Total Syntheses of Mannopeptimycins

2022.11.19. Literature Seminar

B4 Takahiro Migita

Contents

1. Introduction

2. Total synthesis of Mannopeptimycin *α* and *β* (by Chen's Group)

3. Total synthesis of Mannopeptimycin *β* (by Li's Group)

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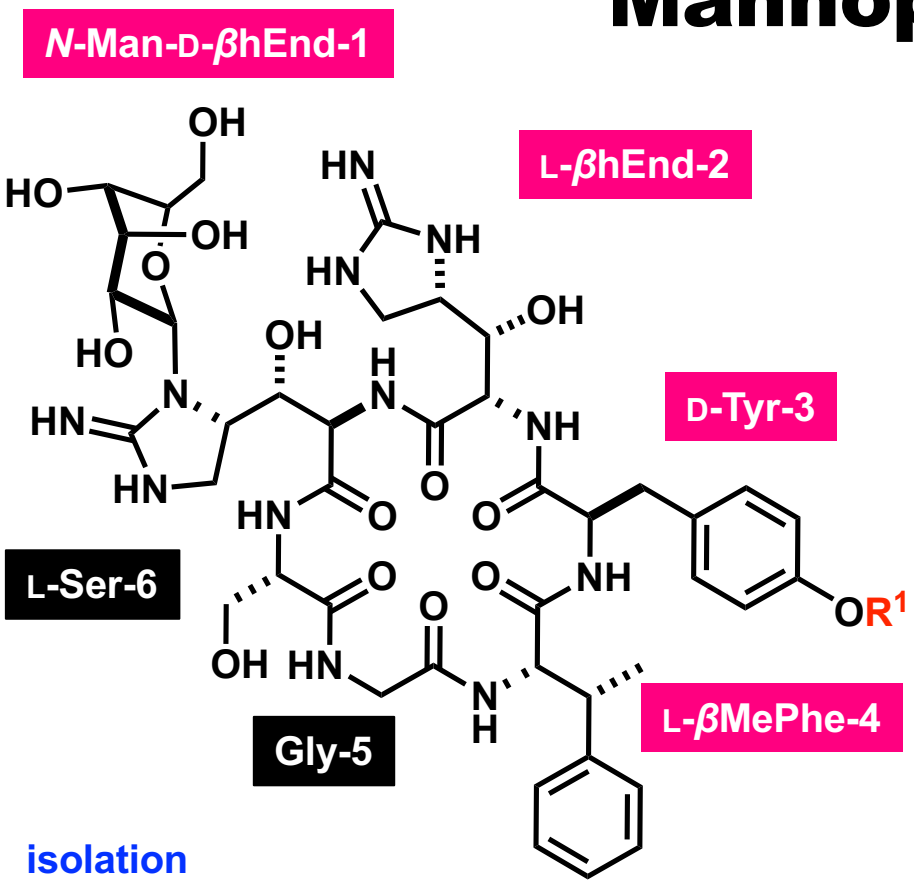
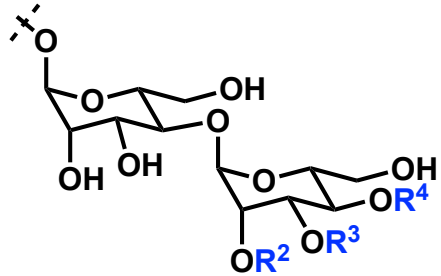
3. Total synthesis of Mannopeptimycin *β* (by Li's Group)

Mannopeptimycins

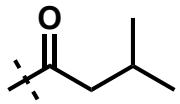


mannopeptimycin β: R^1 = H
mannopeptimycin α, γ, δ, ε:

R^1 =



i-valeryl =



	R^2	R^3	R^4
mannopeptimycin α	H	H	H
mannopeptimycin γ	*i*-valeryl	H	H
mannopeptimycin δ	H	*i*-valeryl	H
mannopeptimycin ε	H	H	*i*-valeryl

isolation
from *Streptomyces hygroscopicus* LL- AC98 (isolated in 1950s[1)], elucidated in 2002[2)])

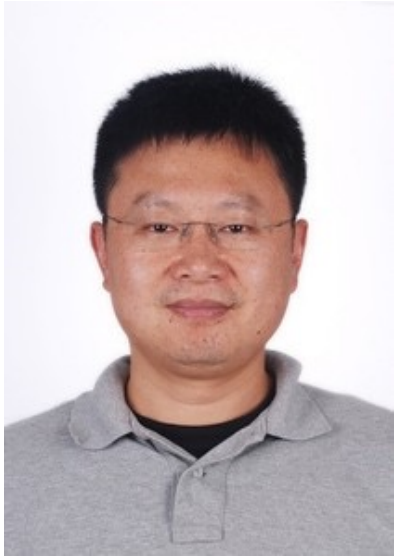
structural features
cyclic glycopeptide
4 nonproteinogenic amino acids
(including β-hydroxyenduracidine (βhEnd))

total syntheses
Doi (2014, aglycon)[3)], Chen (2016, α and β)[4)], Li (2021, β)[5)]

bioactivity[6)7)8)]
antibiotic activity against Gram-positive pathogens
(including drug-resistant pathogens)
inhibit peptidoglycan synthesis
by binding to lipid II in the unique manner

1) De Voe, S. E.; Kunstmann, M. P. U.S. Patent 3495004, 1970. 2) He, H.; Williamson, R. T.; Shen, B.; Graziani, E. I.; Yang, H. Y.; Sakya, S. M.; Petersen, P. J.; Carter, G. T. *J. Am. Chem. Soc.* **2002**, *124*, 9729. 3) Fuse, S.; Koinuma, H.; Kimbara, A.; Izumikawa, M.; Mifune, Y.; He, H.; Shin-ya, K.; Takahashi, T.; Doi, T. *J. Am. Chem. Soc.* **2014**, *136*, 12011. 4) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926. 5) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784. 6) Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Janso, J. E.; Luckman, S. W.; Lenoy, E. B.; Bradford, P. A.; Testa, R. T.; Greenstein, M. *Antimicrob. Agents Chemother.* **2003**, *47*, 62. 7) Ruzin, A.; Singh, G.; Severin, A.; Yang, Y.; Dushin, R. G.; Alan, G.; Sutherland; Minnick, A.; Greenstein, M.; May, M. K.; Shlaes, D. M.; Bradford, P. A. *Antimicrob. Agents Chemother.* **2004**, *48*, 728. 8) Breukink, E.; de Kruijff, B. *Nat. Rev. Drug Discovery*. **2006**, *5*, 321.

Introduction of Prof. Chen and Prof. Li



Prof. Gong Chen

1998 B.S. @ Nanjing University
2004 Ph.D. @ Columbia University (Prof. Dalibor Sames)
2005- Postdoctoral fellow @ Memorial Sloan-Kettering Cancer Center (Prof. Samuel Danishefsky)
2008- Assistant Professor @ The Pennsylvania State University
2014- Associate Professor @ The Pennsylvania State University
2015- Professor @ Nankai University
2018-2021 Adjunct professor @ The Pennsylvania State University

Research topics: metal catalysis, radical chemistry, peptide, carbohydrate

Prof. Xuechen Li

1999 B.S. @ Nankai University
2003 M.S. @ University of Alberta (Prof. Ole Hindsgaul)
2007 Ph.D. @ Harvard University (Prof. Dan Kahne)
2007- Postdoctoral fellow @ Memorial Sloan-Kettering Cancer Center (Prof. Samuel Danishefsky)
2009- Assistant Professor @ University of Hong Kong
2014- Associate Professor @ University of Hong Kong
2018- Professor @ University of Hong Kong

Research topics: method developing for bio-macromolecules synthesis, medicinal chemistry of natural products, drug development, function definition of macromolecules and their PTMs

1) http://www.gongchenlab.com/col.jsp?id=103
2) https://chemistry.hku.hk/staff/xcli/XCLiGroup/people.html

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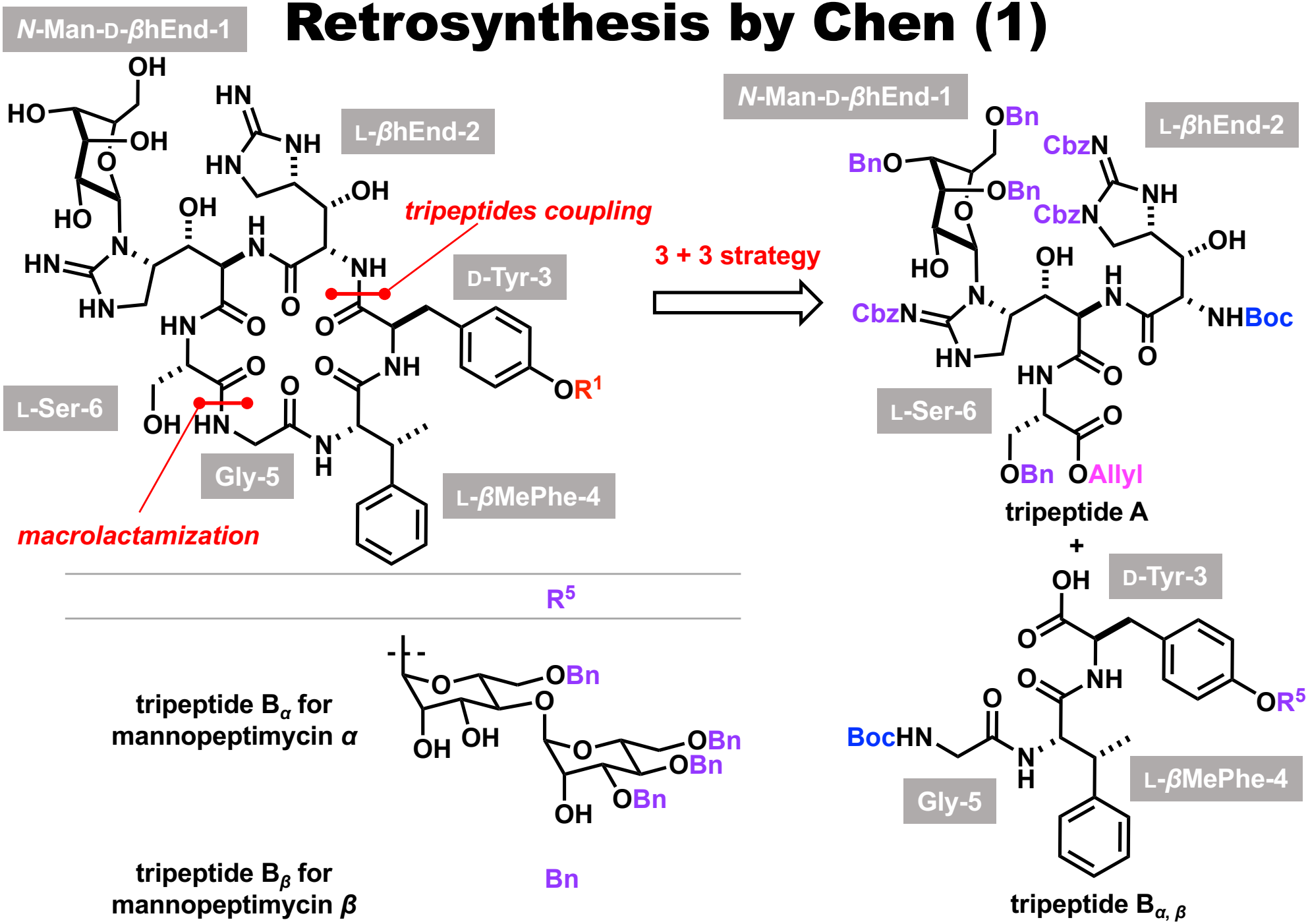
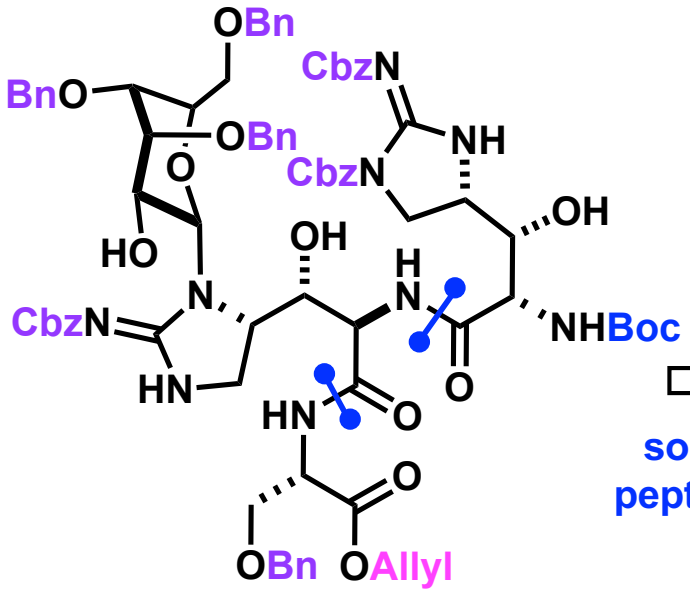
Retrosynthesis by Chen (1)



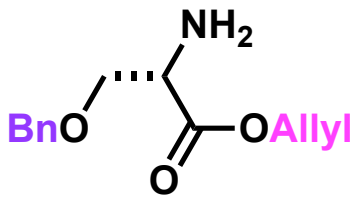
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

Retrosynthesis by Chen (2)

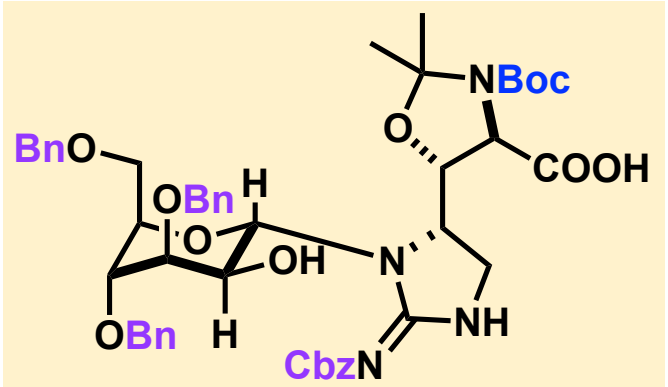


tripeptide A

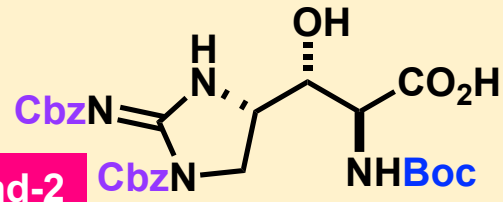
solution-phase
peptide elongation



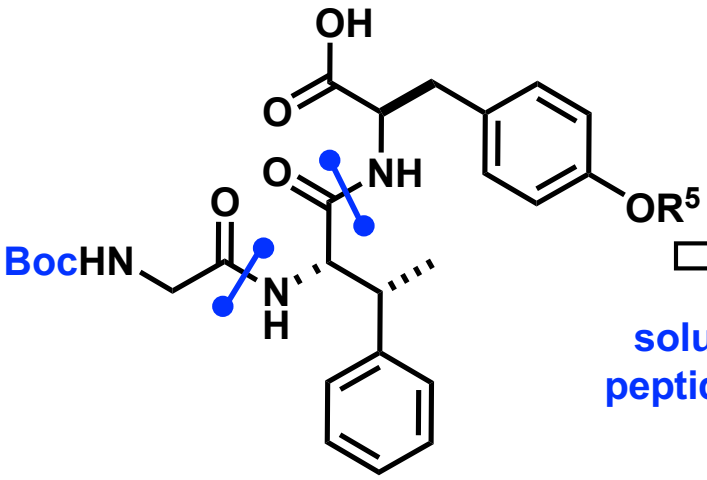
L-Ser-6



N-Man-D-*β*hEnd-1

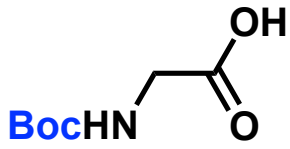


L-*β*hEnd-2

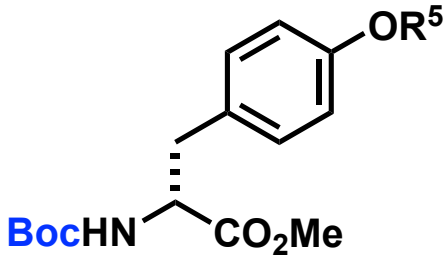


tripeptide B

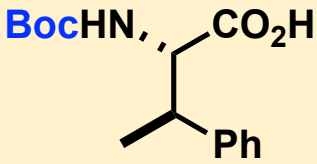
solution-phase
peptide elongation



Gly-5



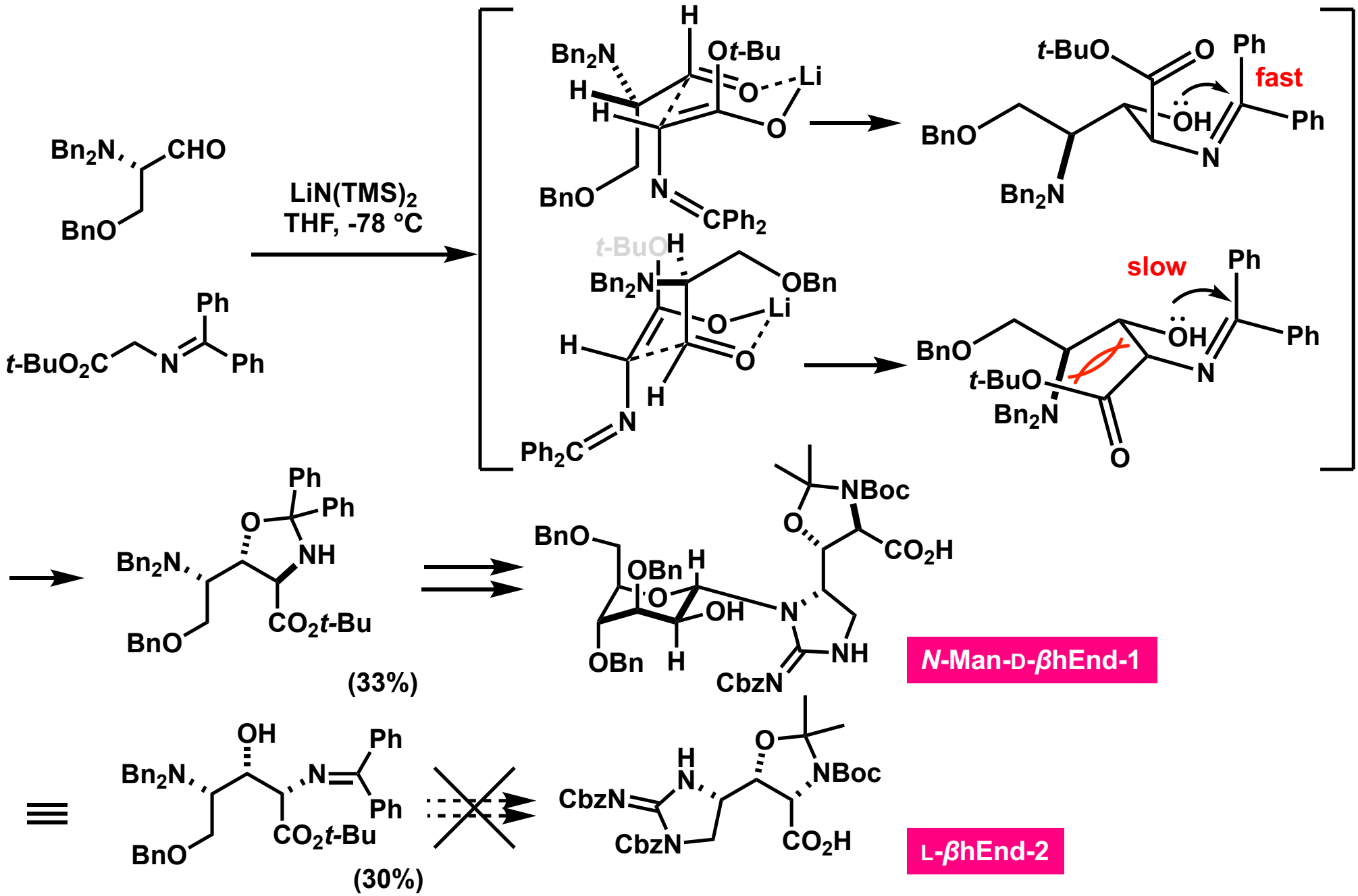
D-Tyr-3



L-*β*MePhe-4

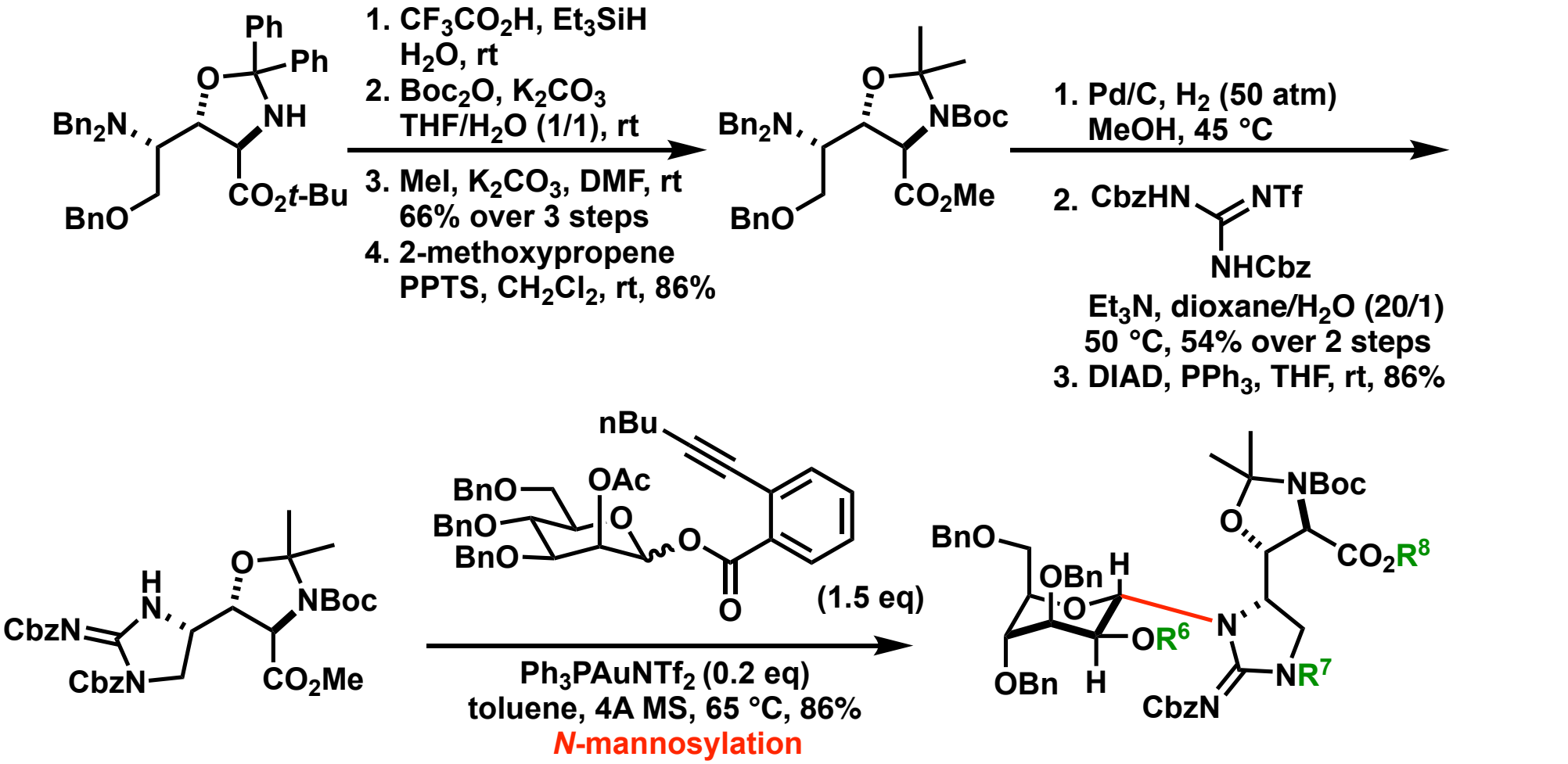
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

Synthesis of βhEnd via Aldol Reaction



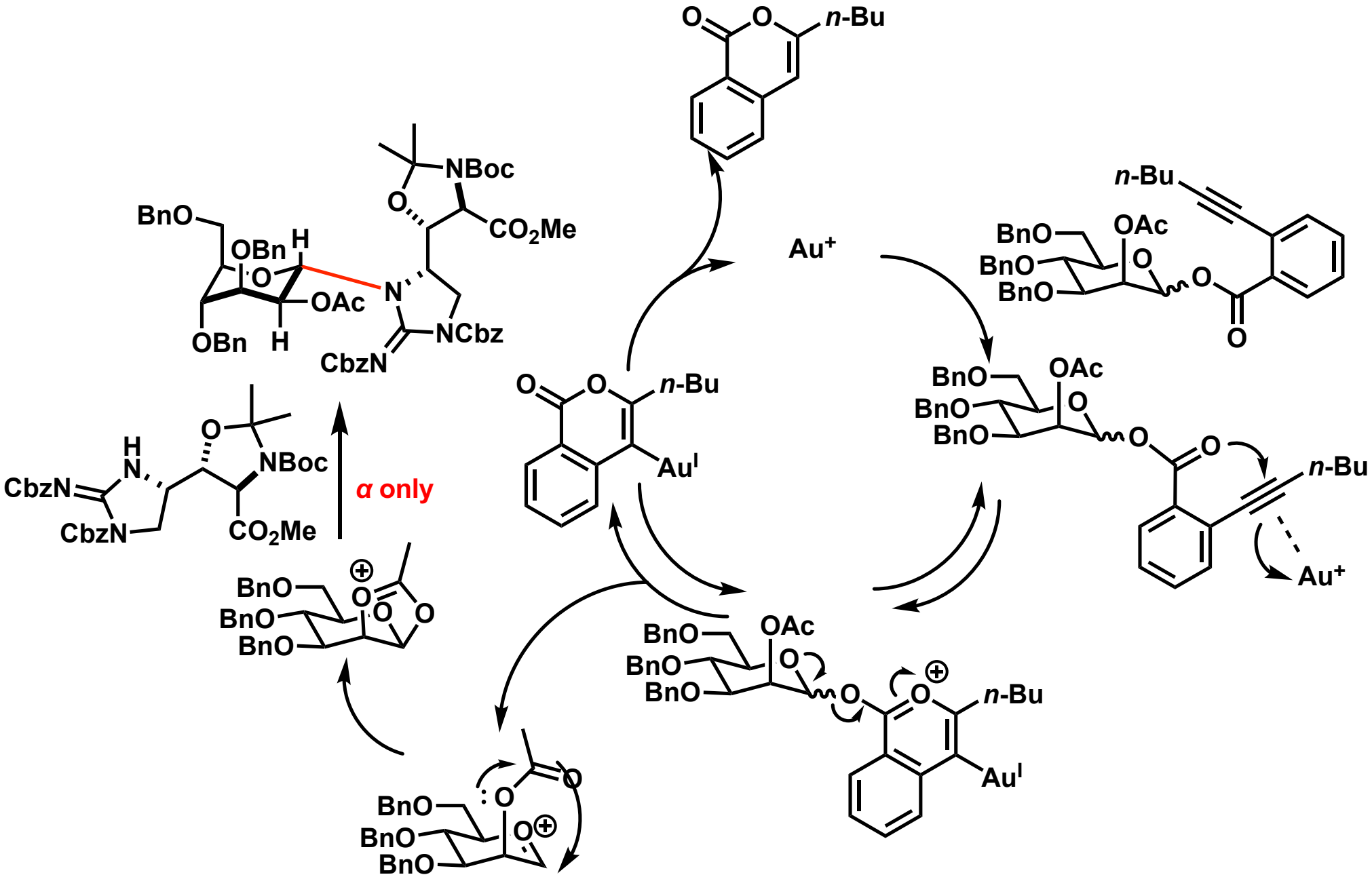
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.
2) Fuse, S.; Koinuma, H.; Kimbara, A.; Izumikawa, M.; Mifune, Y.; He, H.; Shin-ya, K.; Takahashi, T.; Doi, T. *J. Am. Chem. Soc.* **2014**, *136*, 12011.

Synthesis of *N*-Man-D-βhEnd-1



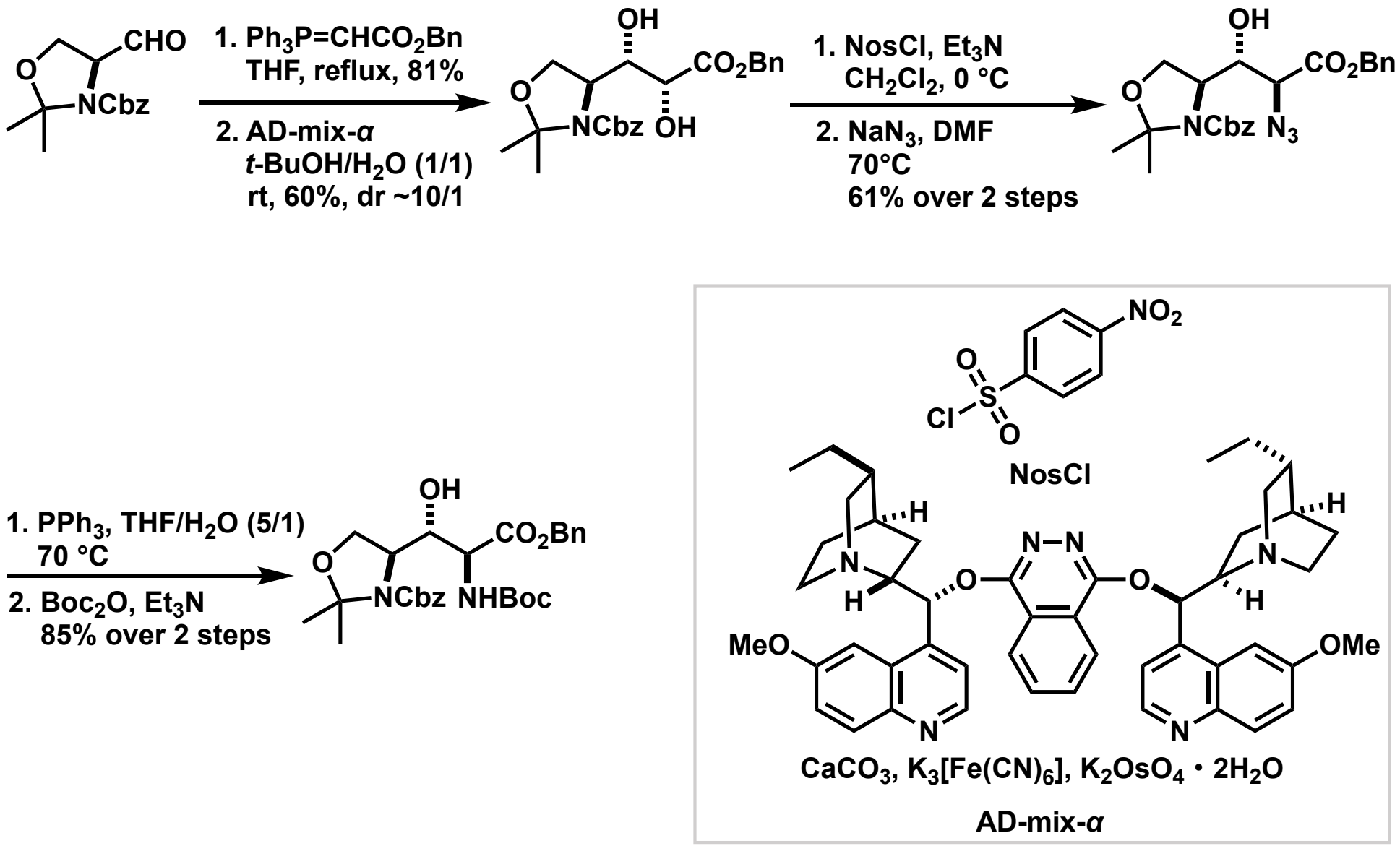
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

Mechanism of Au-Catalyzed *N*-Mannosylation



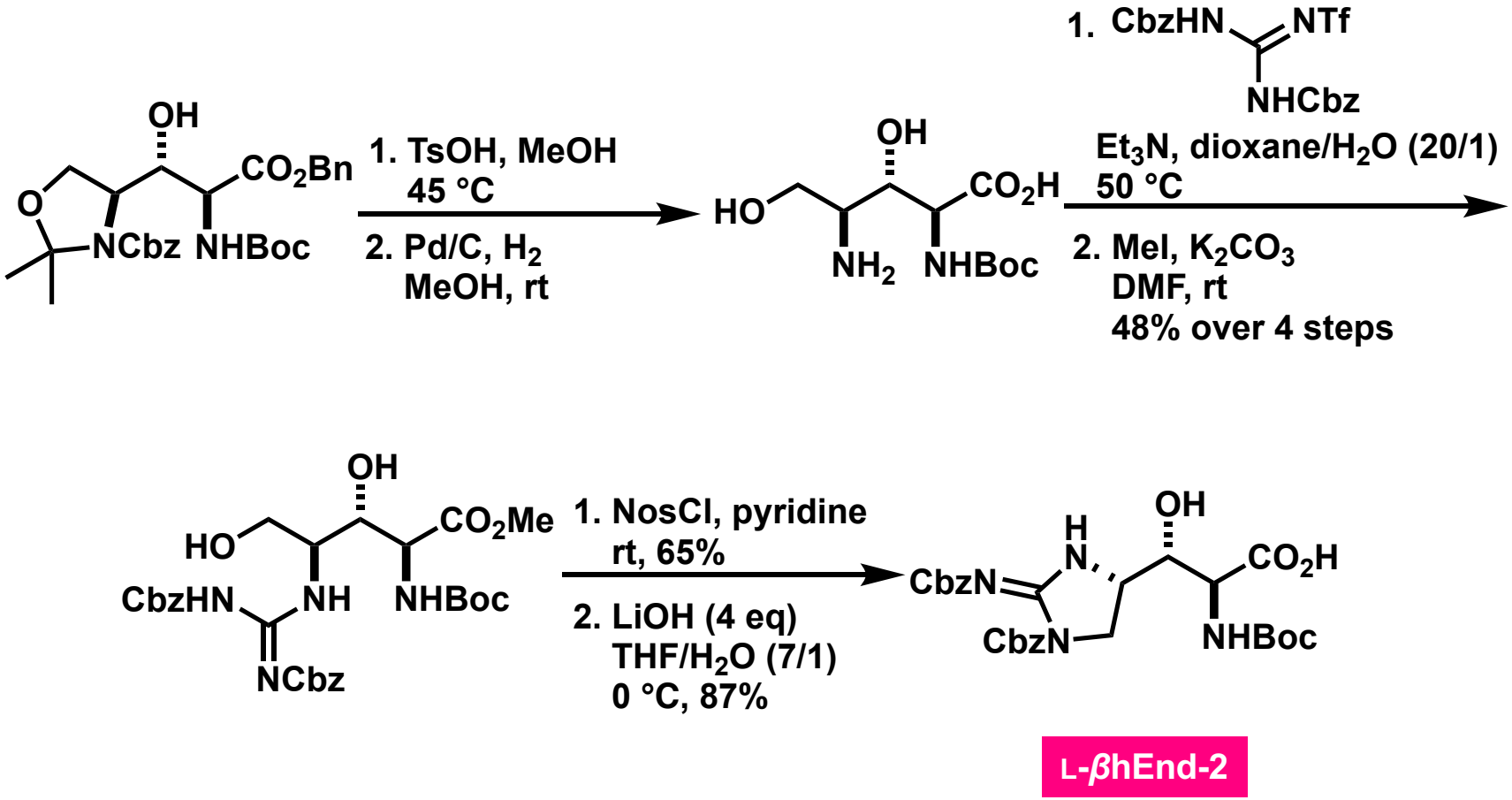
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.
2) Nie, S.; Li, W.; Yu, B. *J. Am. Chem. Soc.* **2014**, *136*, 4157.

Synthesis of L-βhEnd-2 (1)



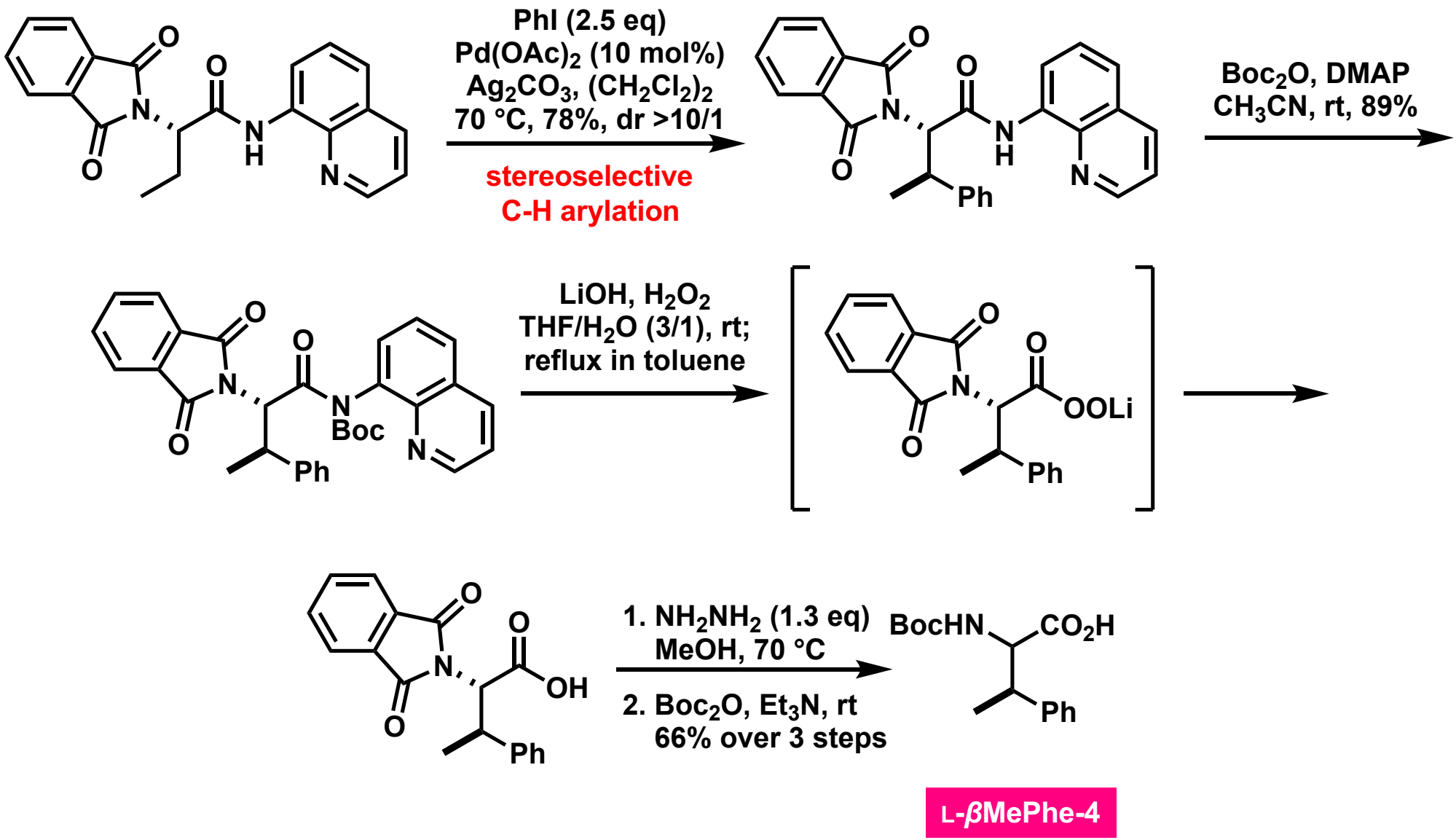
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

Synthesis of L-βhEnd-2 (2)



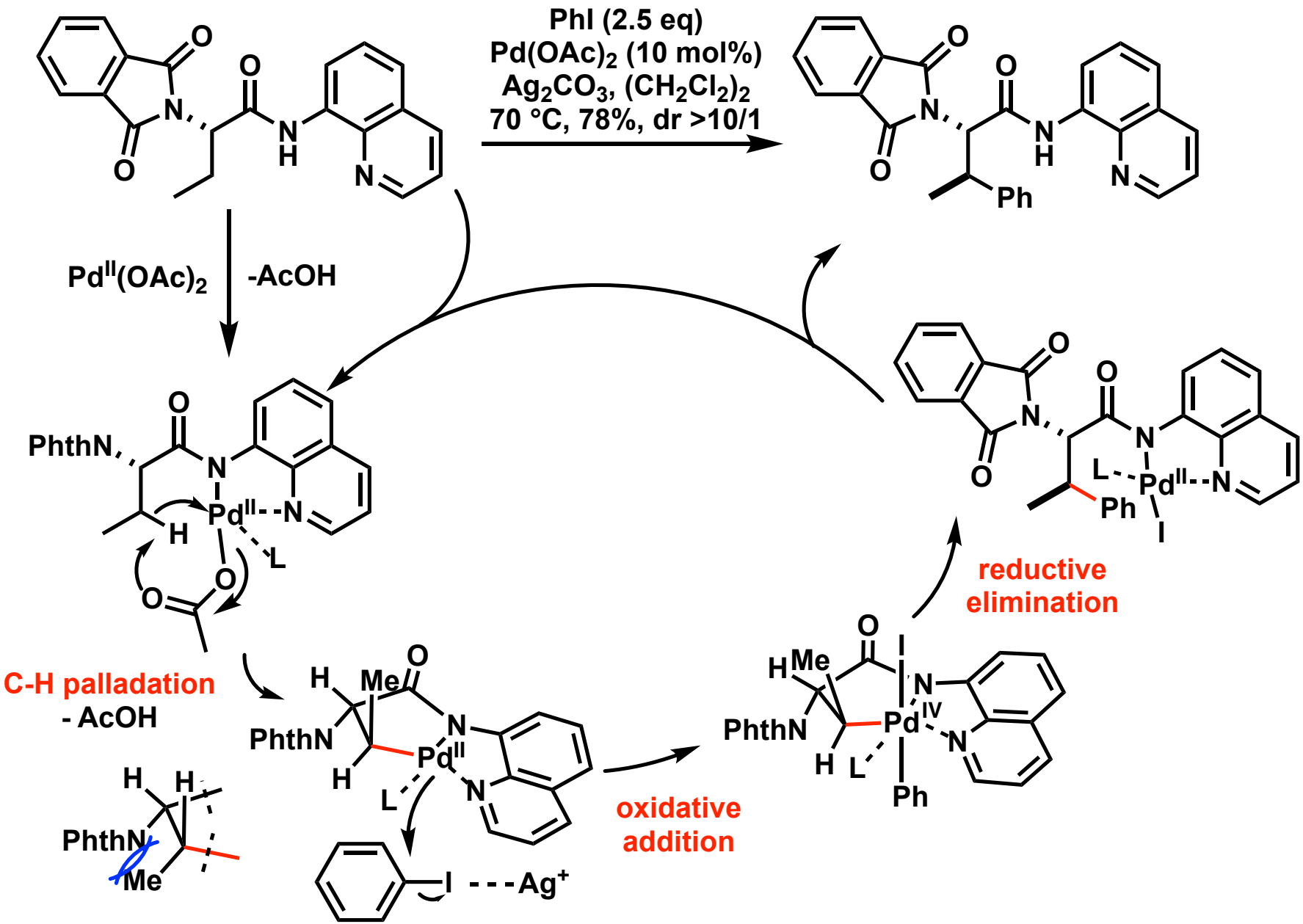
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

Synthesis of L-βMePhe-4



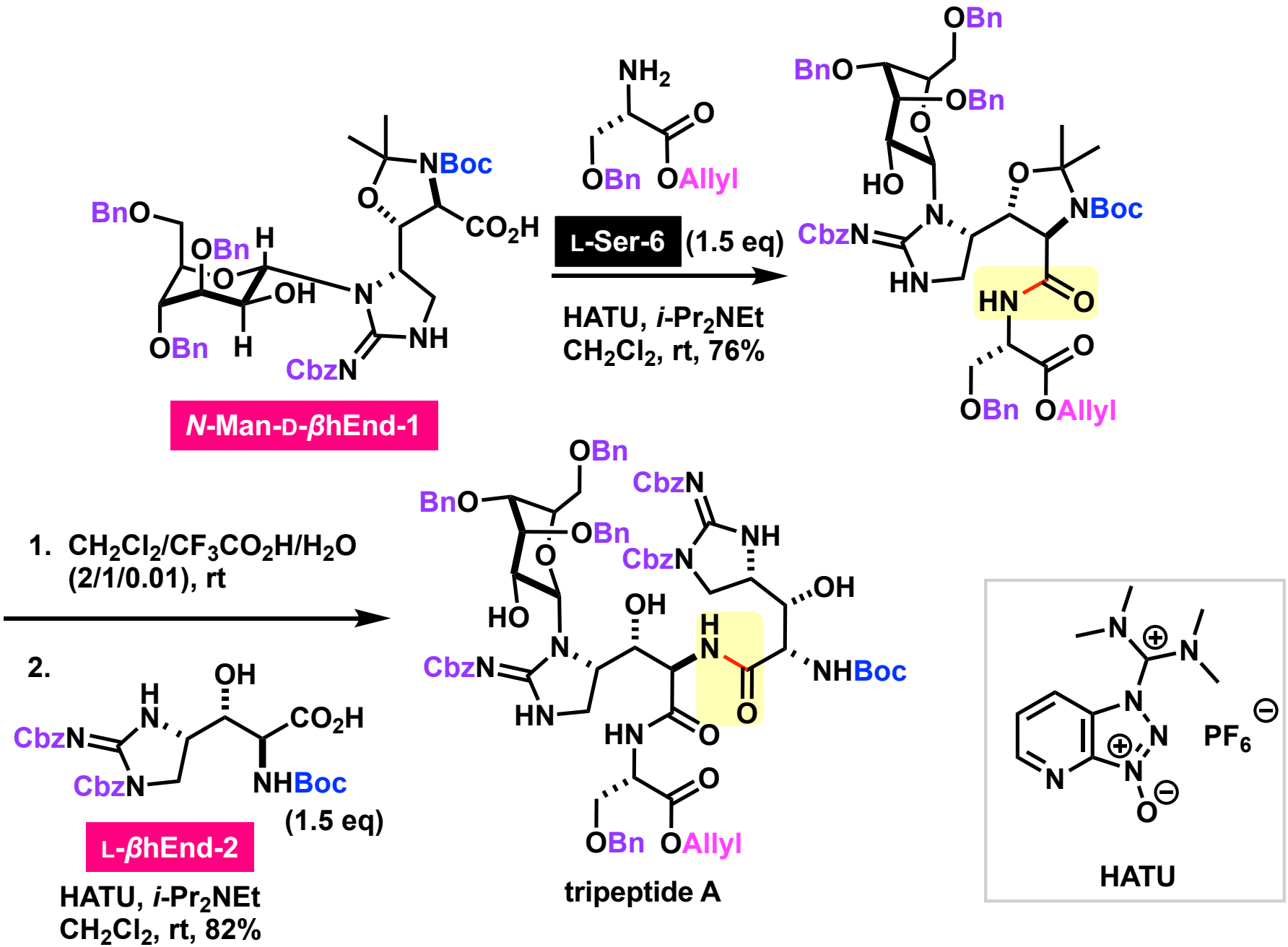
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.
2) Beutner, G. L., Cohen, B. M., DelMonte, A. J., Dixon, D. D., Fraunhoffer, K. J., Glace, A. W., Lo, E., Stevens, J. M., Vanyo, D., Wilbert, C. *Org. Process Res. Dev.* **2019**, *23*, 1378.

Pd-Catalyzed C-H Arylation



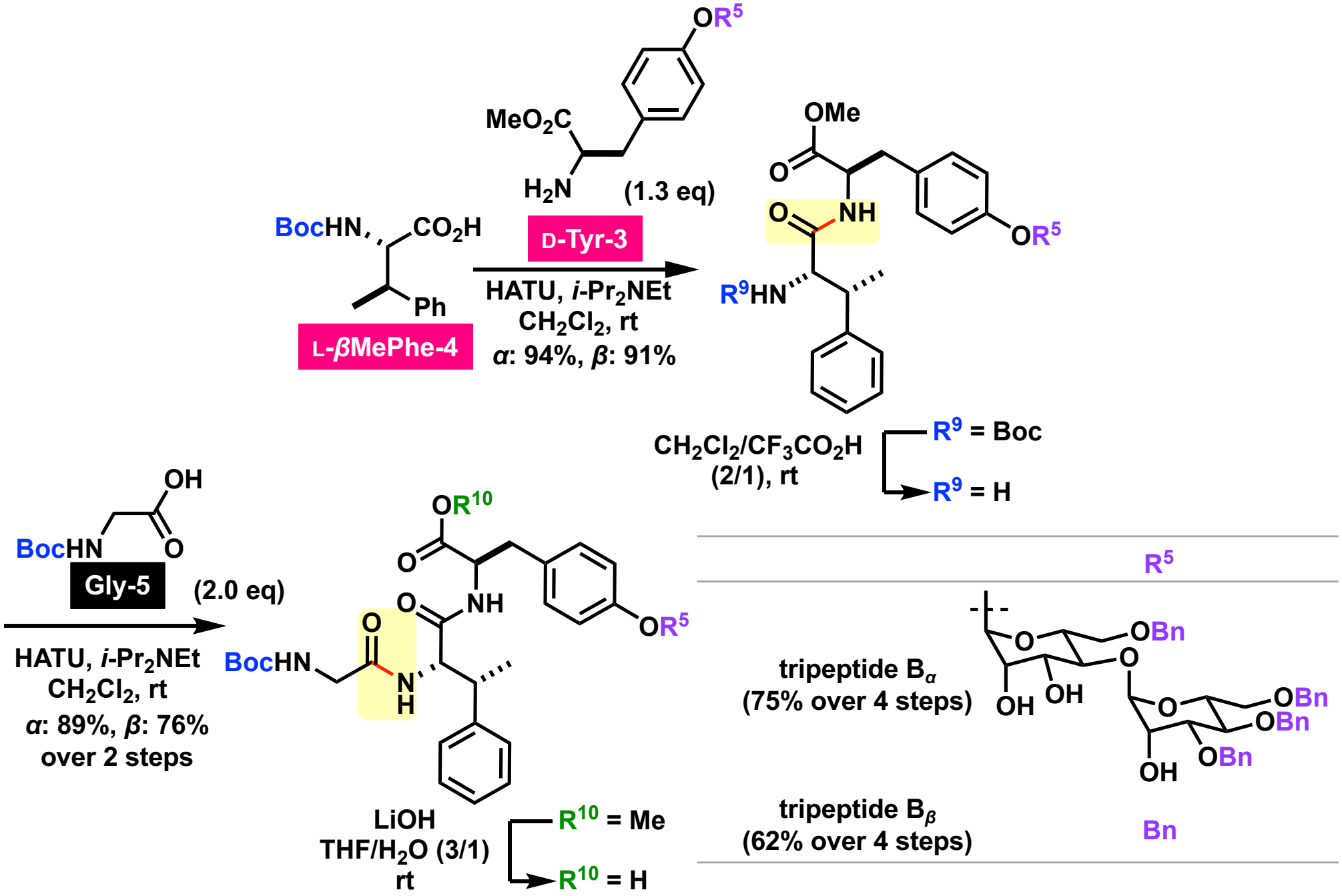
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926. 2) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. 3) Daugulis, O., Roane, J., & Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053.

Synthesis of Tripeptide A



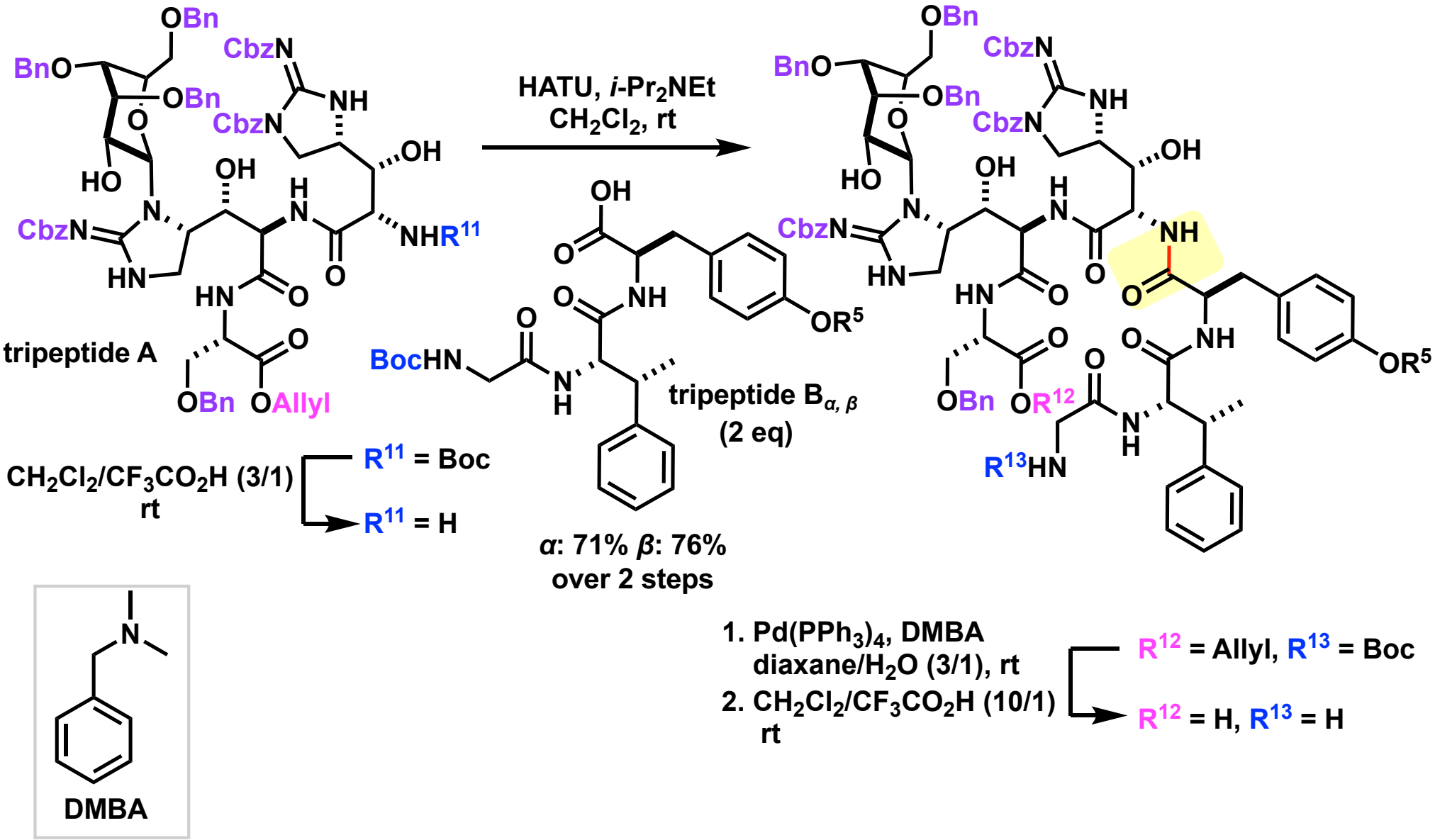
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

Synthesis of Tripeptide B



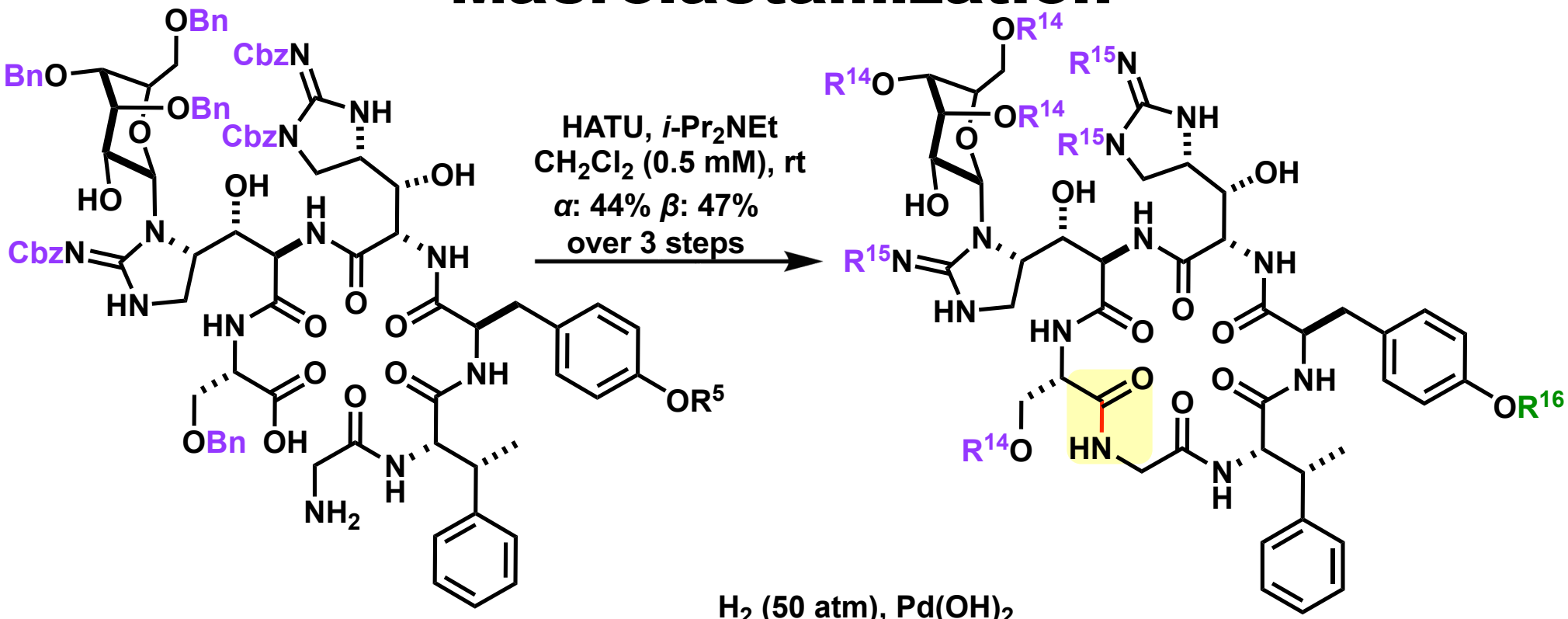
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

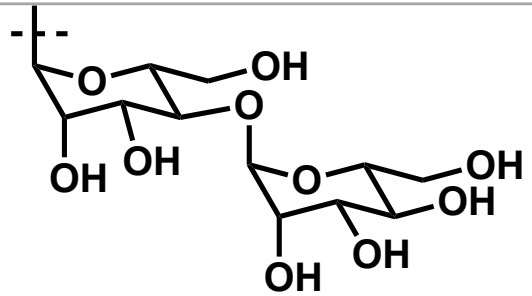
Tripeptides Coupling



1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

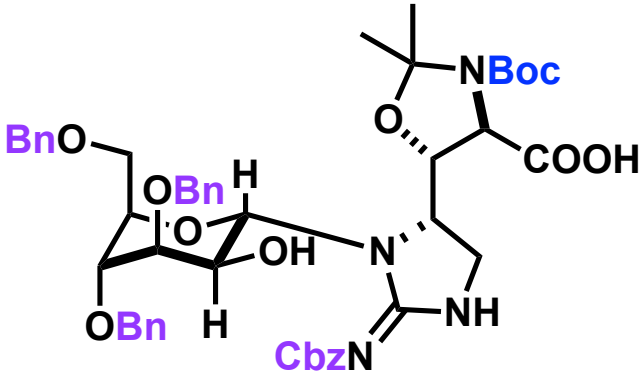
Macrolactamization



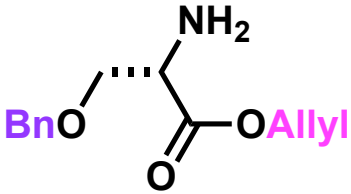
	R^1	overall yield (13 steps)
mannopeptimycin α		10%
mannopeptimycin β	H	8%

1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

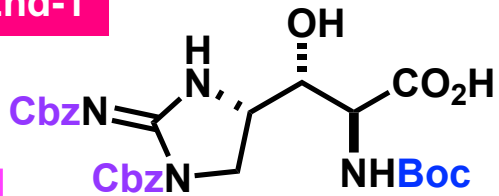
Short Summary



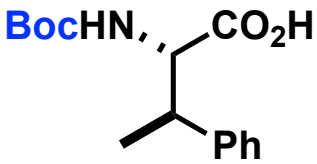
N-Man-D-βhEnd-1



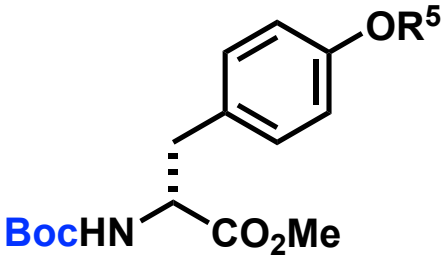
L-Ser-6



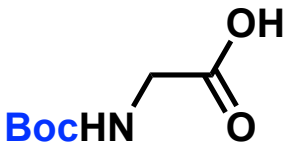
L-βhEnd-2



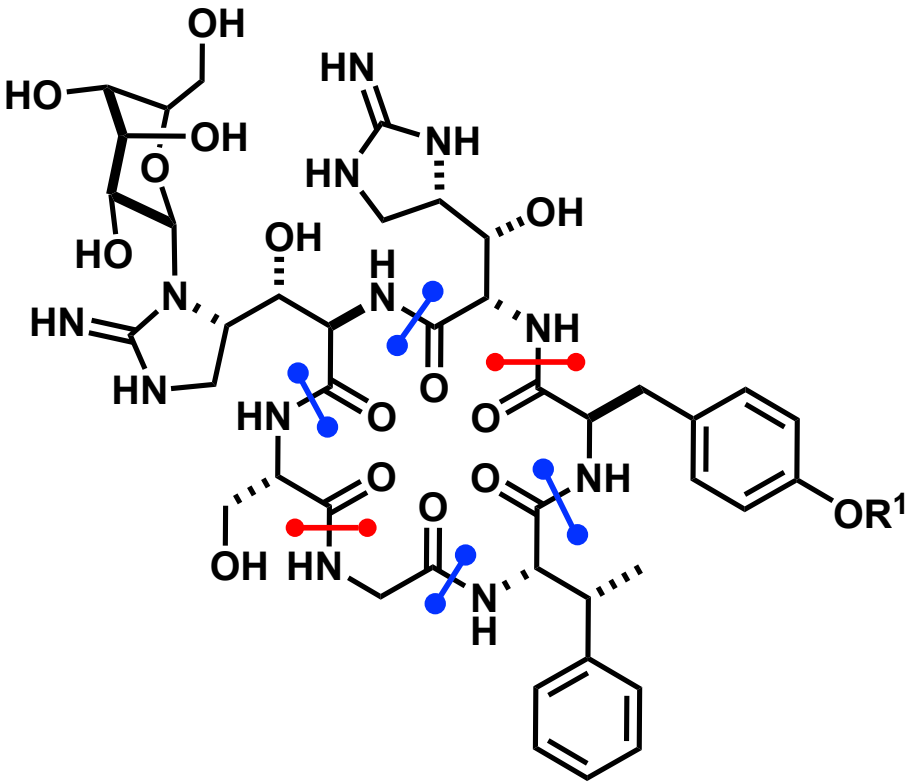
L-βMePhe-4



D-Tyr-3



Gly-5



- solution-phase peptide elongation
- 3+3 strategy
  (tripeptides coupling and macrolactamization)

1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

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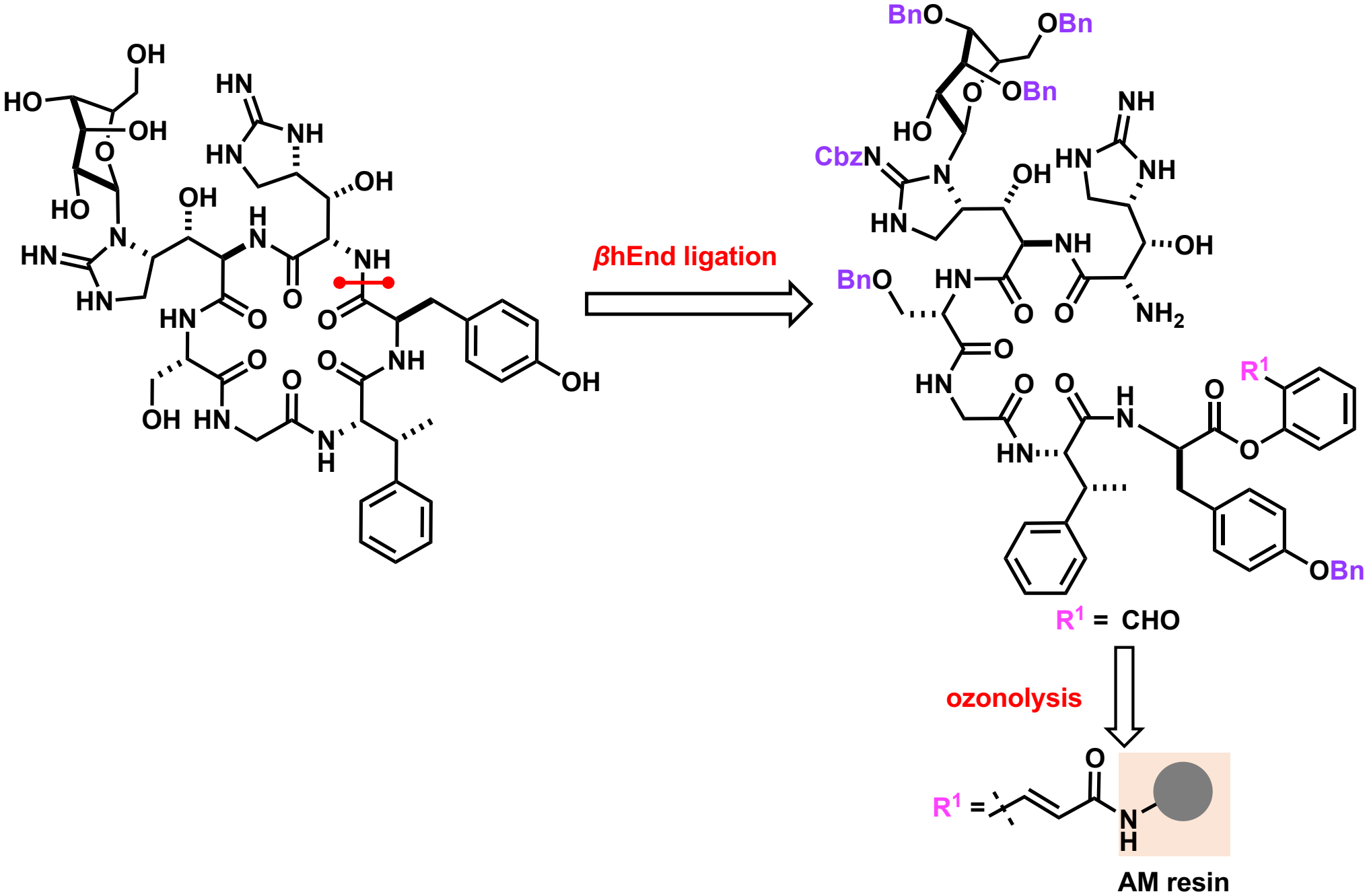
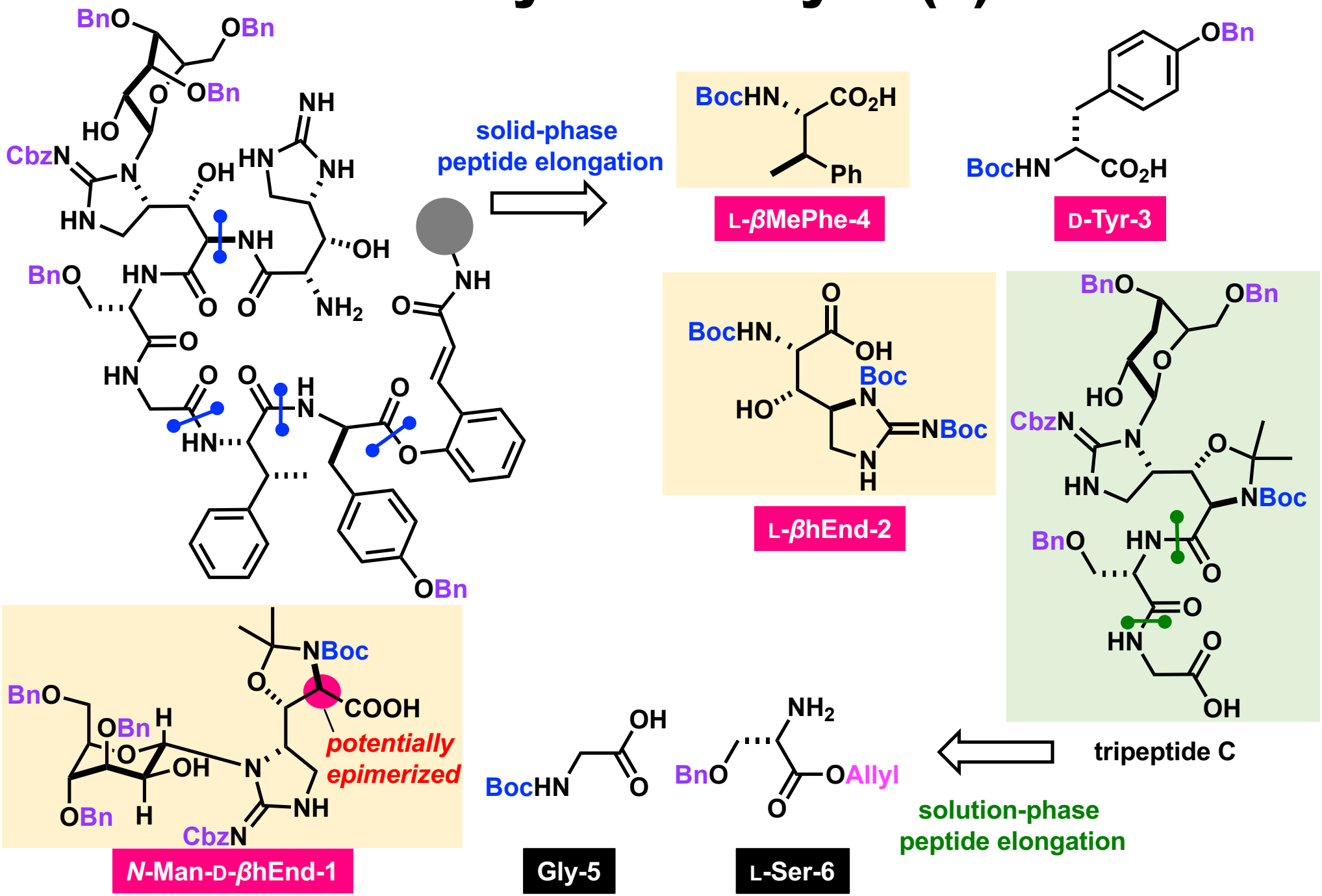
3. Total synthesis of Mannopeptimycin *β* (by Li's Group)

Retrosynthesis by Li (1)



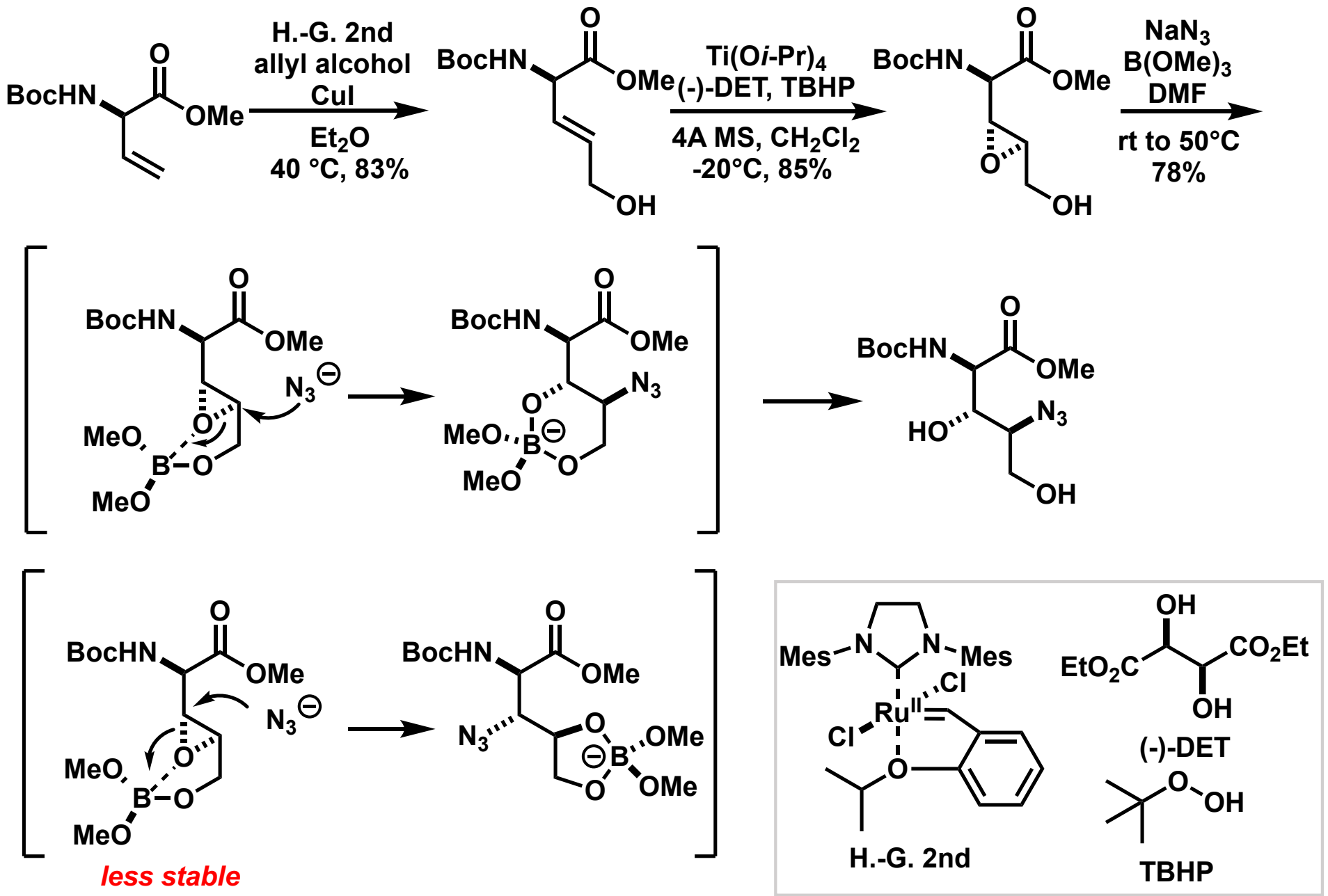
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Retrosynthesis by Li (2)



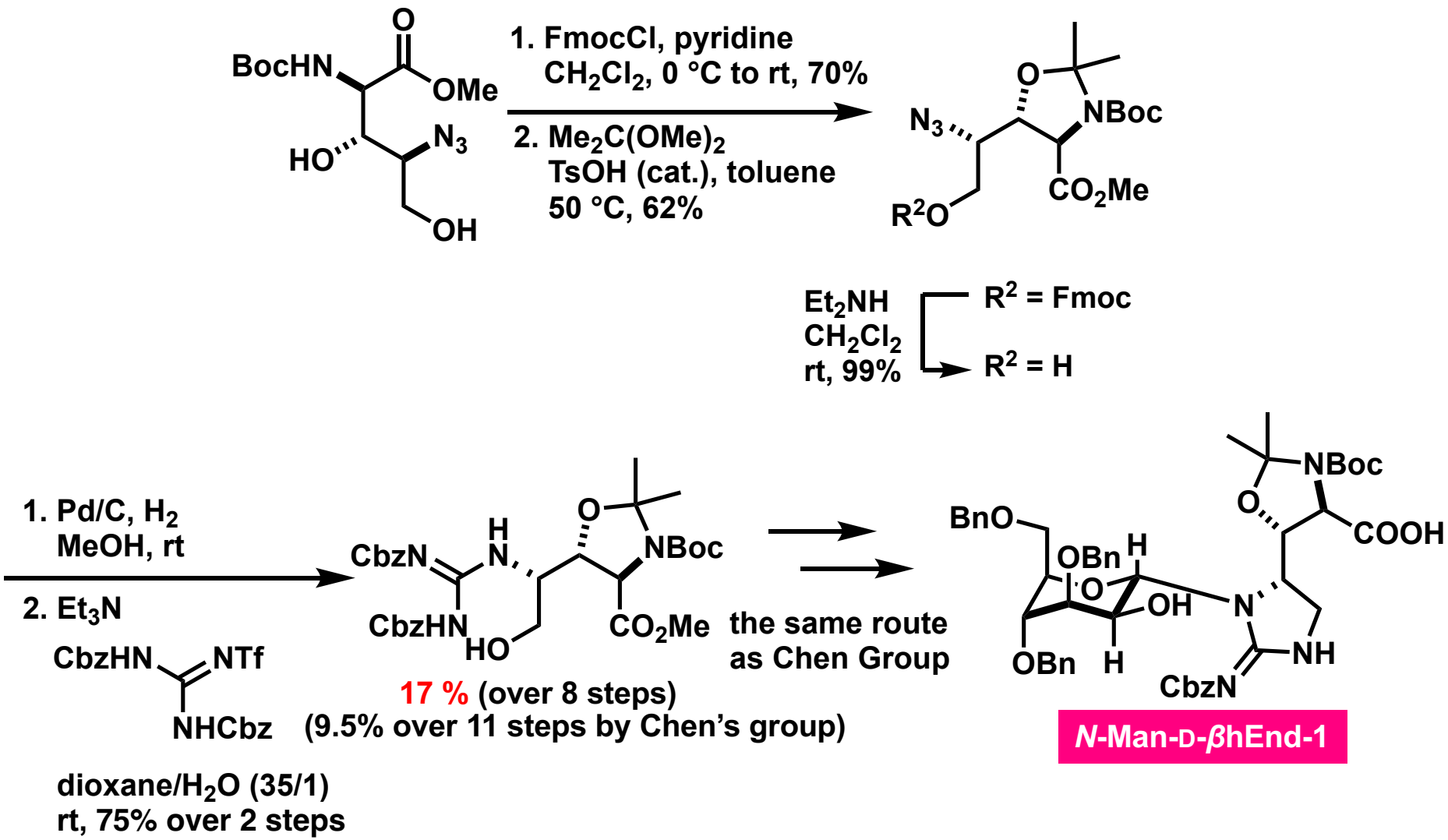
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Efficient Synthesis of *N*-Man-D-βhEnd-1 (1)



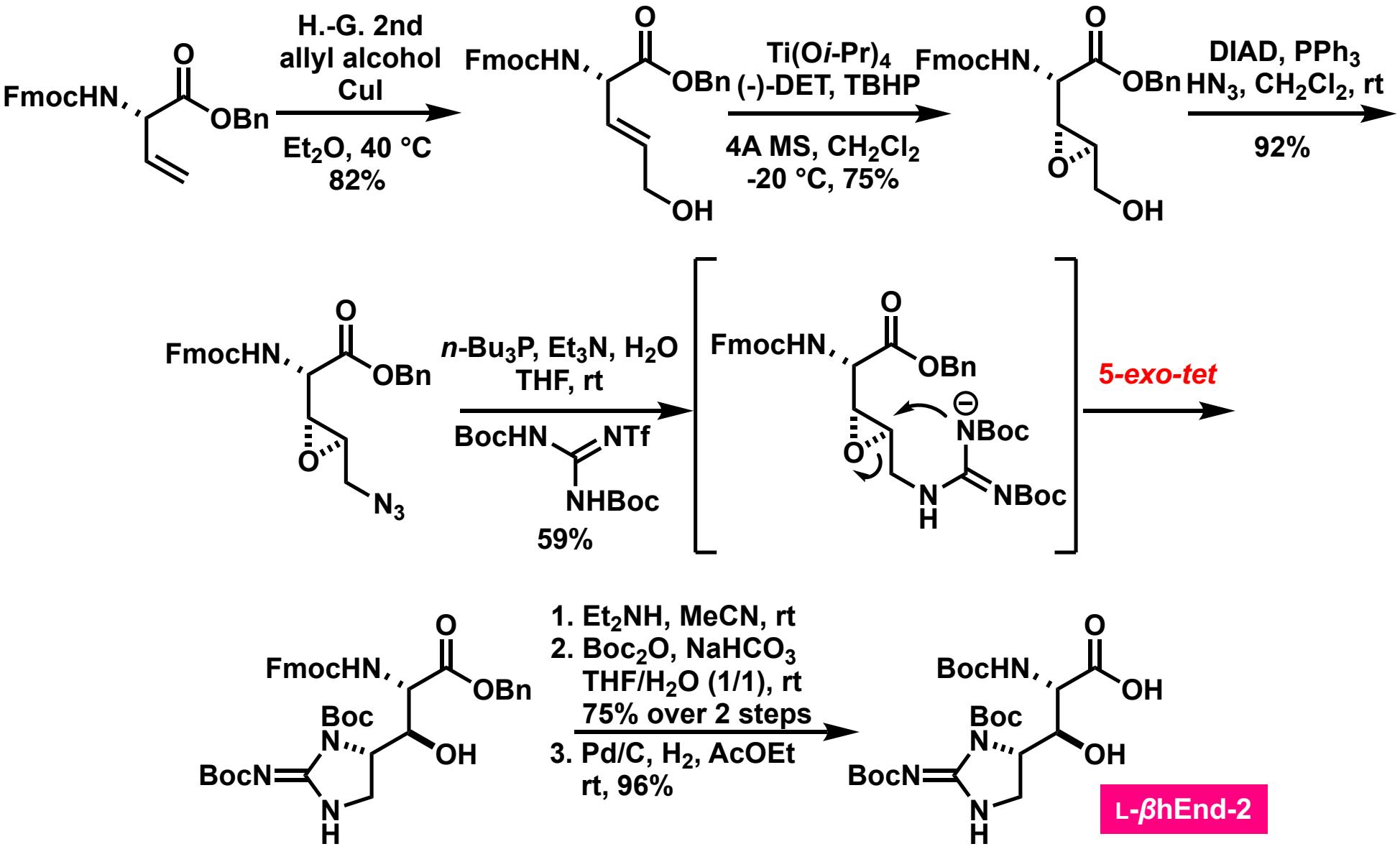
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.
2) Sasaki, M.; Tanino, K.; Hirai, A.; Miyashita, M. *Org. Lett.* **2003**, *5*, 1789.

Efficient Synthesis of *N*-Man-D-βhEnd-1 (2)



1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

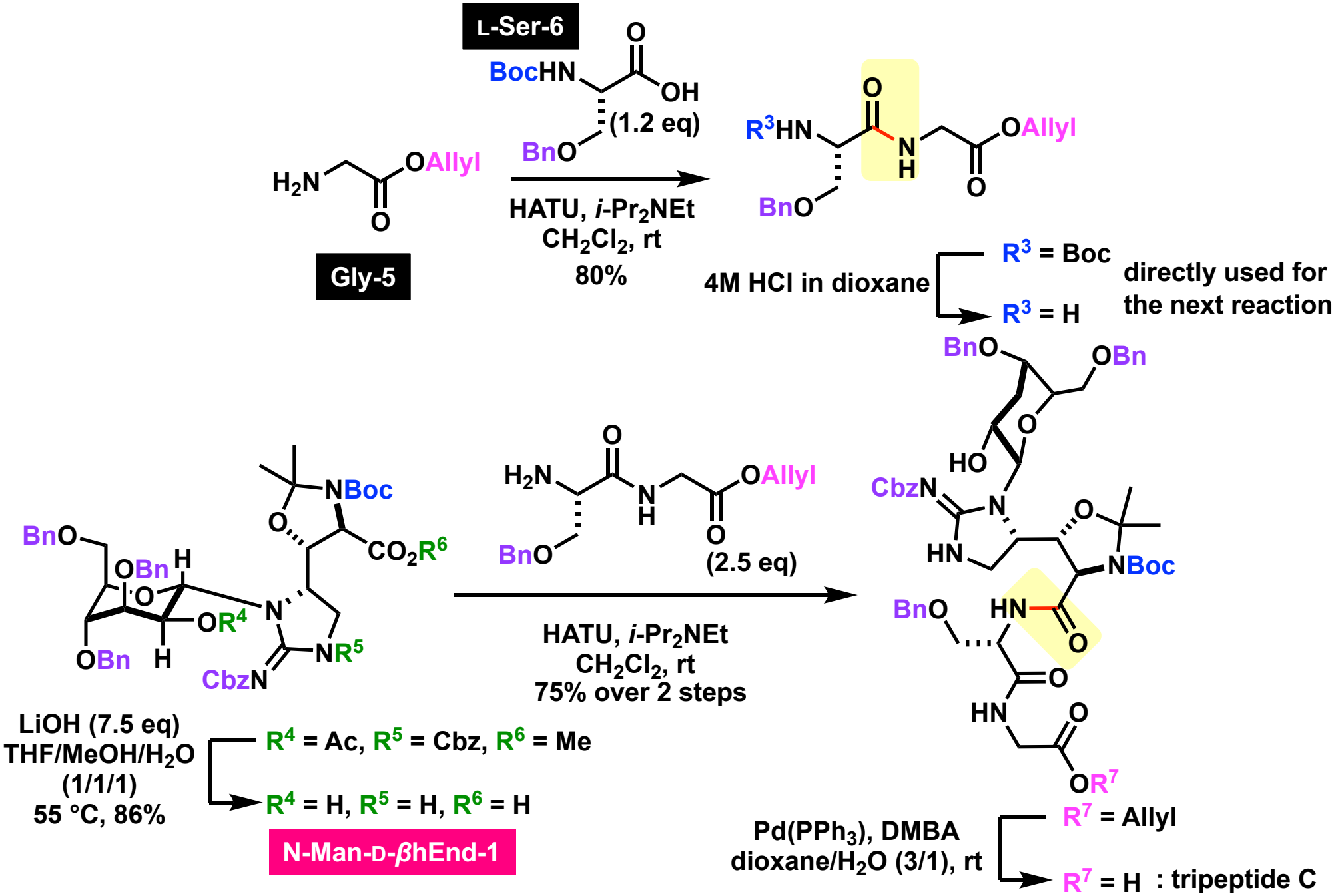
Efficient Synthesis of L-βhEnd-2



25% over 7 steps
(7.4 % over 12 steps by Chen's Group)

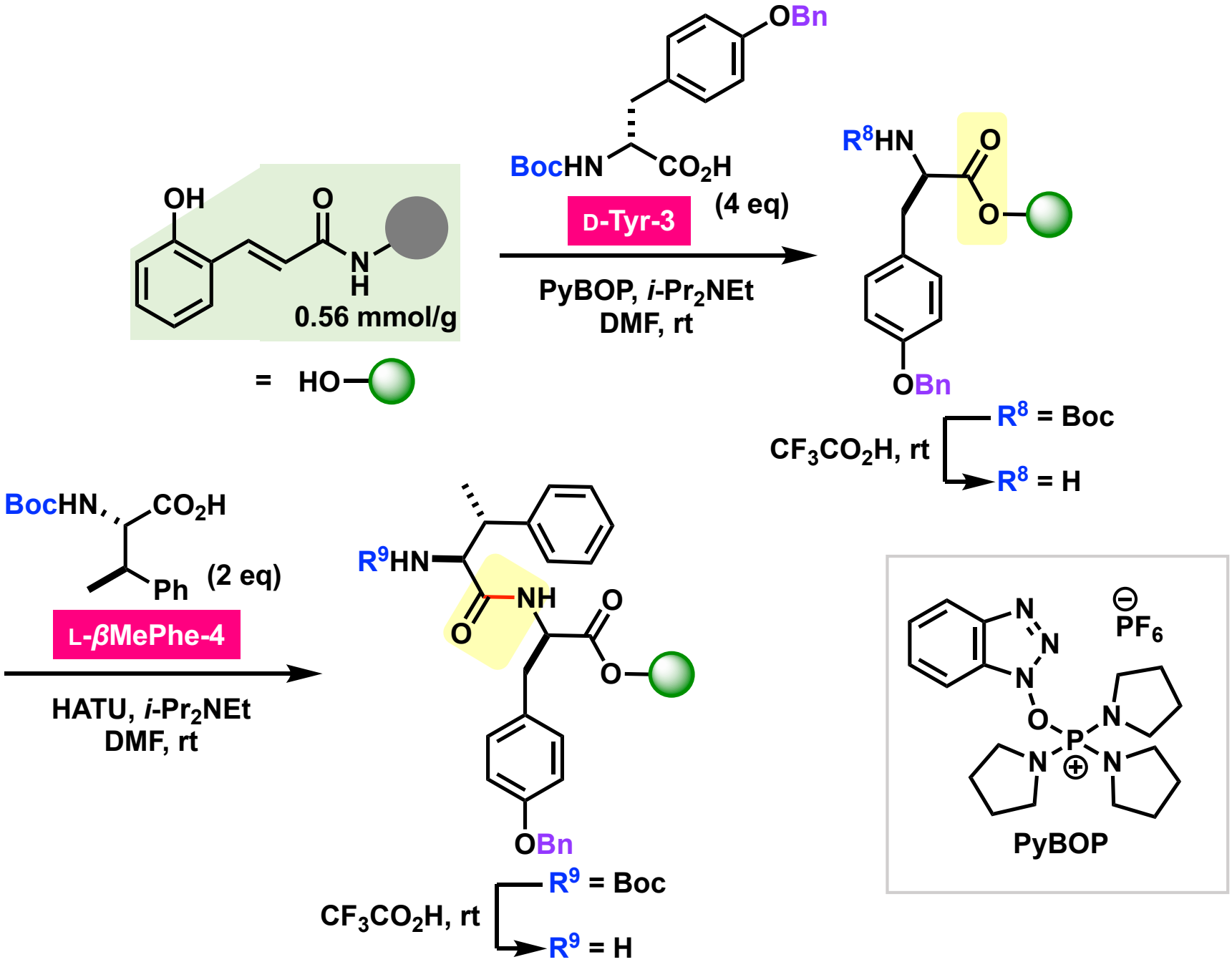
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Synthesis of Tripeptide C



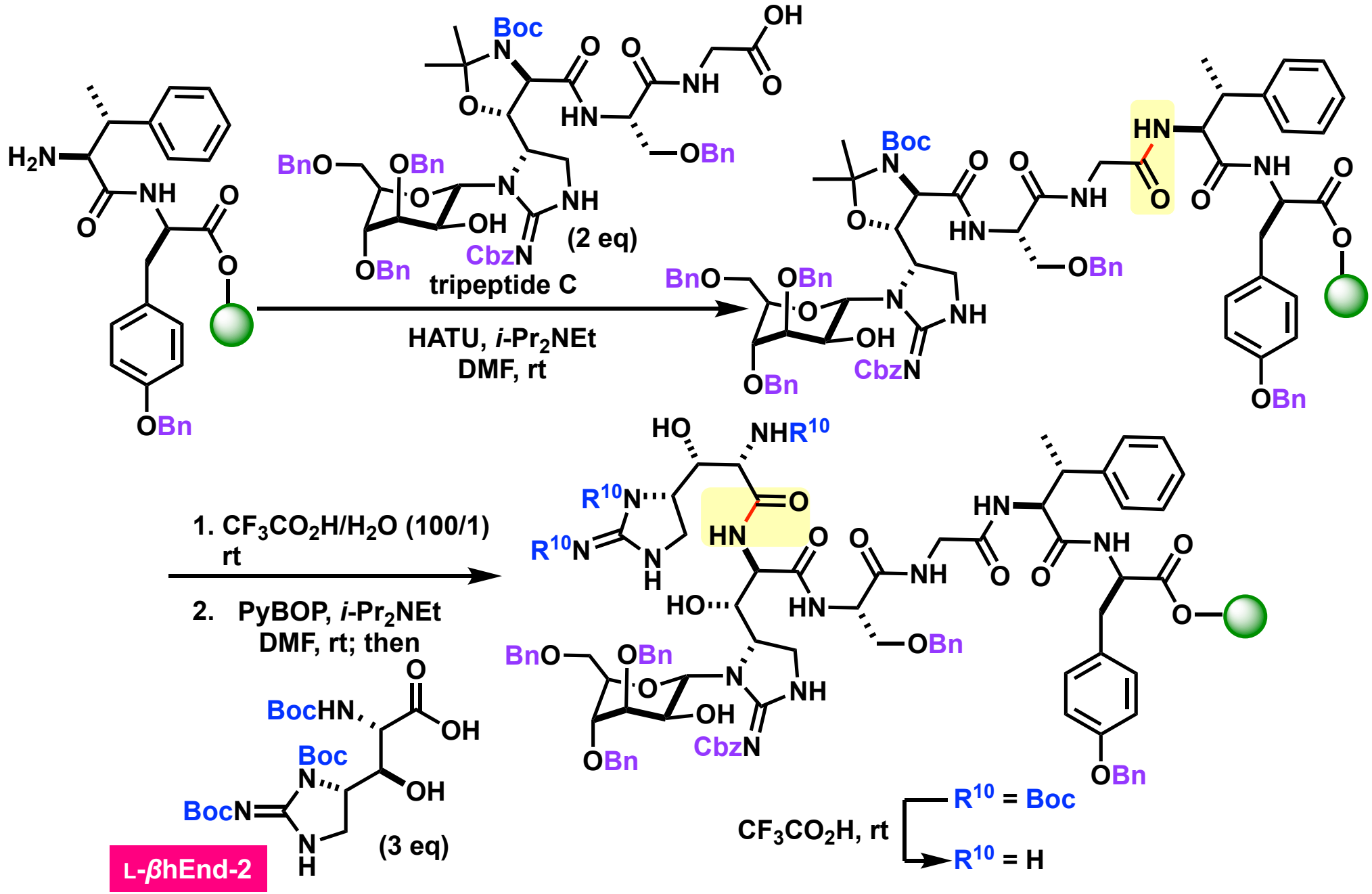
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Solid-Phase Peptide Elongation (1)



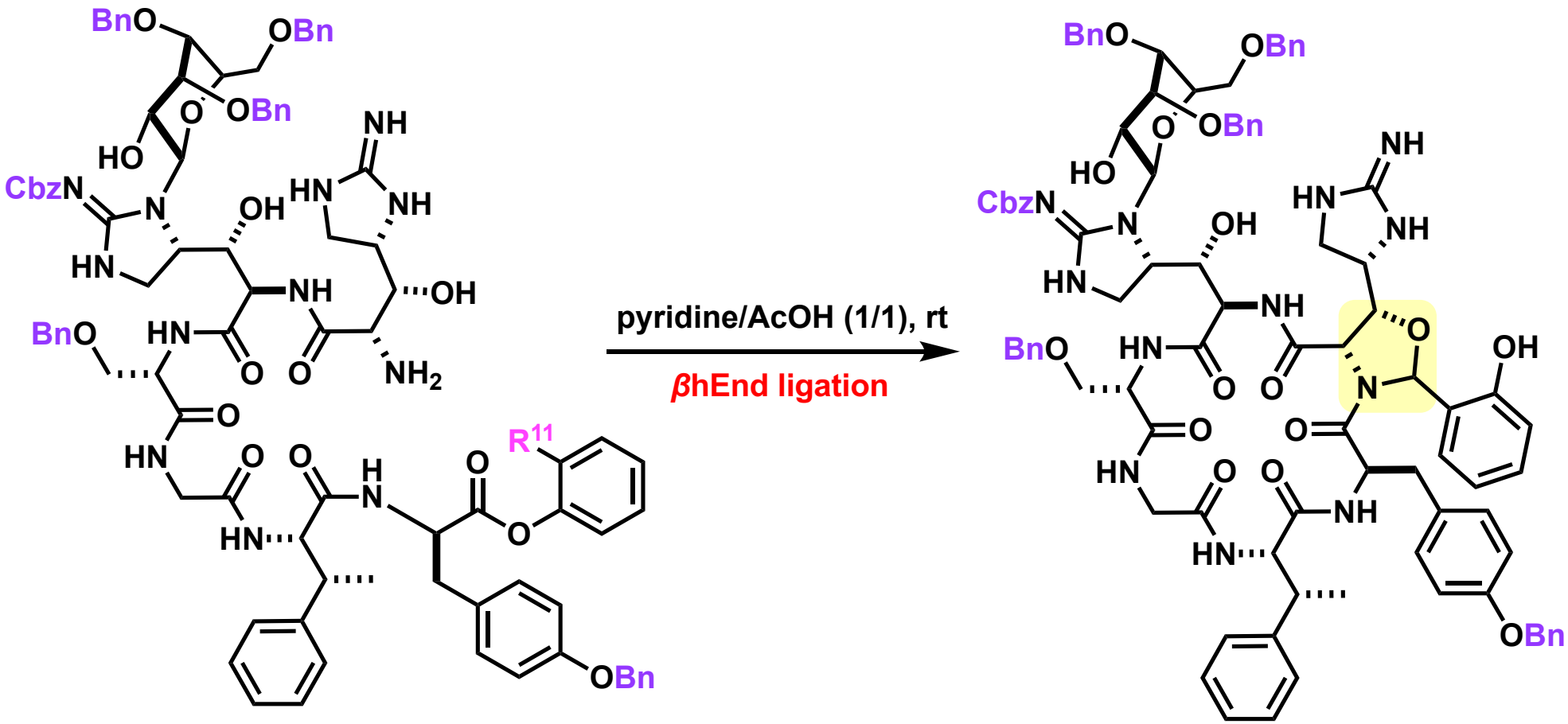
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Solid-Phase Peptide Elongation (2)

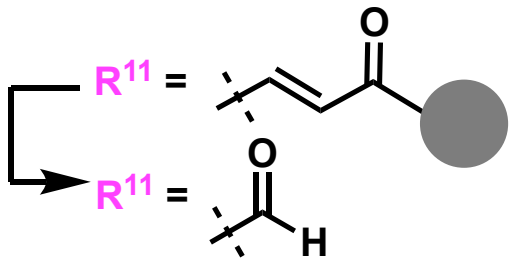


1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

βhEnd Ligation

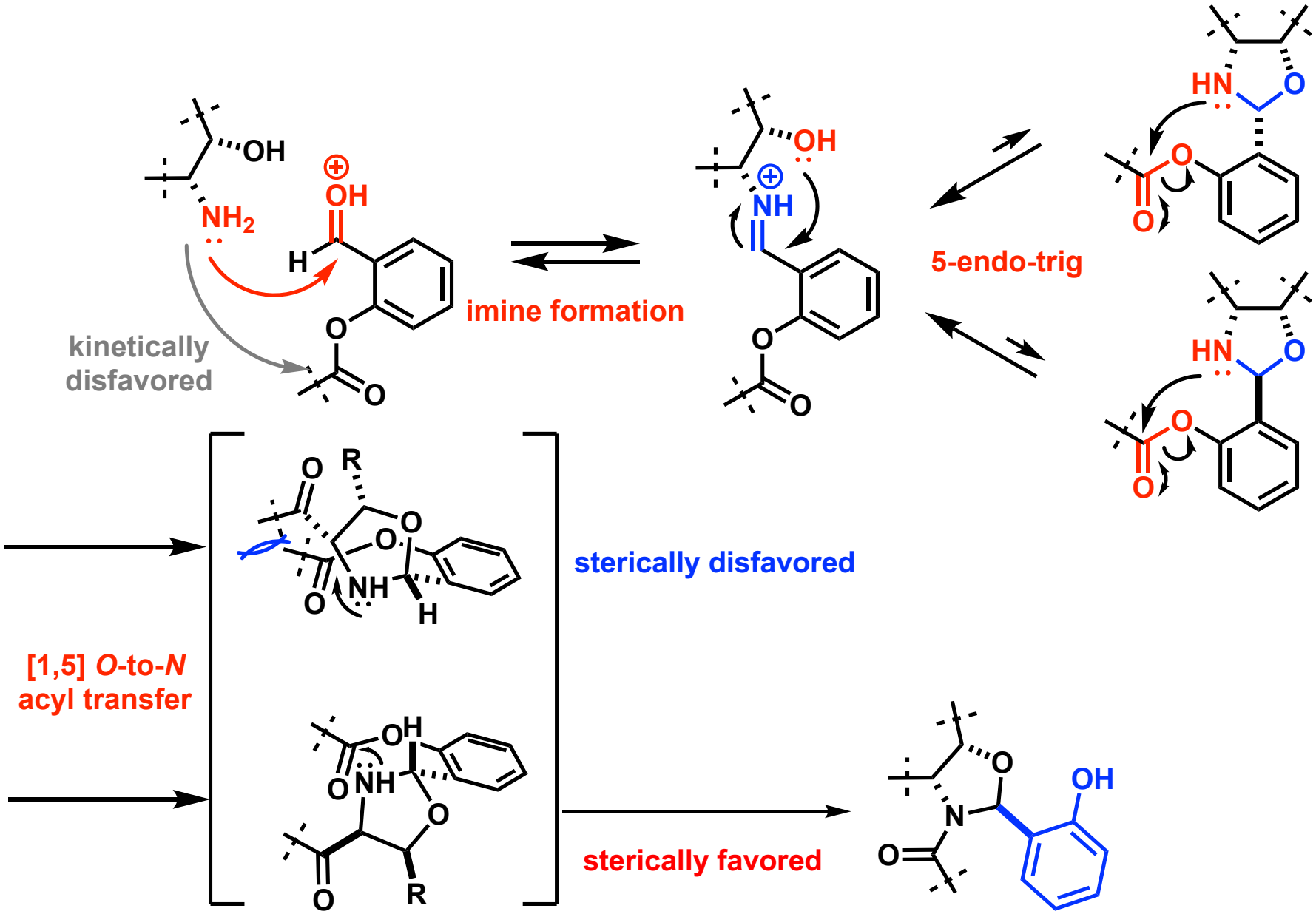


O_3
CF_3CO_2H/CH_2Cl_2 (19/1)
-78 °C;
Me_2S, -78 °C to rt



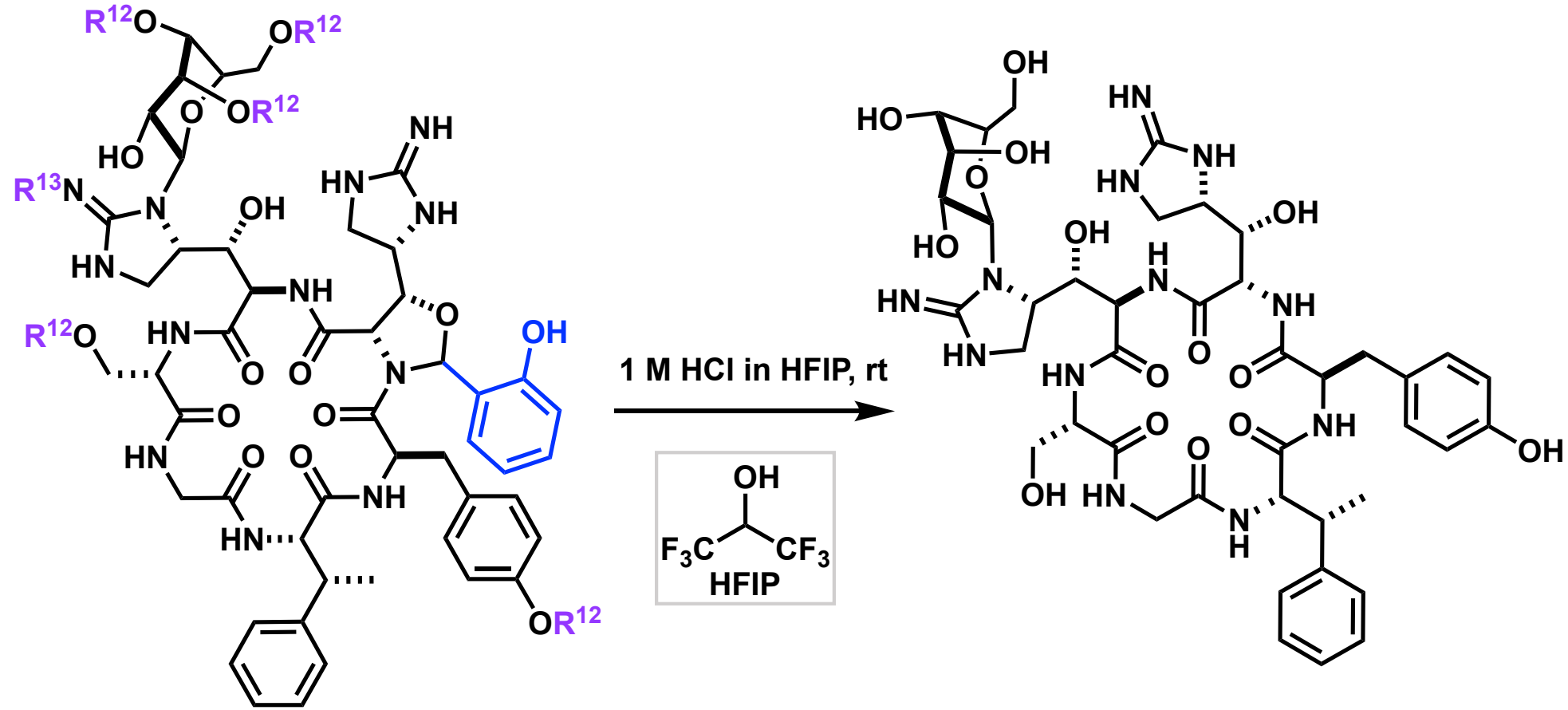
1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Mechanism of βhEnd Ligation



1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. 143, 12784.
2) Liu, H.; Li, X. *Acc. Chem. Res.* **2018**, *51*, 1643.
3) Lam, H. Y.; Zhang, Y.; Liu, H.; Xu, J.; Wong, C. T. T.; Xu, C.; Li, X. *J. Am. Chem. Soc.* **2013**, *135*, 6272.

Global Deprotection



$Pd(OAc)_2$, H_2
$THF/MeOH/H_2O/HCO_2H$
(1/1/1/0.05)
rt

R^{12} = Bn, R^{13} = Cbz

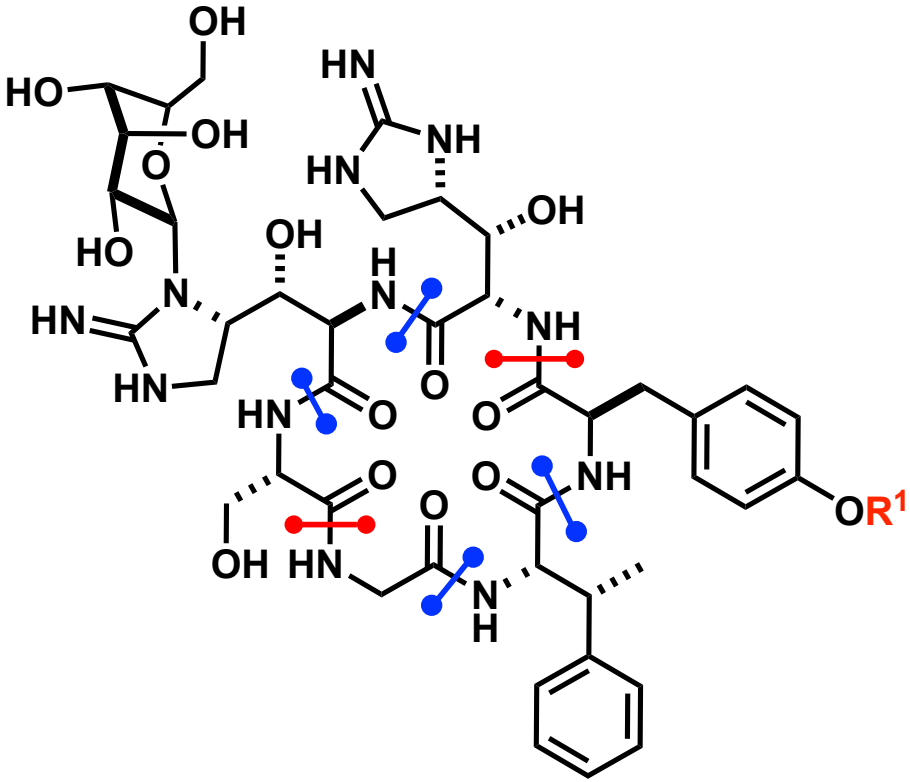
R^{12} = H, R^{13} = H

mannopeptimycin *β*
11% from resin
(over 12 steps)

1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

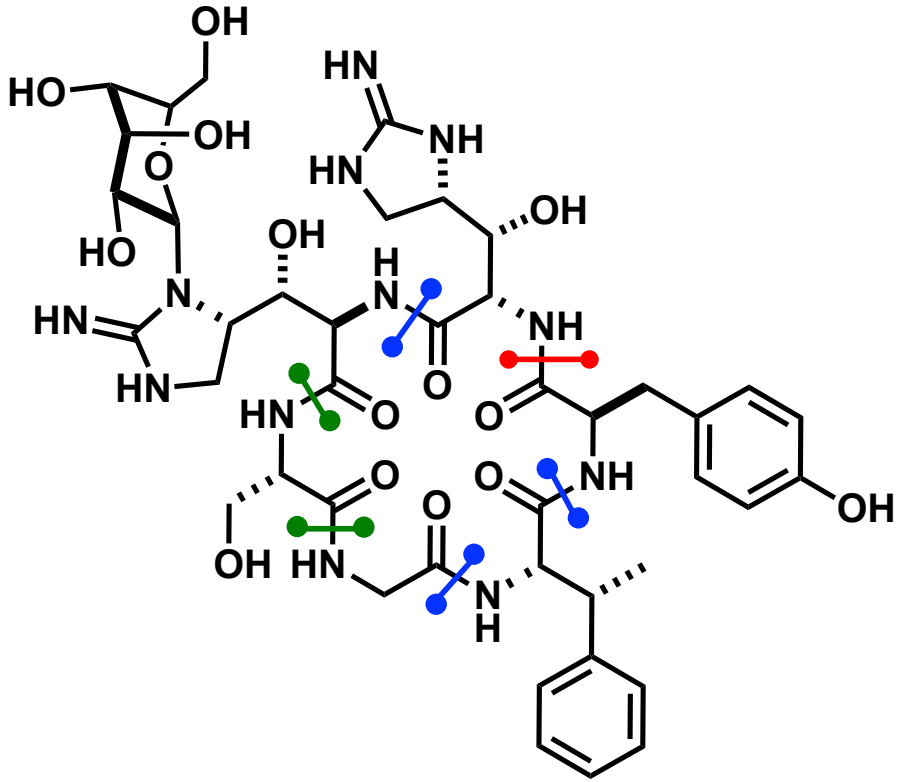
Summary

Chen's group



- solution-phase peptide synthesis
- 3+3 strategy
- mannopeptimycin *α*: 10%
  mannopeptimycin *β*: 8%
  from *N*-Man-D-*β*hEnd-1 (9 steps)

Li's group

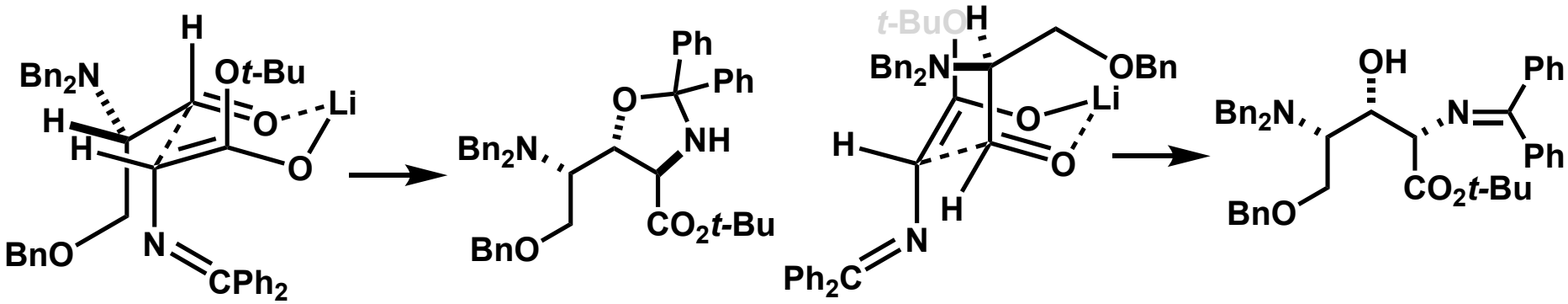


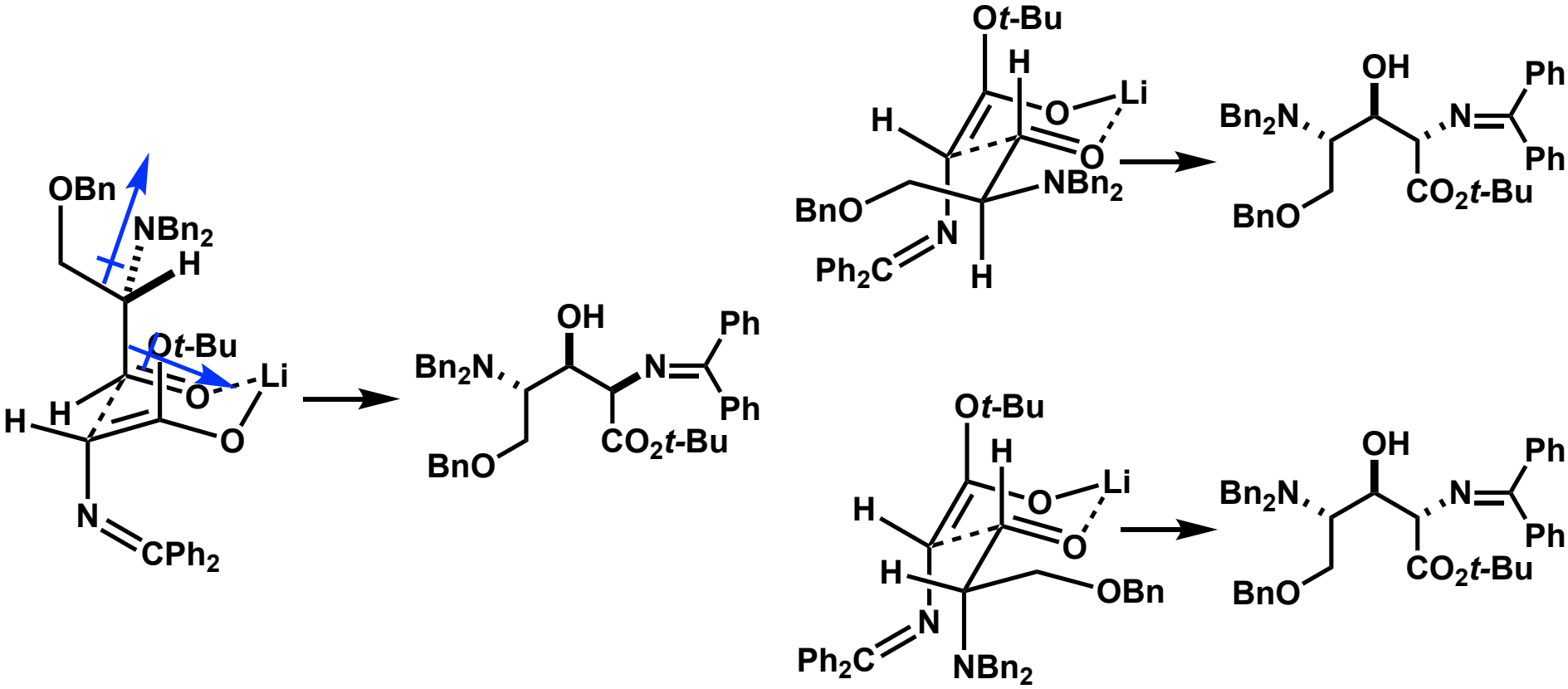
- solution-phase tripeptide synthesis
- solid-phase peptide synthesis
- *β*hEnd ligation
- mannopeptimycin *β*: 11%
  from modified AM resin (12 steps)

1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.
2) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Appendix

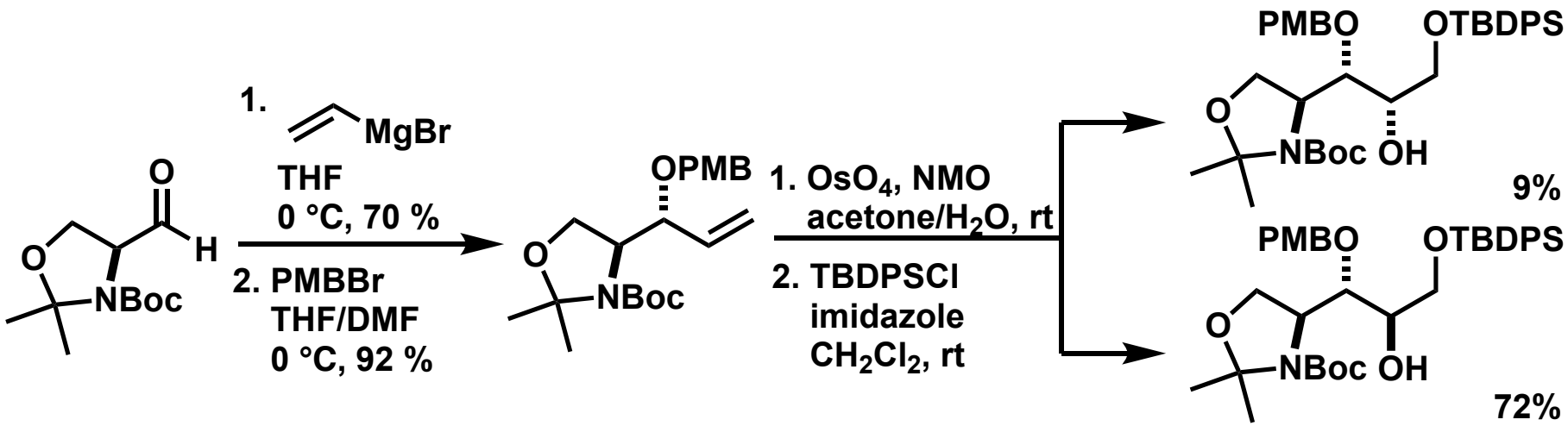
Possible Transition States

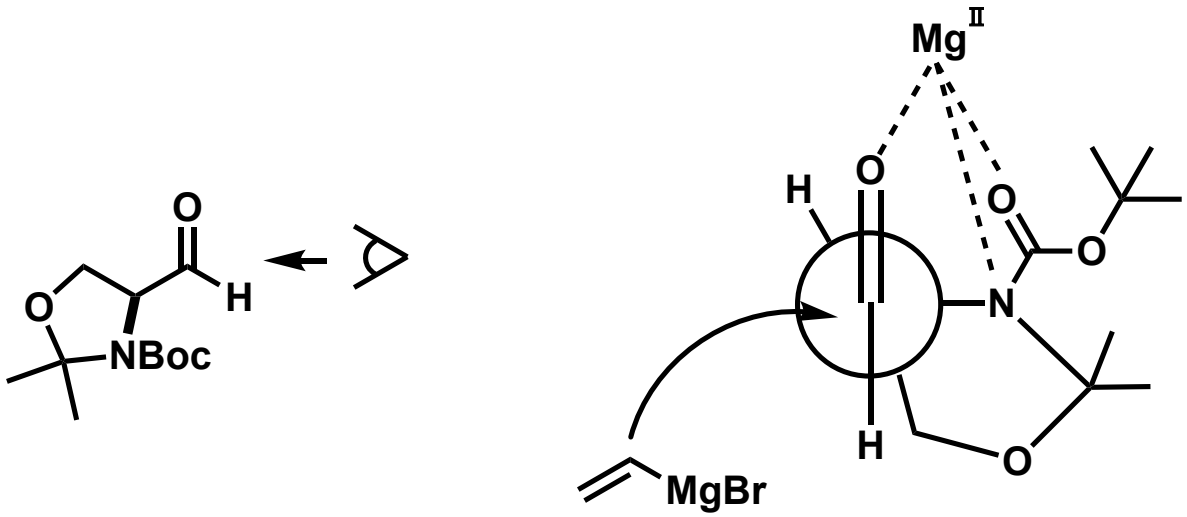




1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.
2) Fuse, S.; Koinuma, H.; Kimbara, A.; Izumikawa, M.; Mifune, Y.; He, H.; Shin-ya, K.; Takahashi, T.; Doi, T. *J. Am. Chem. Soc.* **2014**, *136*, 12011.

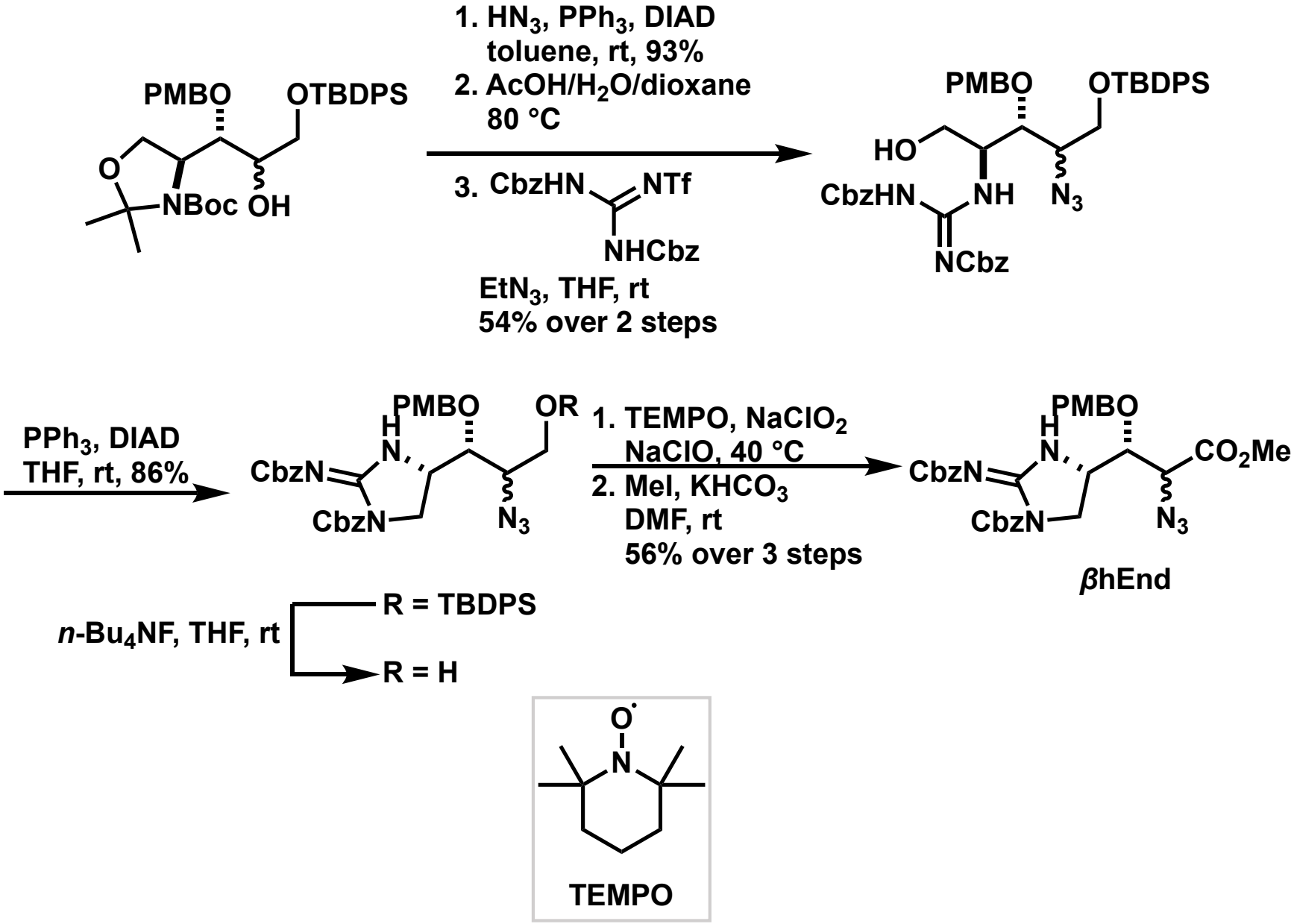
Initial Synthetic Route for βhEnd (1)





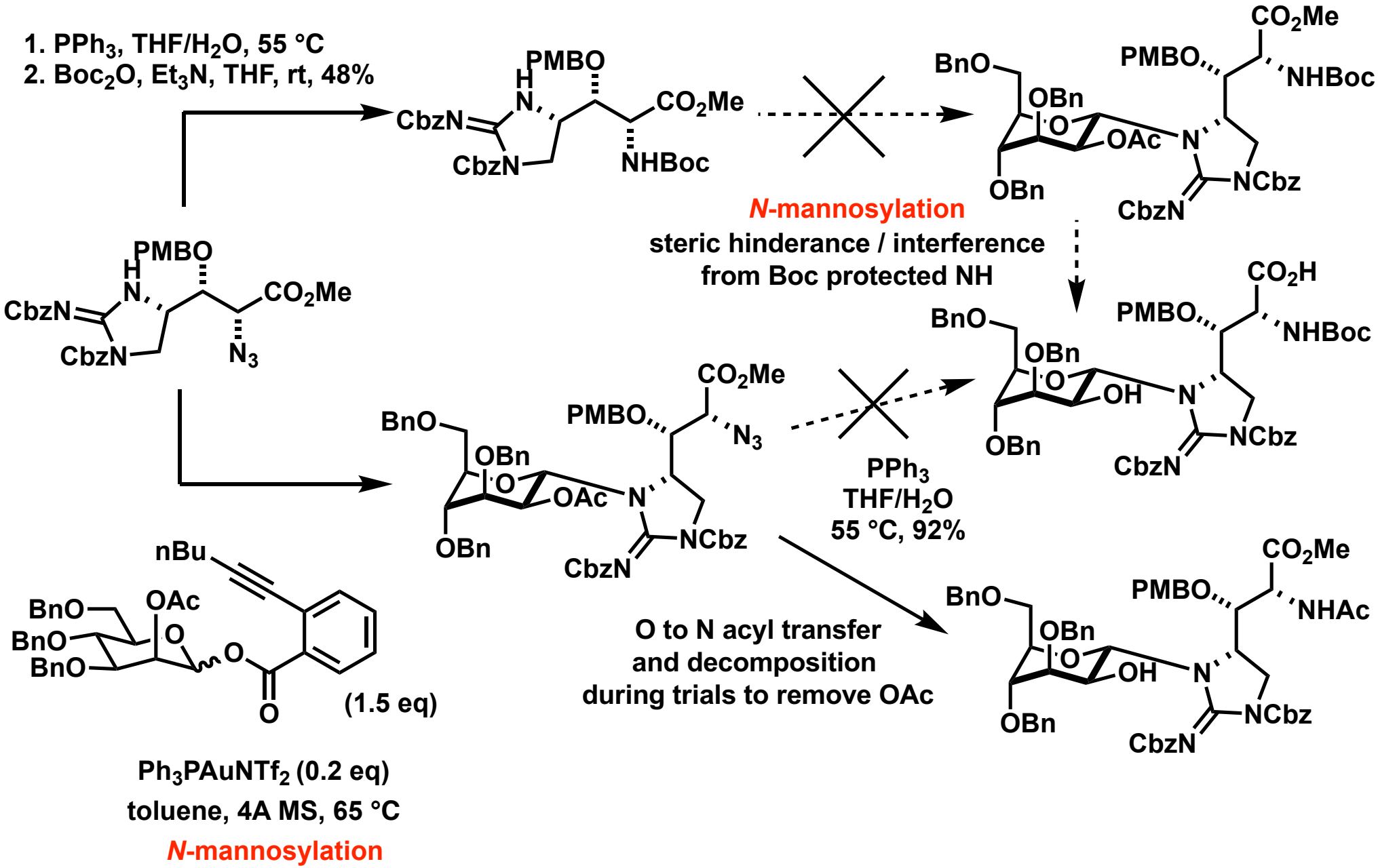
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.
2) Liang, X.; Andersch, J.; Bols, M. *J. Chem. Soc., Perkin Trans 1*. **2001**, *18*, 2136.

Initial Synthetic Route for βhEnd (2)



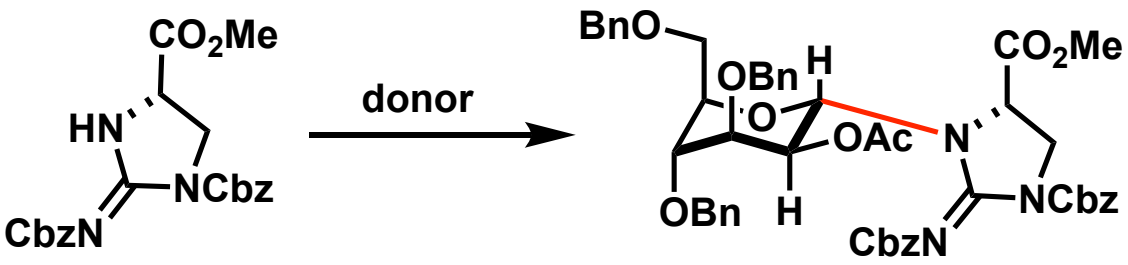
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

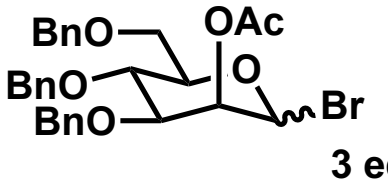
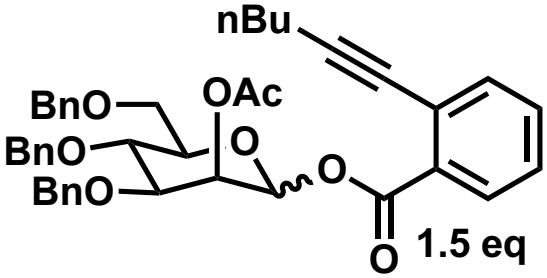
Initial Synthesis Route for βhEnd (3)



1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3932.

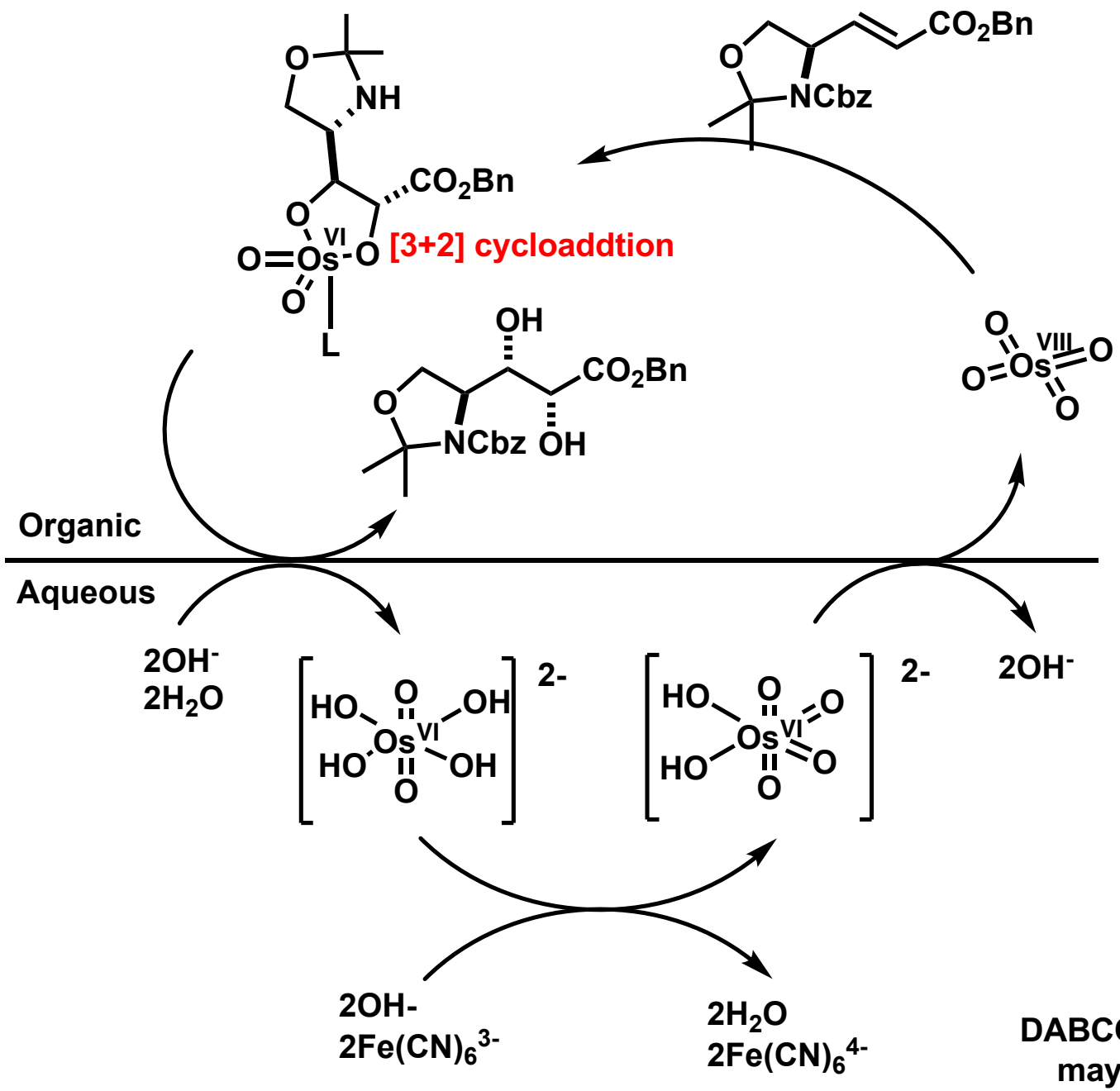
Optimization of Mannosylation

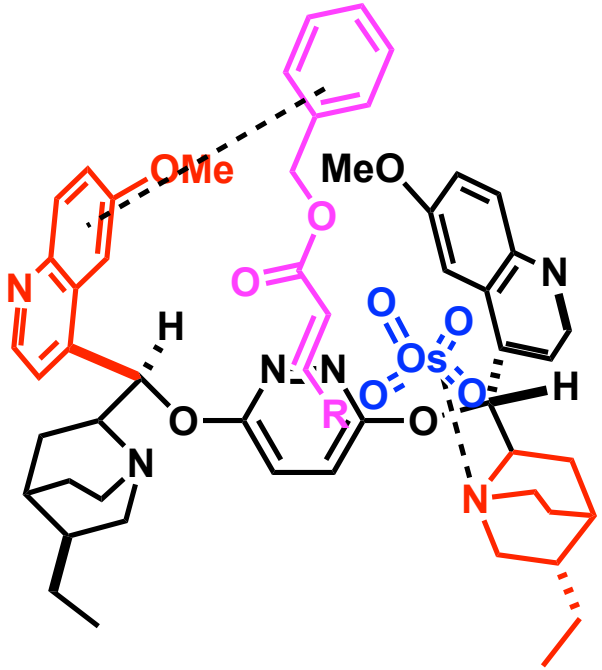


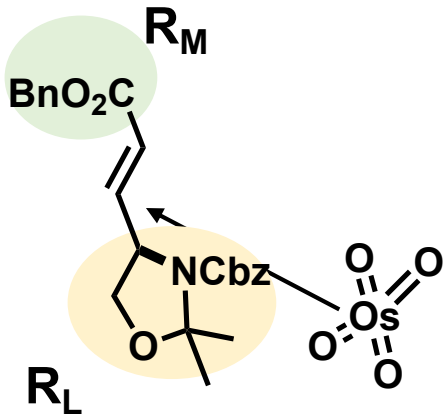
entry	*donor*	reagents, conditions	yield
1		Ag_2CO_3 (2 eq) 4A MS, toluene 80 °C, 12h	12%
2		PPh_3AuNTf_2 (0.2 eq) 4A MS, CH_2Cl_2 65 °C, 4 h	83%

1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3932.

Mechanism of AD Reaction



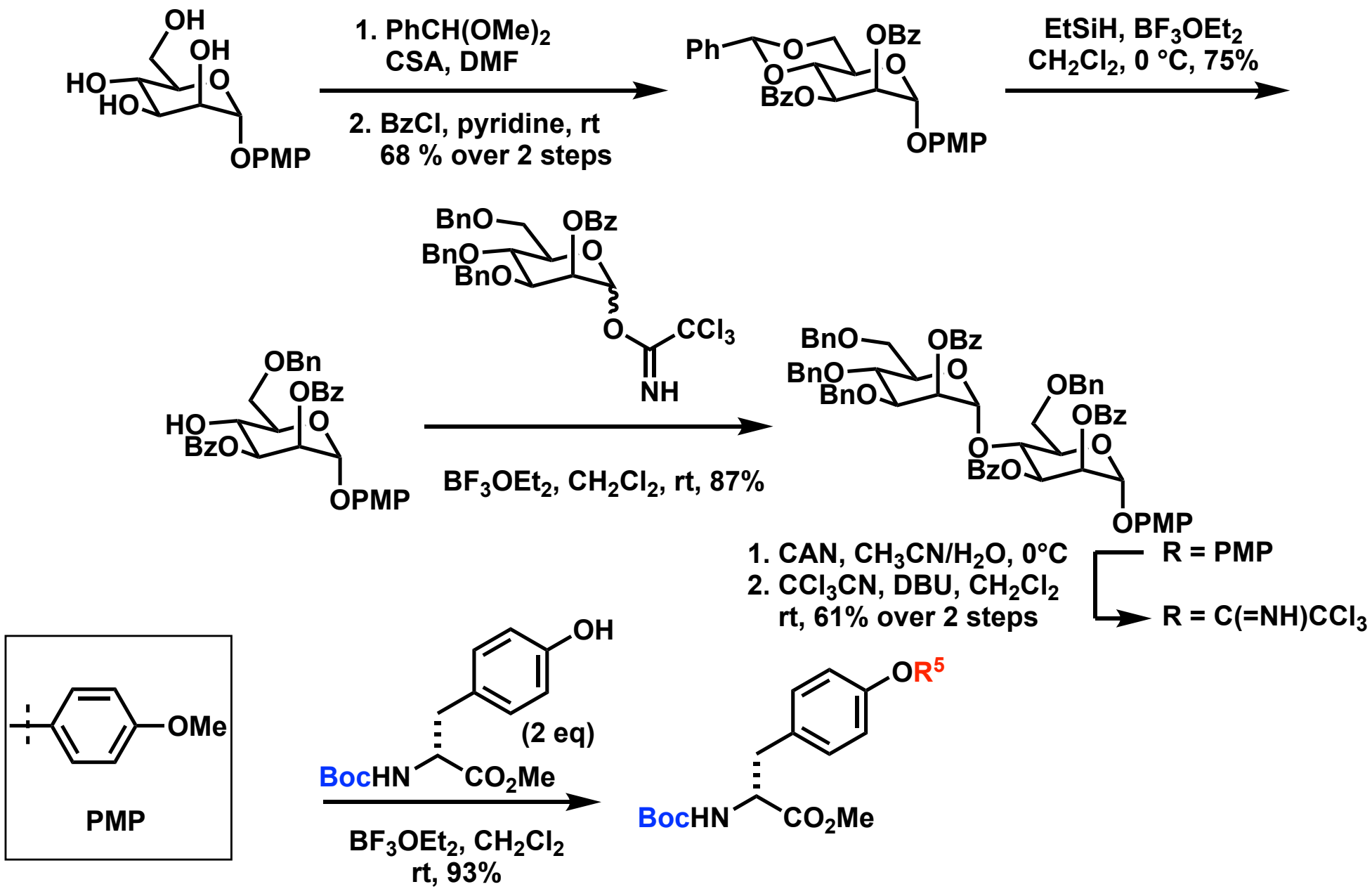




DABCO-like structure of $(DHQ)_2PHAL$ may accelerate the reaction rate.

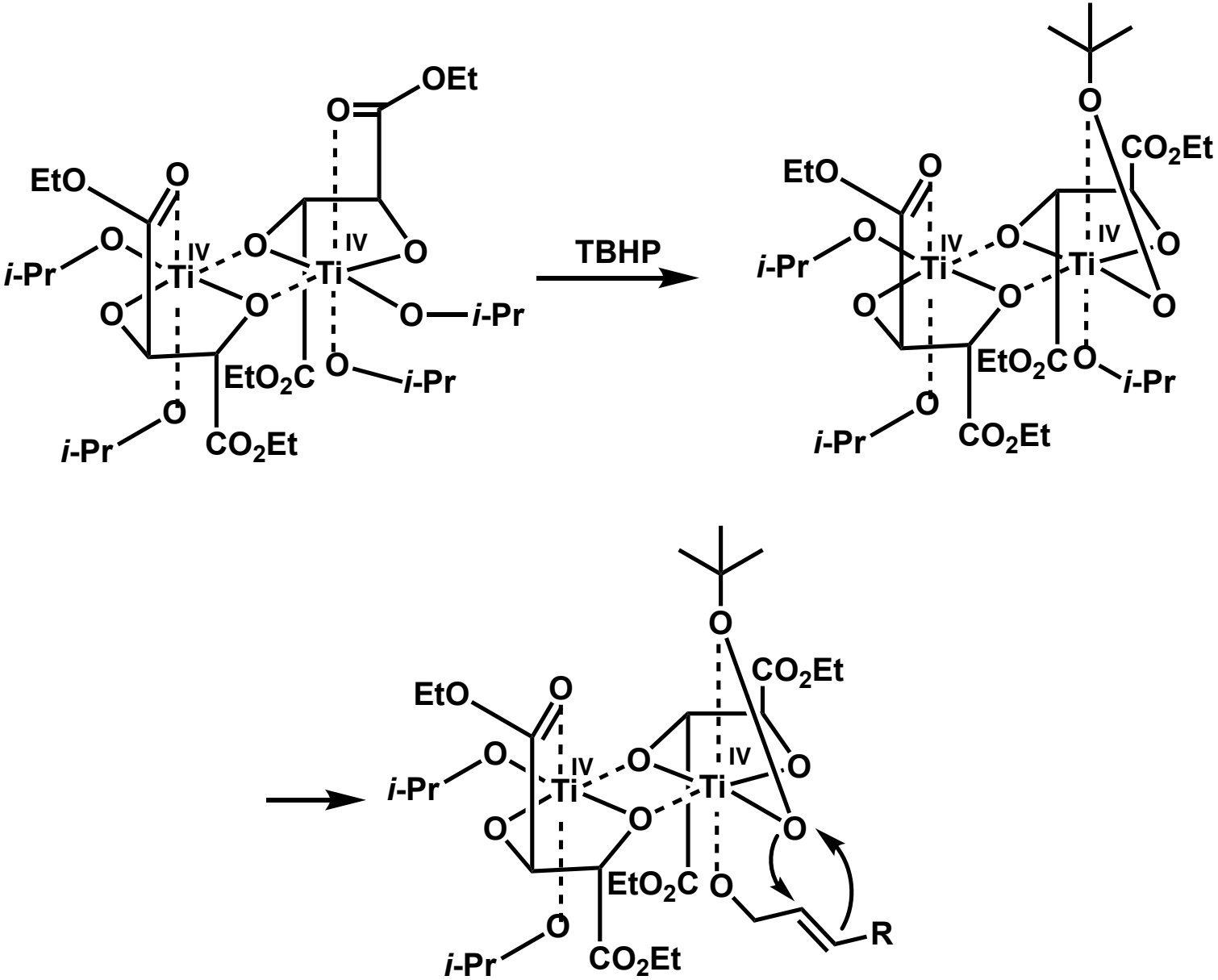
1) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.
2) Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *Tetrahedron Lett.* **1995**, *36*, 3481. 3) Minato, M., Yamamoto, K., & Tsuji, J. *J. Org. Chem.* **1990**. *55*. 766.

Preparation of Sugar Moiety of D-Tyr-3



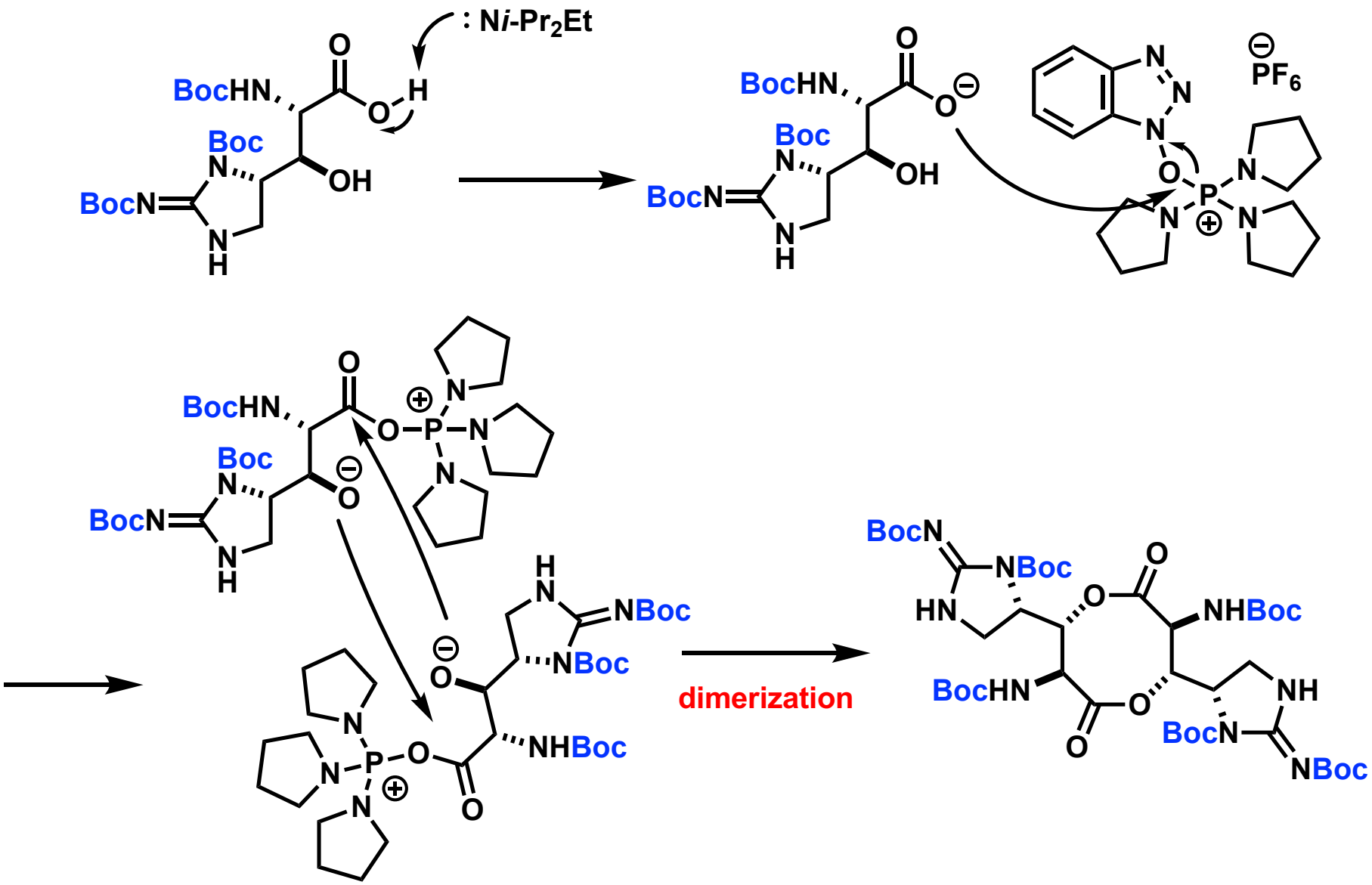
1) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138,* 3926.

Sharpless-Katsuki Asymmetric Epoxidation



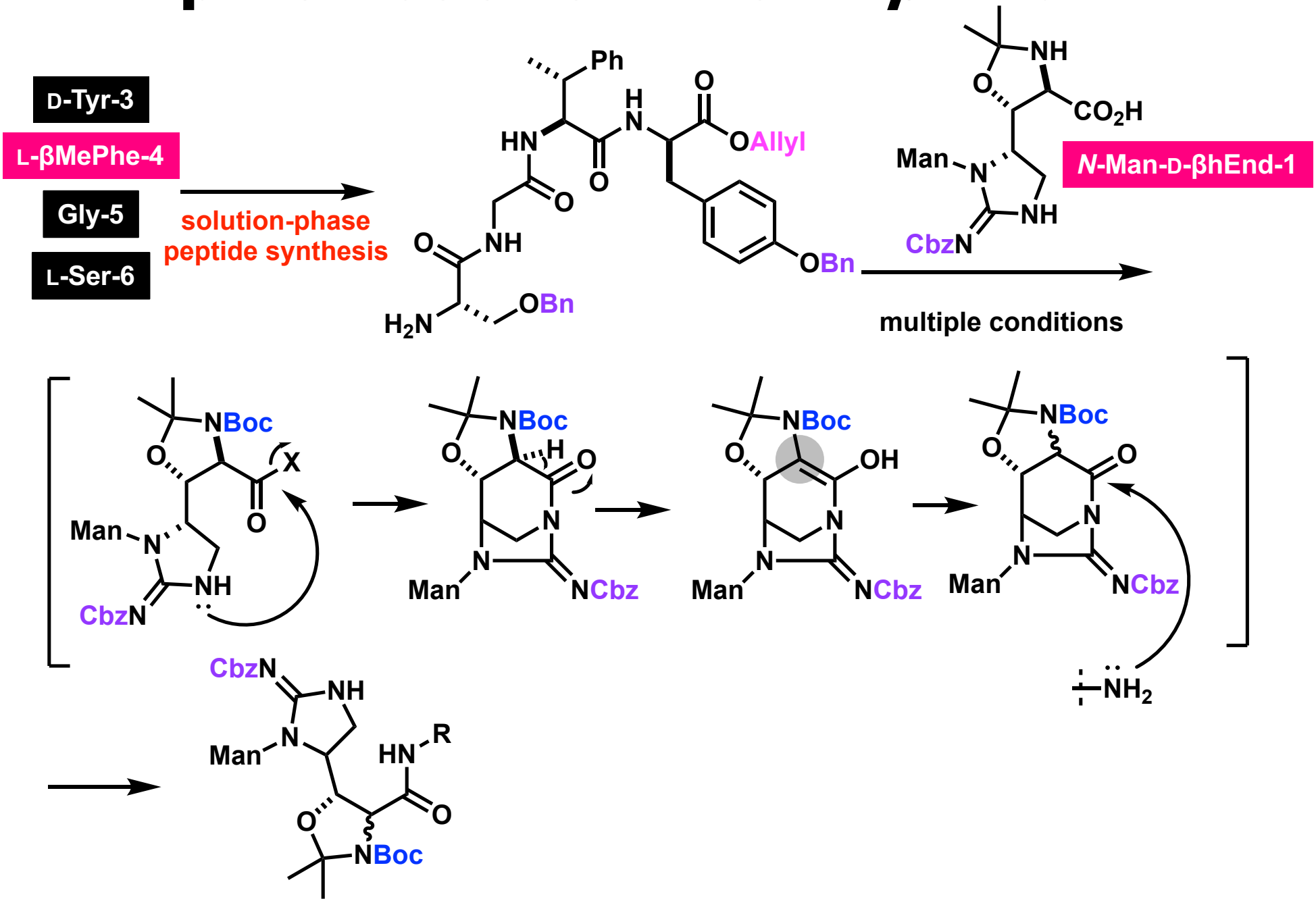
1) Williams, I. D., Pedersen, S. F., Sharpless, K. B., & Lippard, S. J. *J. Am. Chem. Soc.,* **1984** *106*, 6430.

Dimerization of L-βhEnd-2



1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.

Epimerization of *N*-Man-D-βhEnd-1



1) Wang, J.; Lin, D.; Liu, M.; Blasco, P.; Sun, Z.; Cheung, Y.C.; Chen, S.; Liu, H.; Li, X. *J. Am. Chem. Soc.* **2021**. *143*, 12784.