phenylalanine-(S)-histidine]



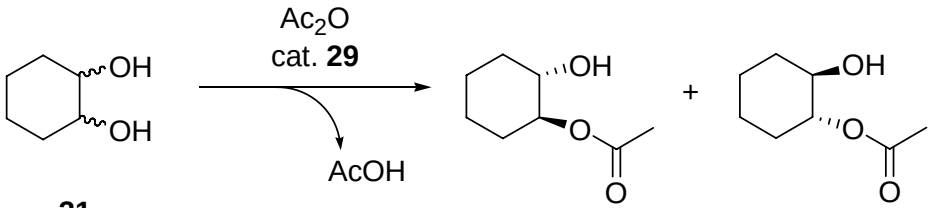
29

cyclo[(S)-phenylalanine-(S)-(τ-bzl)-histidine]



30

cyclo[(S)-phenylalanine-(S)-(π-Me)-histidine]



31

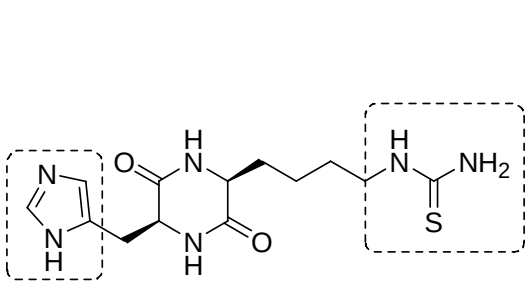
(*trans*-racemate)

32

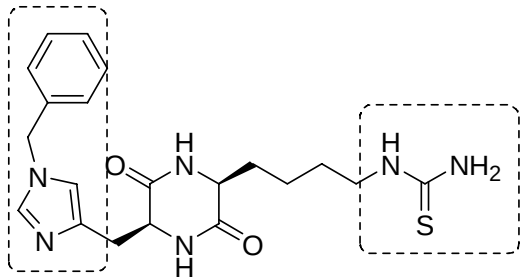
0,375 mmol *trans*-cyclohexane-1,2-diol
0,5 equiv. acetic anhydride
1 mol% cyclopeptide catalyst
1 mL $CHCl_3$ + 2,25 mL toluene
concentration of catalyst: c = 0,0012 mol/L
room temperature (20 °C)

Entry	*Reaction time [h]*	*Conversion in %*	*e.r.*
1	16	4,2	53,3 : 46,7
2	54,5	15,5	52,5 : 47,5
3	81,5	20,6	52,3 : 47,7
4	102,5	29,5	52,0 : 48,0

Bifunctional DKP Catalysts for Baylis-Hillman Reactions



34



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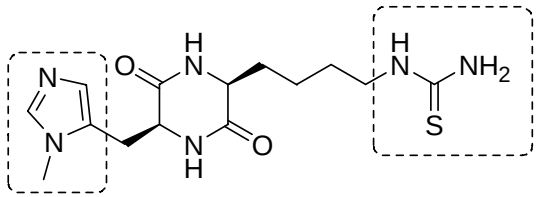
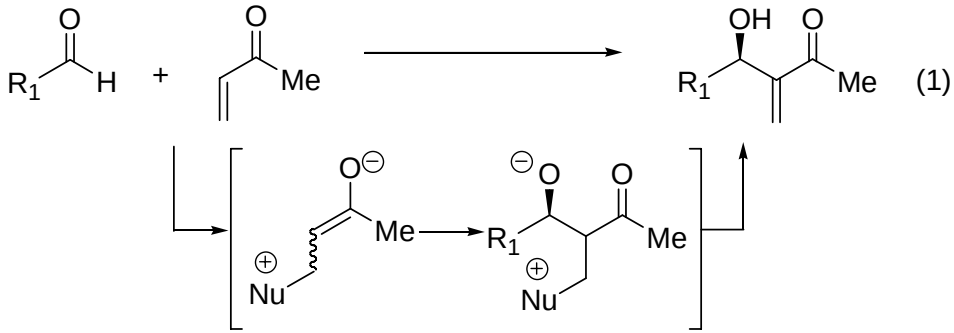


36

Bifunctional [His-Lys]-DKP derivatives



(1)