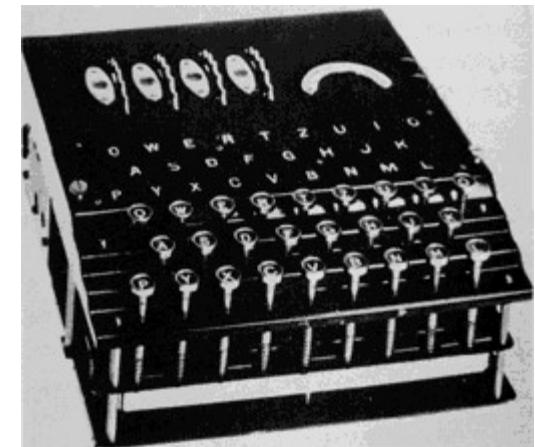


Total synthesis of enigmazole A

-Late stage transannulation-

2016.1.30

B4 Daiki Kuwana



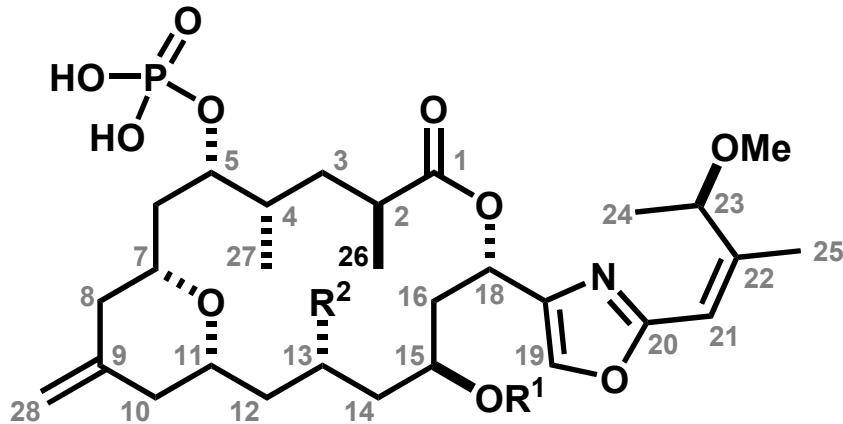
Contents

- 1. Introduction**
- 2. Alkyne metathesis**
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Enigmazole A



$R^1 = R^2 = H$ (Enigmazole A)

$R^1 = Me, R^2 = H$

$R^1 = Me, R^2 = OH$

Isolation¹

genus of *Cinahyrella enigmata*

Structural features

- 18 membered ring, 6 membered ether ring
- 8 or 9 stereocenters
- phosphorylated macrolide

Biological activity¹

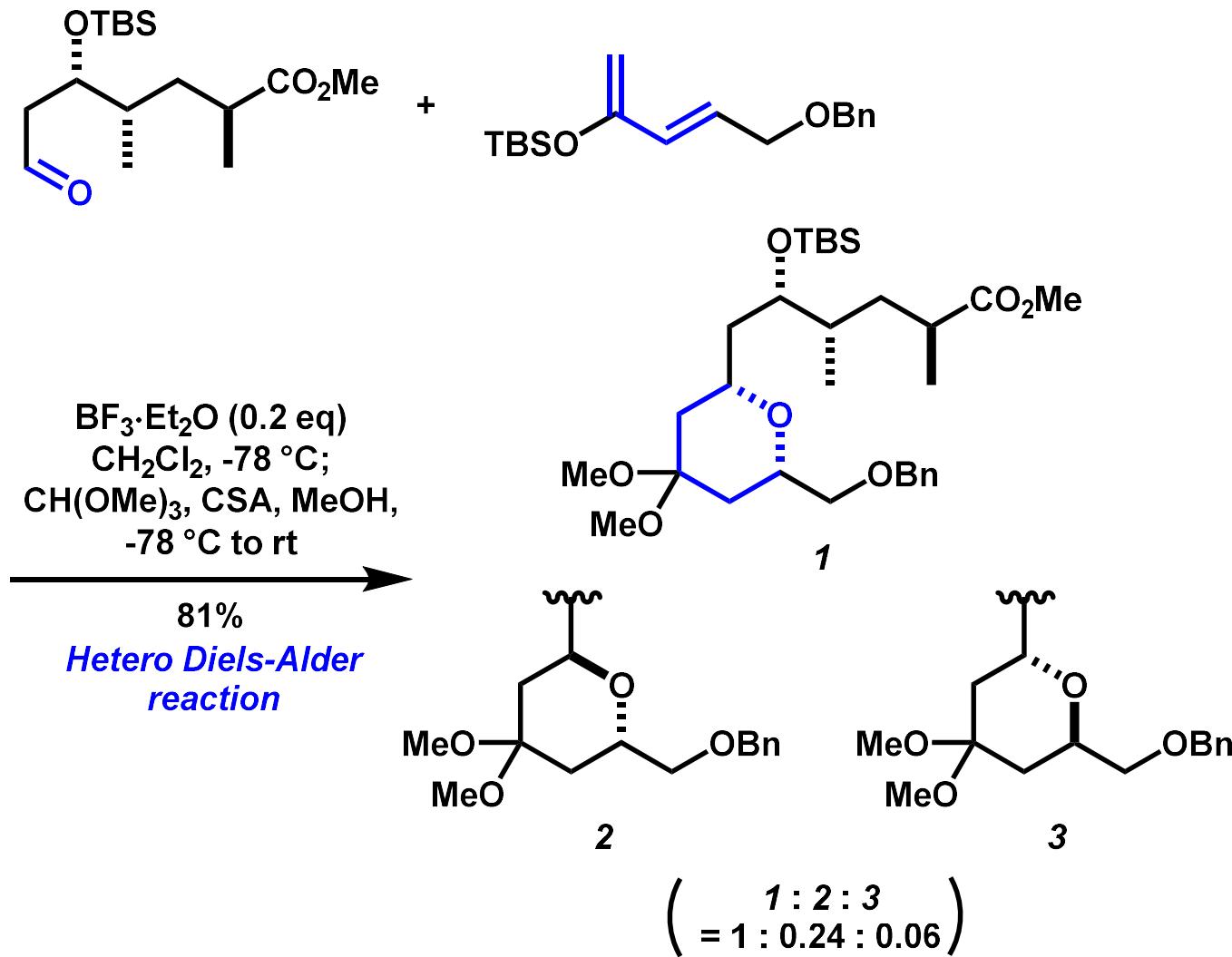
strong cytotoxicity against the NCI 60
(human tumor cell lines)

Total synthesis

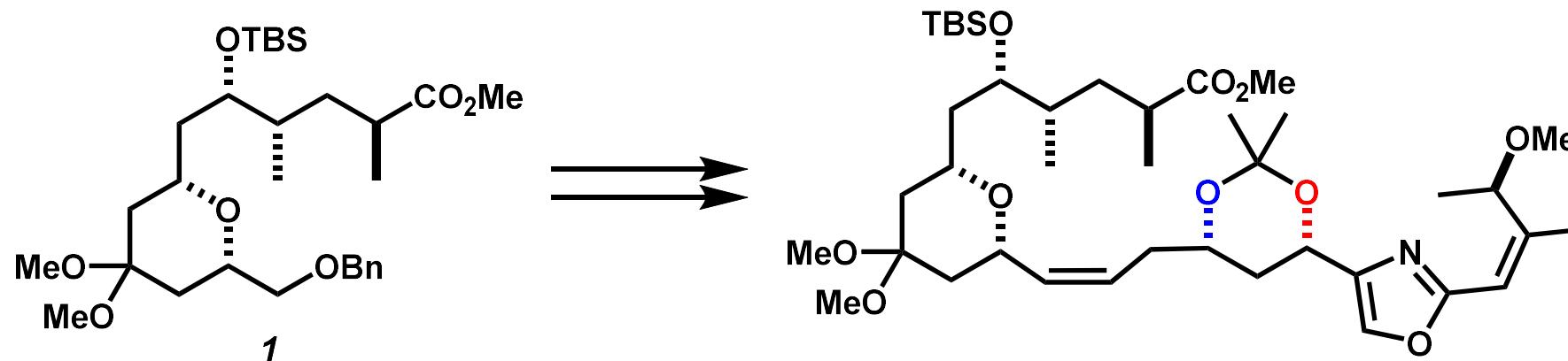
1. Skepper, C. K.; Quach, T.; Molinski, T. F. *J. Am. Chem. Soc.* **2010**, 132, 10286
2. Ai, Y.; Kozytska, M. V.; Zou, Y.; Khartulyari, A. S.; Smith, A. B. *J. Am. Chem. Soc.* **2015**, 137, 15426
3. Ahlers, A.; Haro, T.; Gabor, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2016**, 55, 1406. (Main paper)

1. Oku, N.; Takada, K.; Fuller, R. W.; Wilson, J. A.; Peach, M. L.; Pannell, L. K.; McMahon, J. B.; Gustafson, K. R. *J. Am. Chem. Soc.* **2010**, 132, 10278

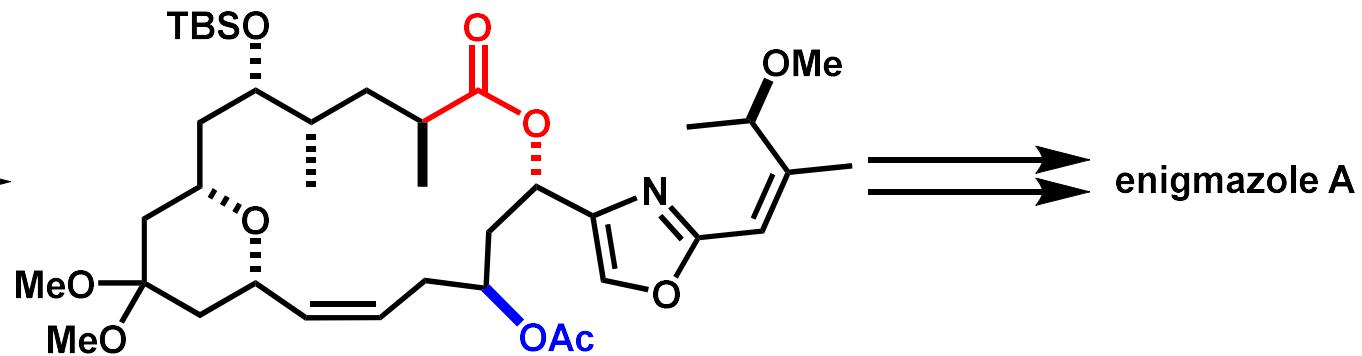
Brief summary of Molinski's synthesis (1)



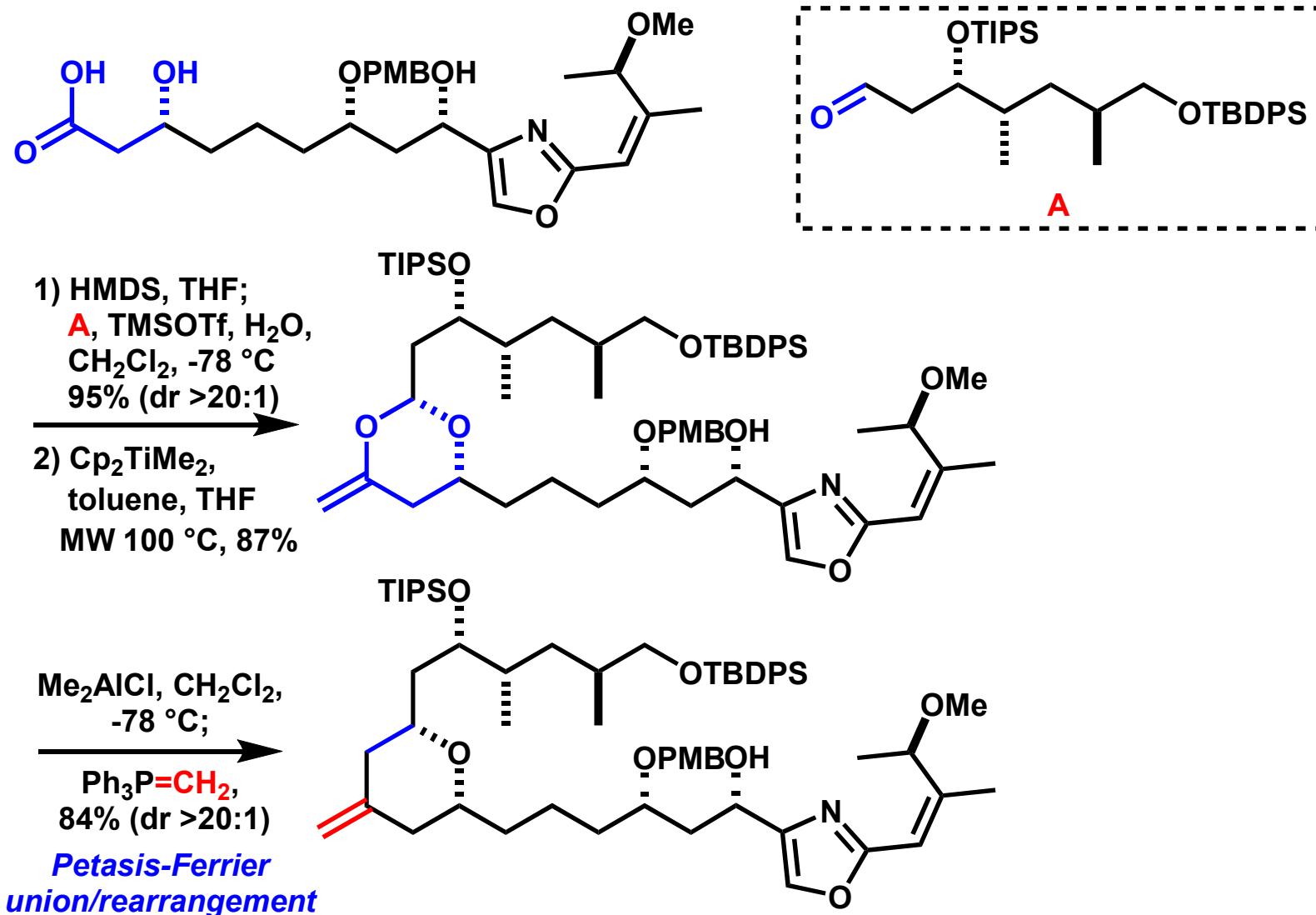
Brief summary of Molinski's synthesis (2)



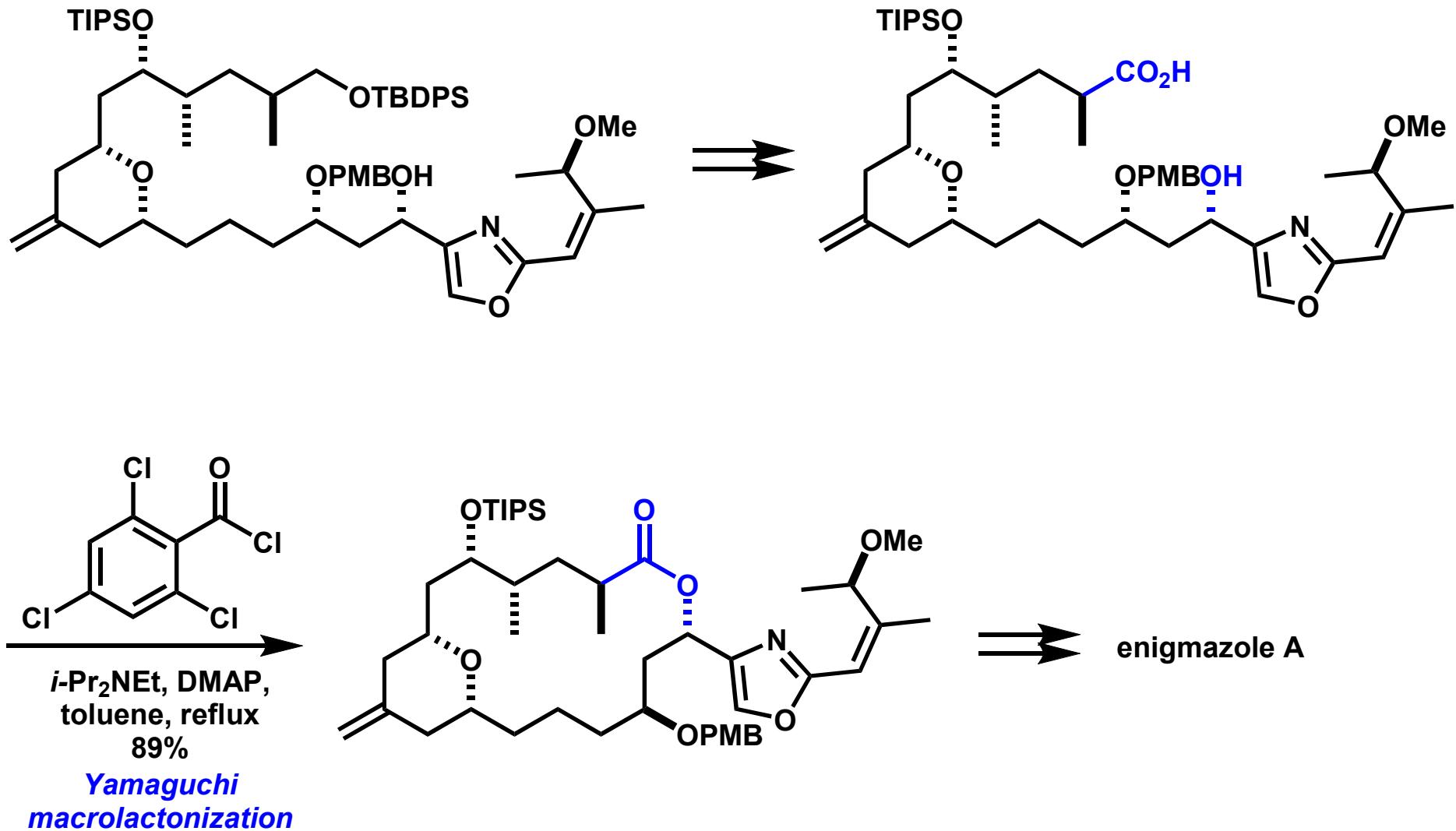
1) LiOH, MeOH/H₂O, 80 °C
quant.
2) CSA, MeOH, quant.
3) DCC, DMAP, DMAP·HCl,
CHCl₃, reflux; AcOH,
MeOH, 35% (3 steps)
Keck
macrolactonization



Brief summary of Smith's synthesis (1)

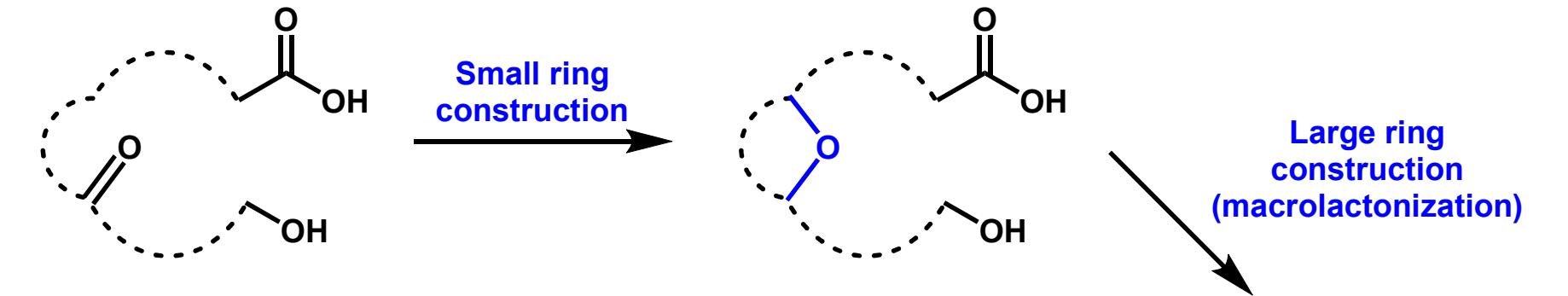


Brief summary of Smith's synthesis (2)

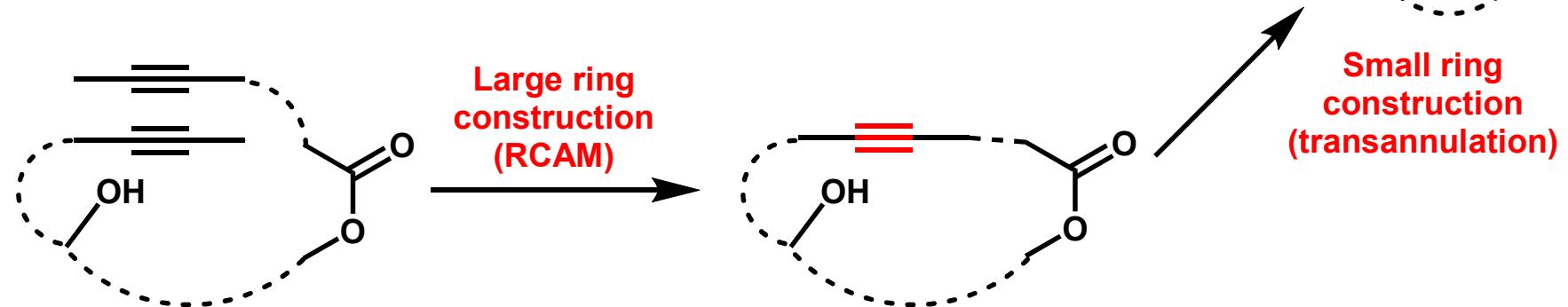


Approach by Fürstner

Molinski & Smith's strategy



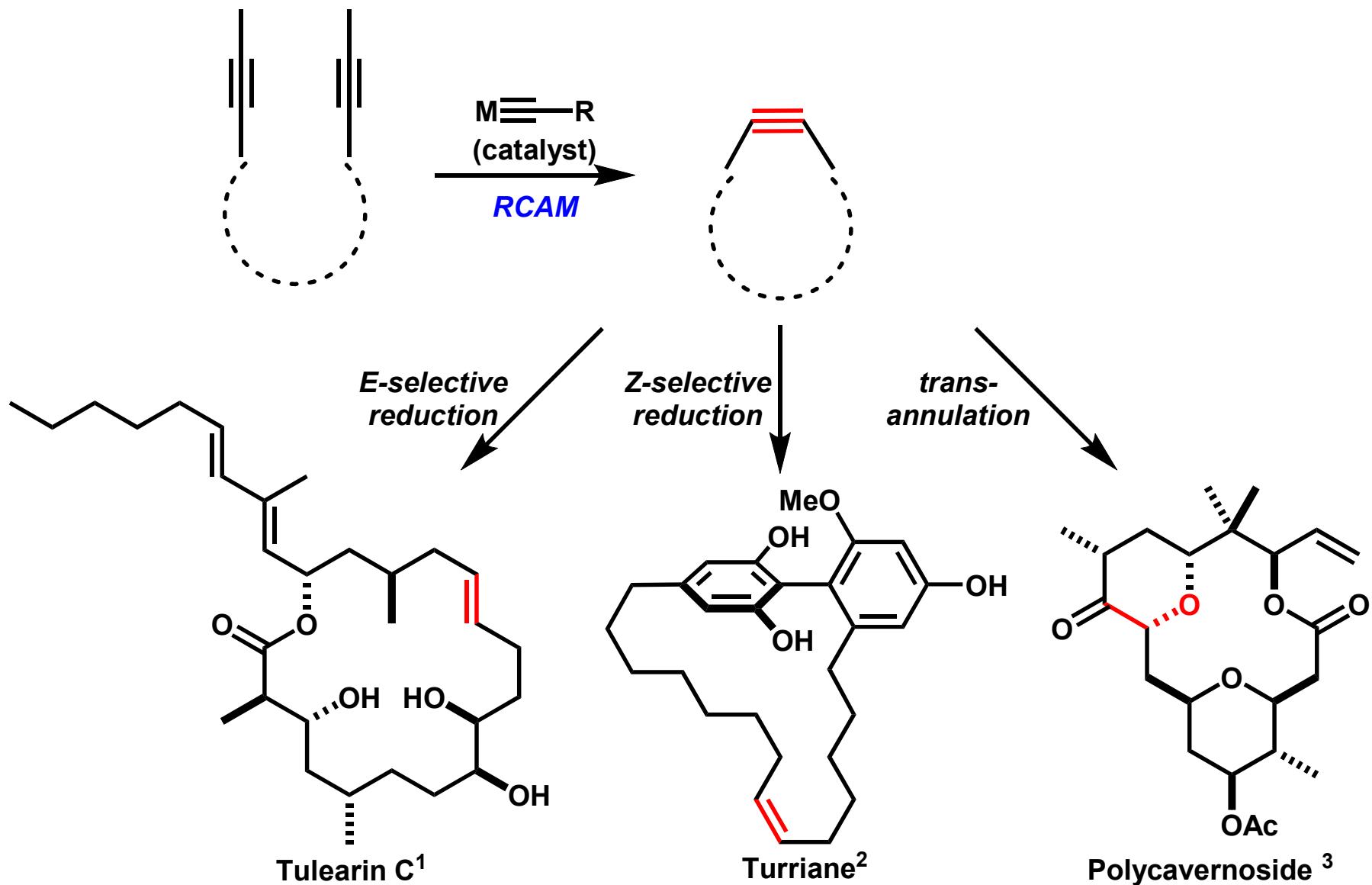
Fürstner's strategy



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- 1. Introduction**
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Ring-closing alkyne metathesis (RCAM)

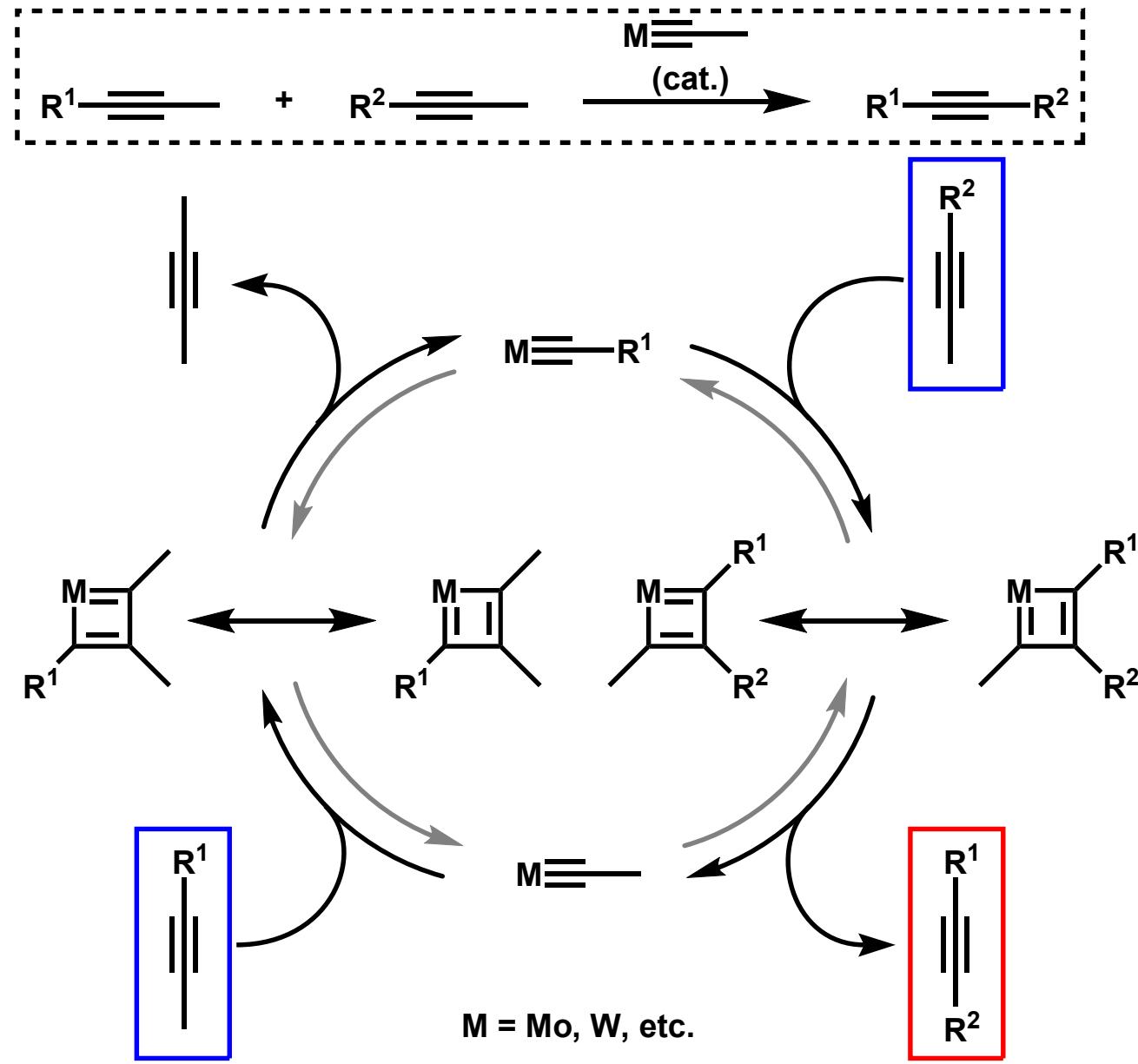


1. Lehr, K.; Mariz, R.; Leseurre, L.; Gabor, B.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 11373

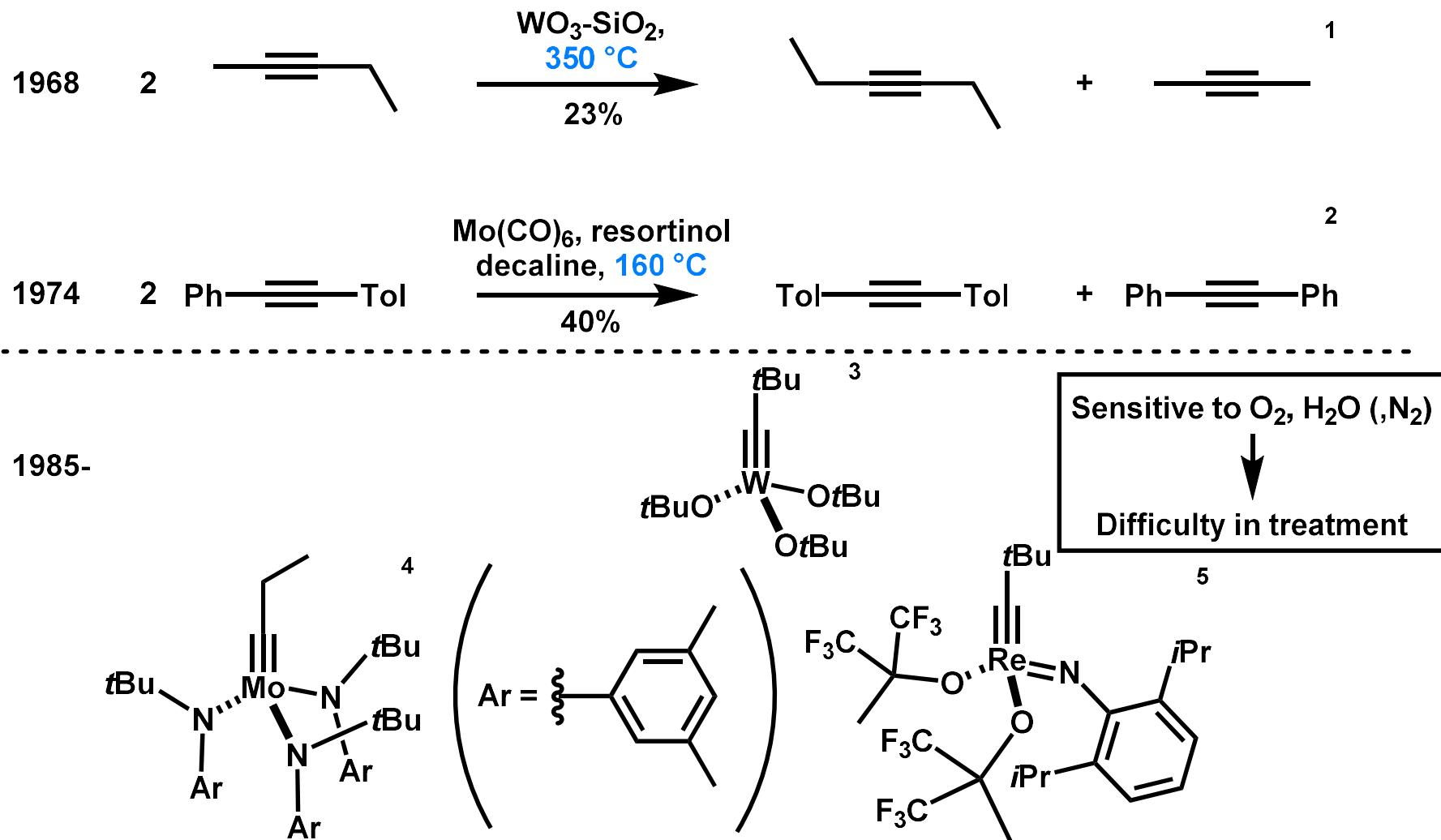
2. Fürstner, A.; Stelzer, F.; Rumbo, A.; Kraus, H. *Chem. Eur. J.* **2002**, *8*, 1856

3. Brewitz, L.; Llaveria, J.; Yada, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 4532

General mechanism of Alkyne metathesis

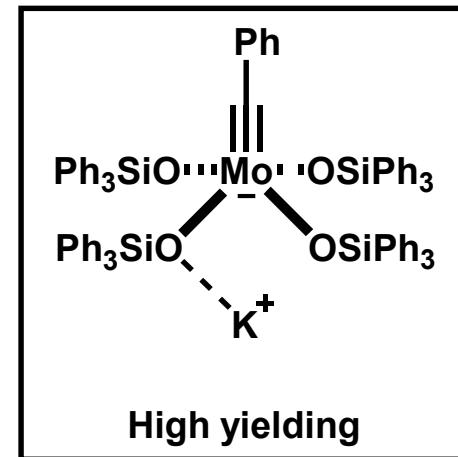
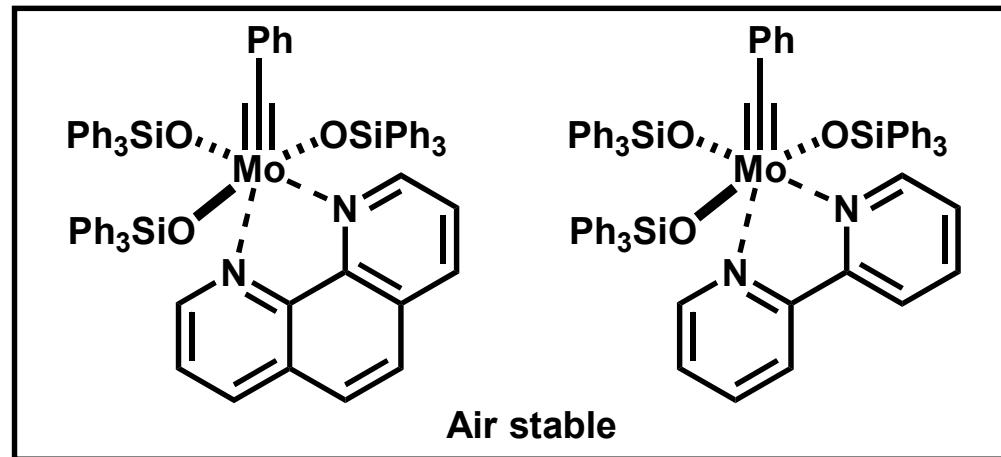
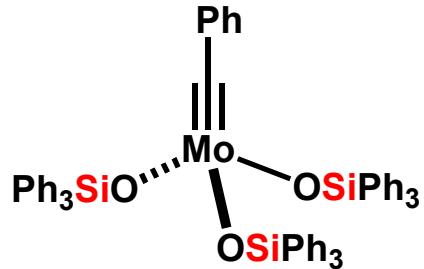


Catalysts used in alkyne metathesis



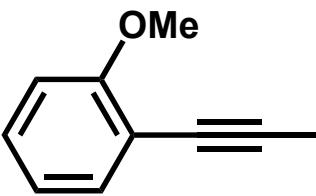
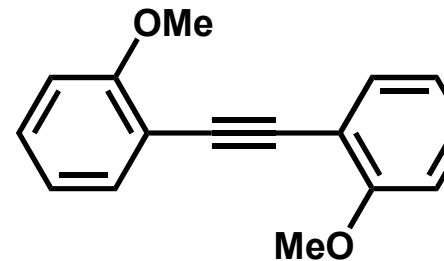
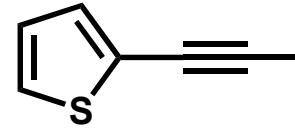
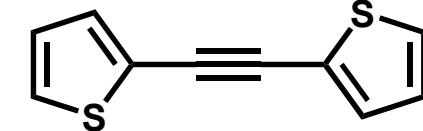
- Pennella, F.; Banks R. L.; Bailey, G. C. *Chem. Commun.*, **1968**, 1548.
- Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 787
- Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, 4, 74
- W. Zhang, S. Kraft, J. S. Moore, *J. Am. Chem. Soc.* **2004**, 126, 329
- Weinstock, I. A.; Schrock, R. R.; Davis, W. M. *J. Am. Chem. Soc.* **1991**, 113, 135.

Ar₃SiO group as a ligand



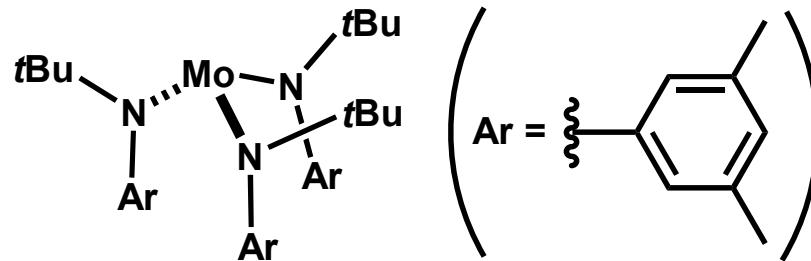
Heppekausen, J.; Stade, R.; Kondoh, A.; Seidei, G.; Goddard, R.; Fürstner, A. *Chem. Eur. J.* **2012**, *18*, 10281

Comparison of yield (Homodimerization)

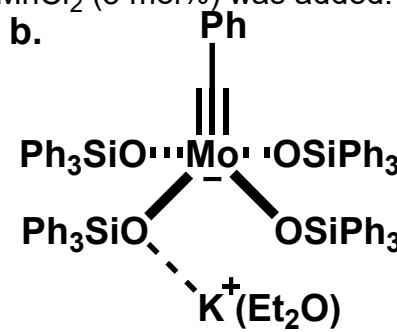
entry	Substrate	product	a ^a	b ^b	c ^{b,c}
1			68%	97%	97%
2			0%	88%	87%

a. The catalyst was activated by CH₂Cl₂. b. 5 Å MS was added. c. MnCl₂ (5 mol%) was added.

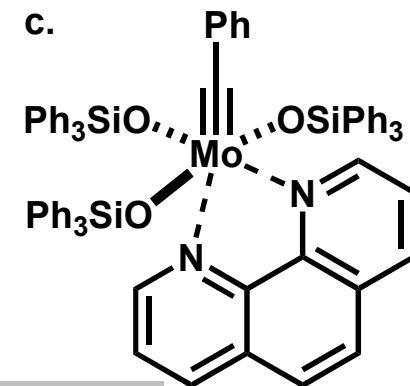
a.



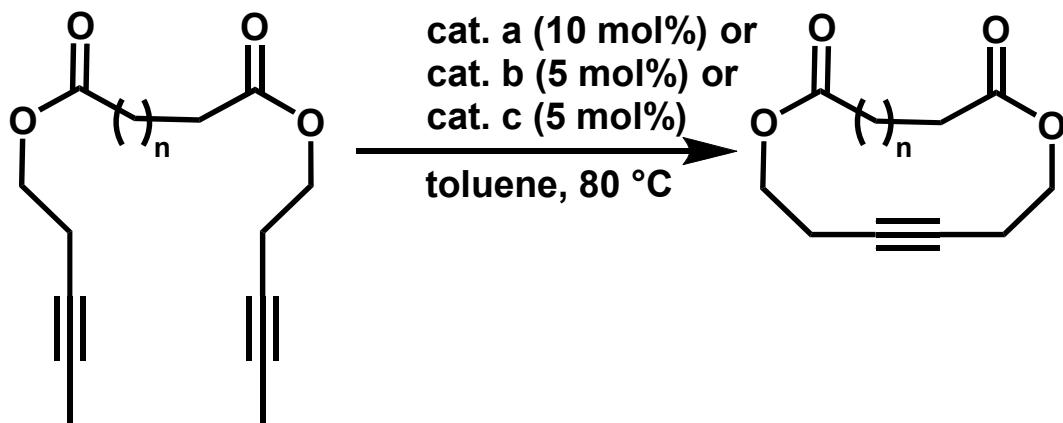
b.



c.

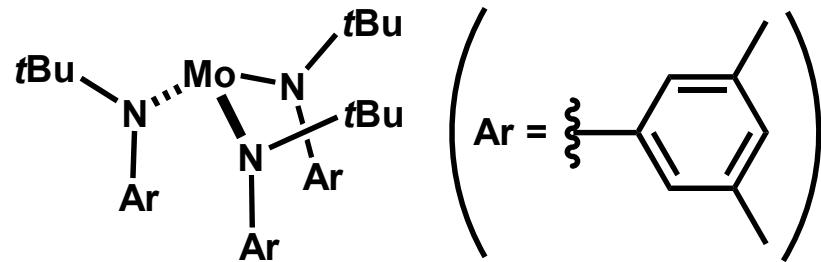


Application to RCAM

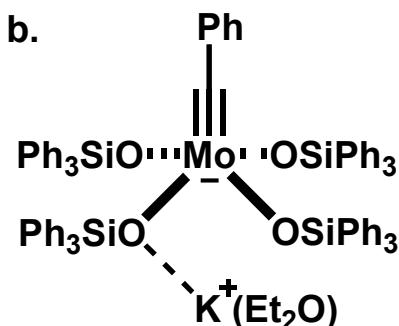


entry	n	a ^a	b ^b	c ^{b,c}
1	1	91%	73%	78%
2	3	81%	92%	90%

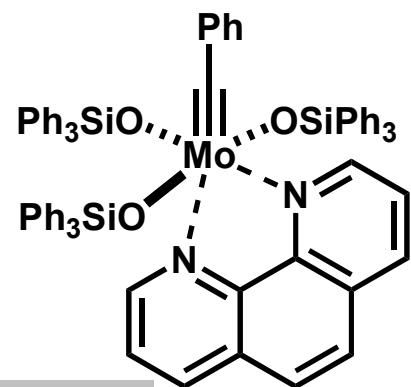
a.



b.



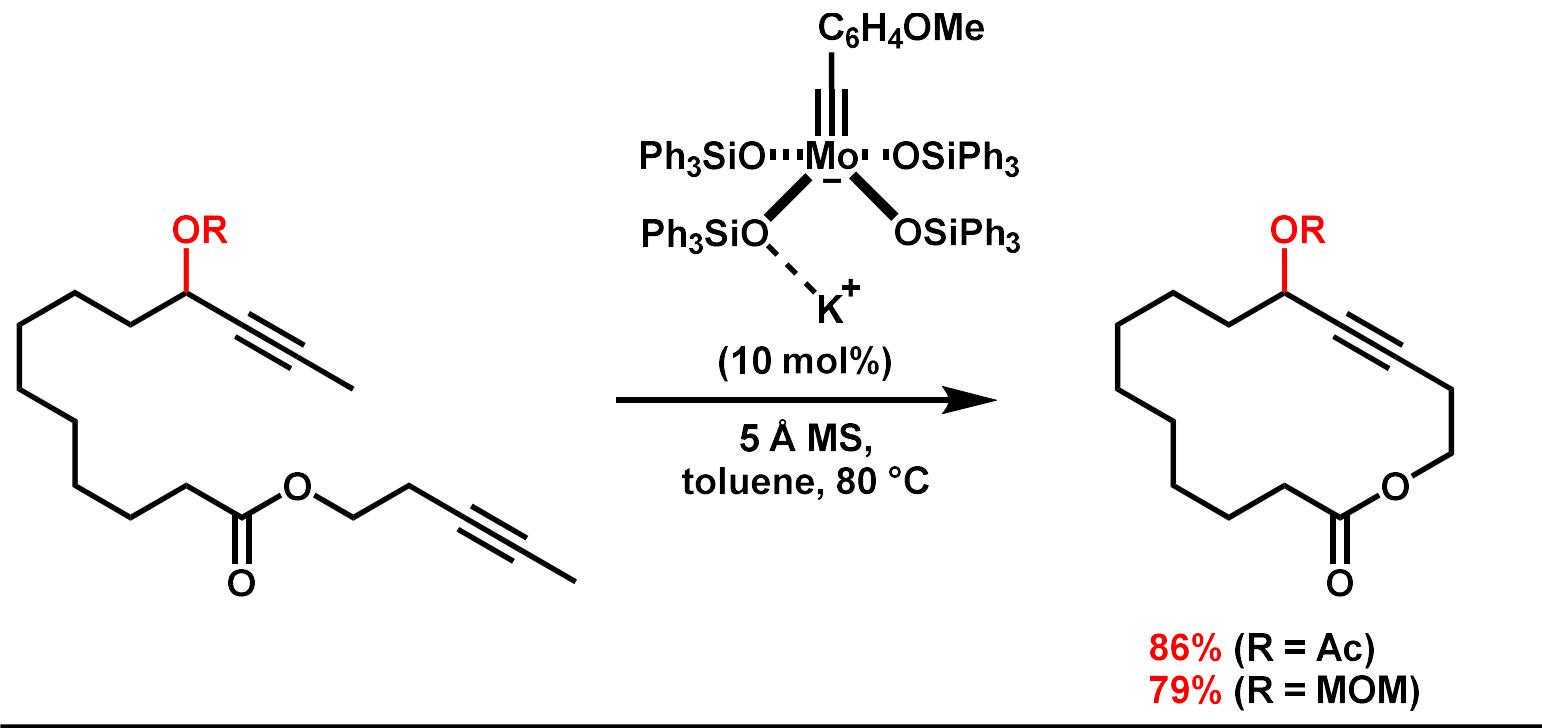
c.



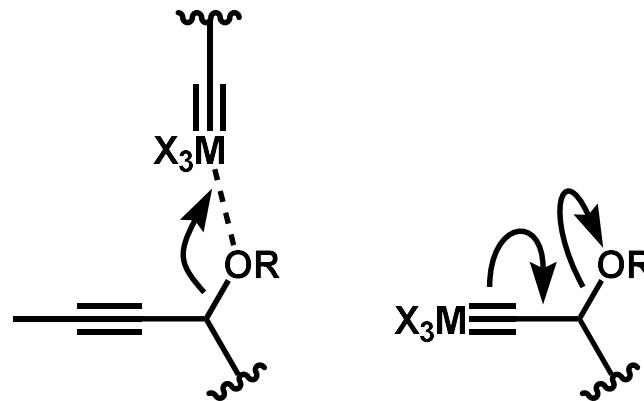
1. Fürstner, A.; Mathes, C.; Lehmann, C. W. *Chem. Eur. J.* **2001**, *7*, 5299

2. Heppekausen, J.; Stade, R.; Kondoh, A.; Seidei, G.; Goddard, R.; Fürstner, A. *Chem. Eur. J.* **2012**, *18*, 10281

Application to propargyl alcohol derivatives



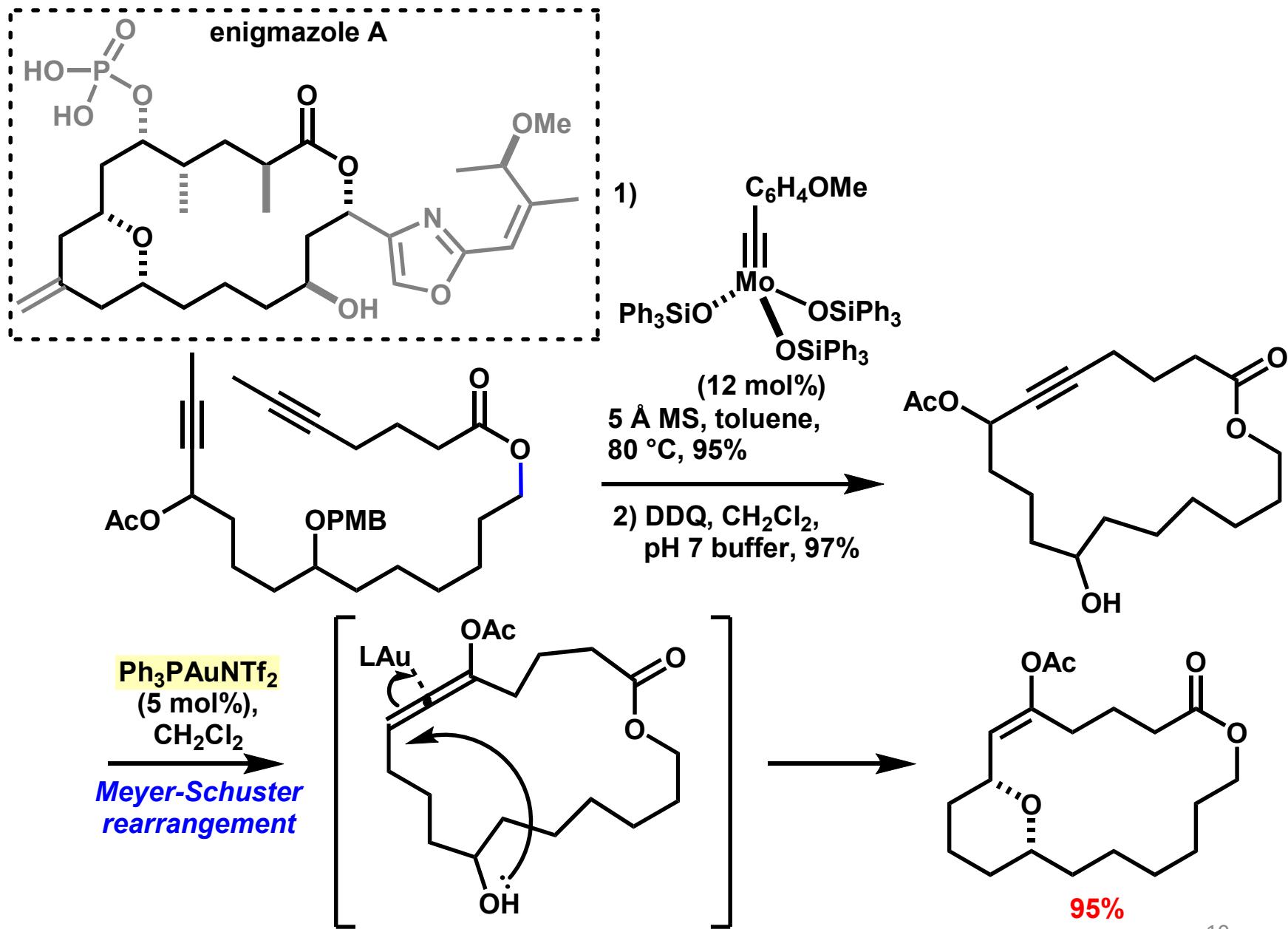
Possible decomposition pathway



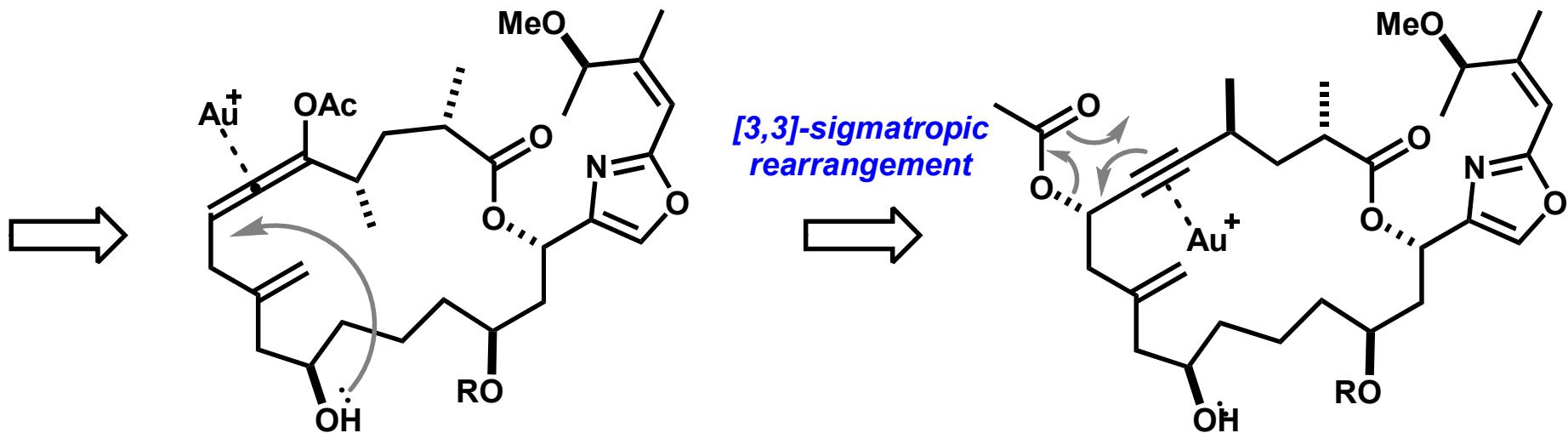
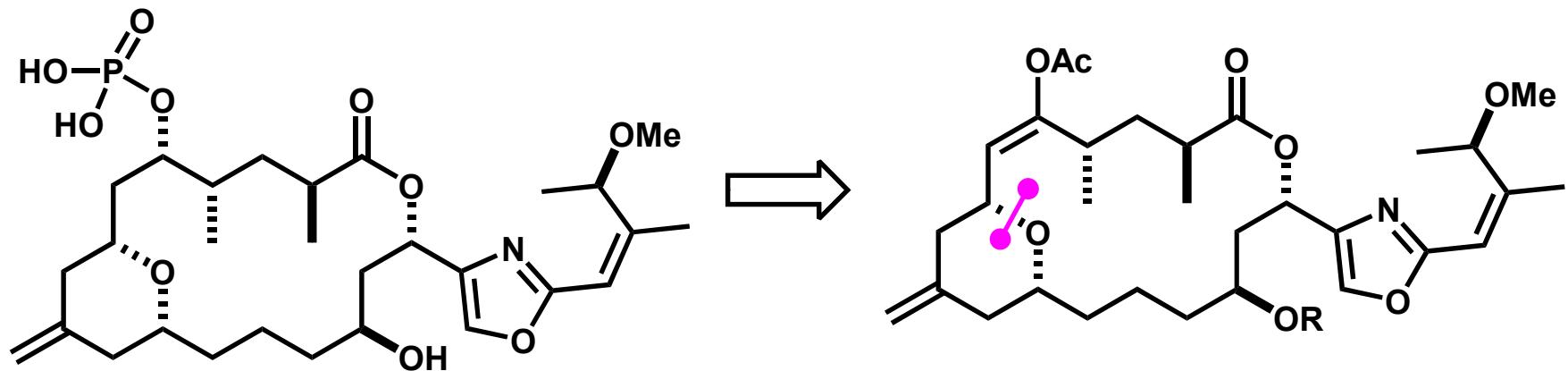
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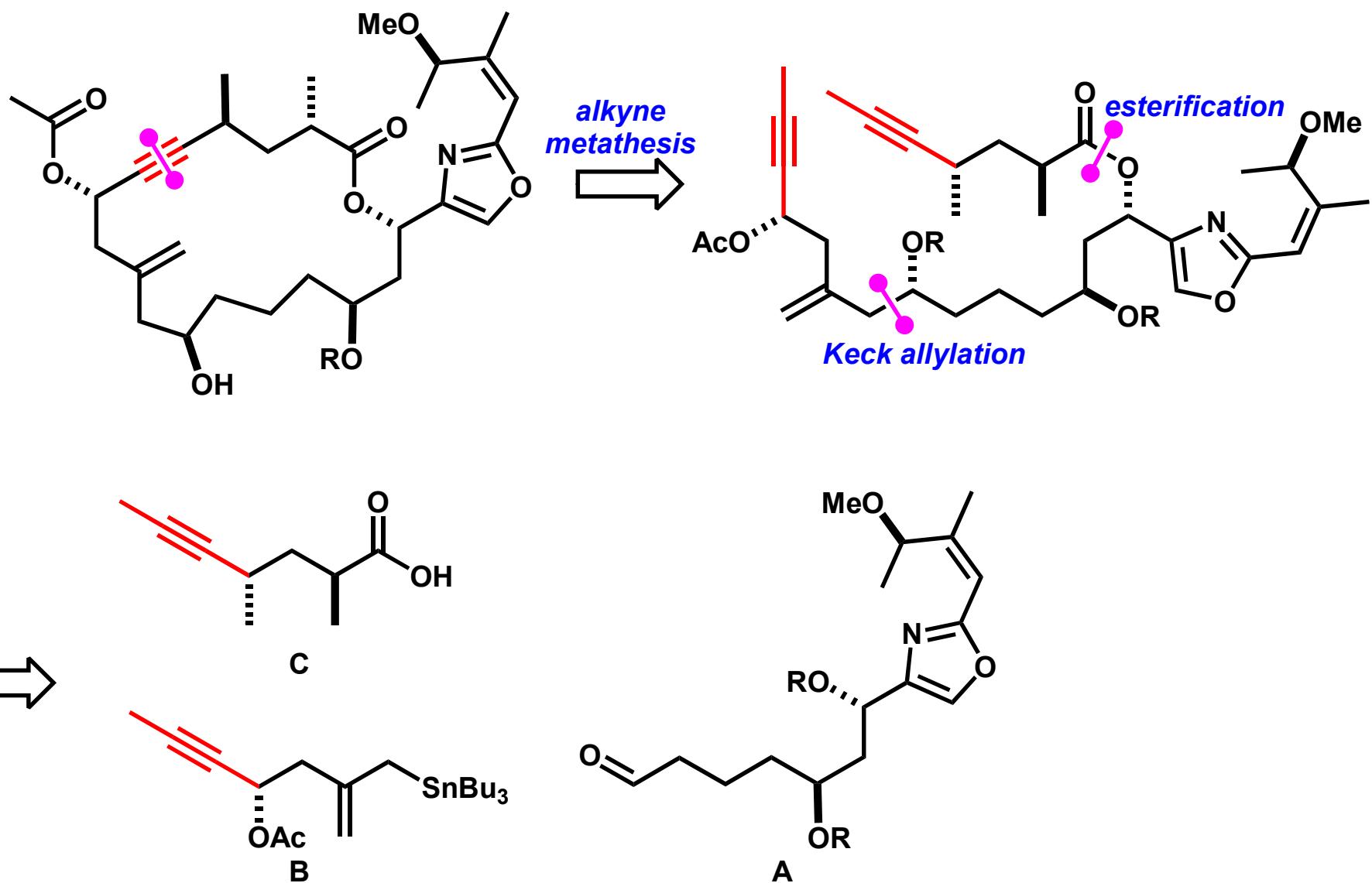
Model experiment



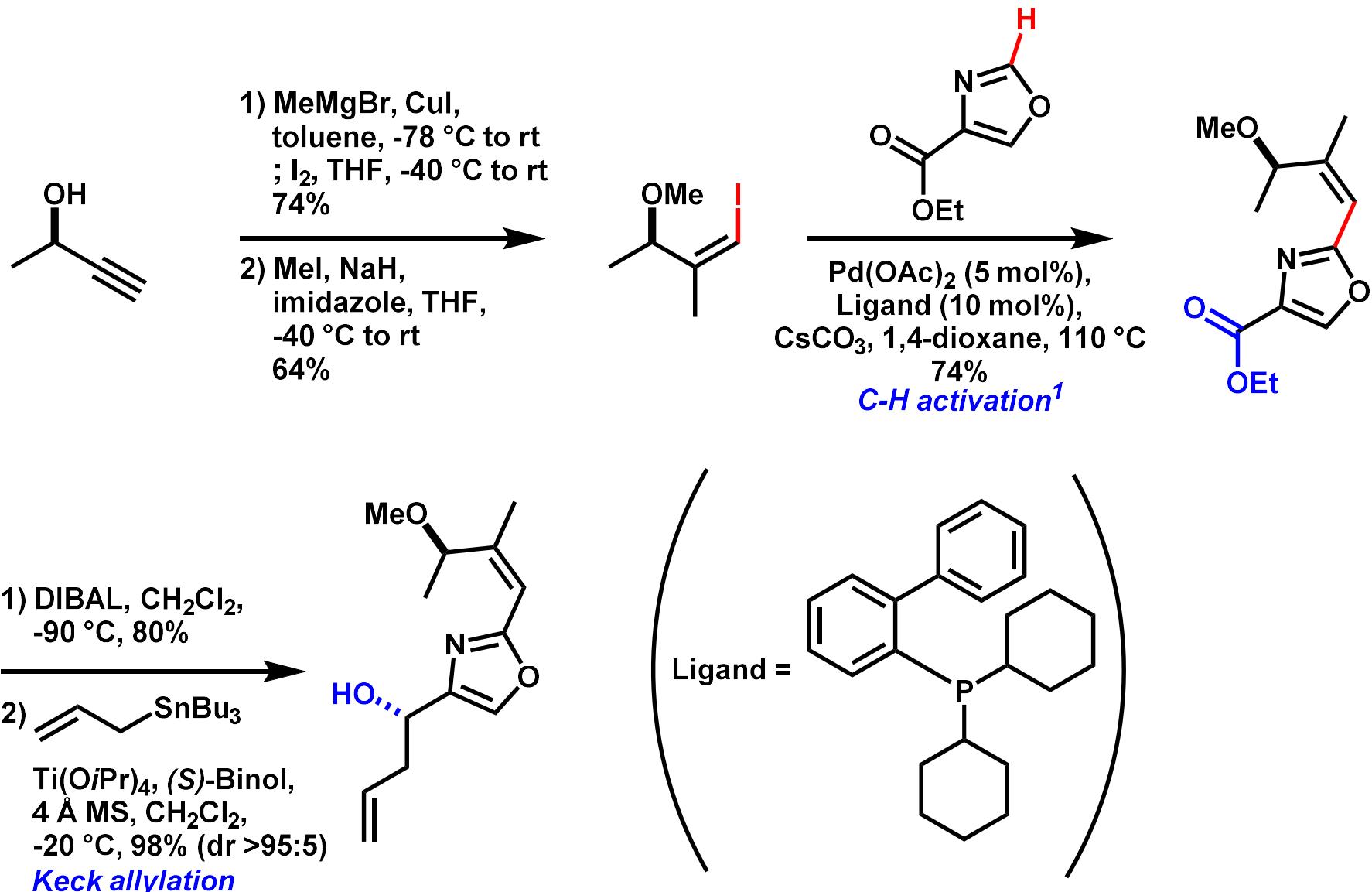
Retrosynthesis by Fürstner (1)



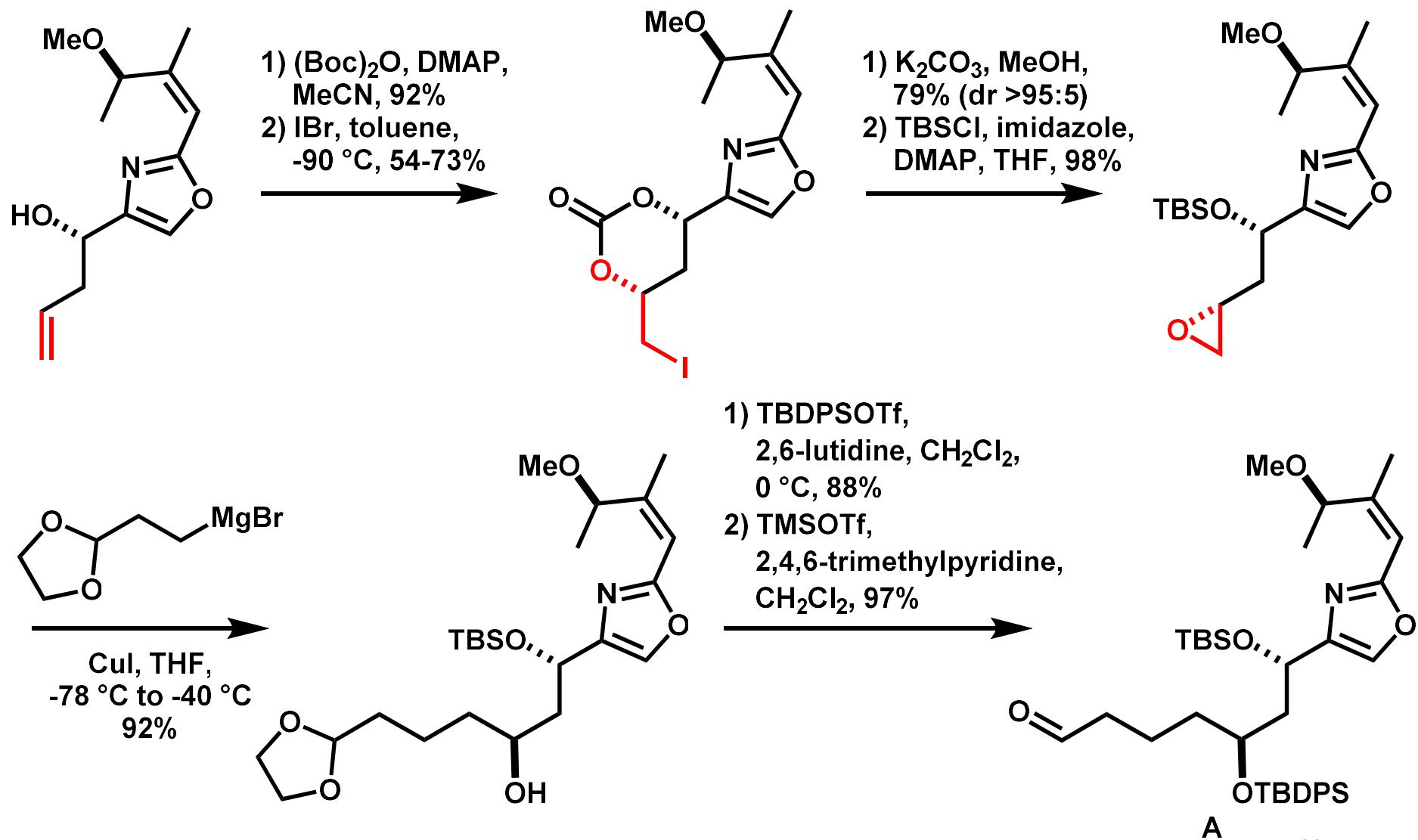
Retrosynthesis by Fürstner (2)



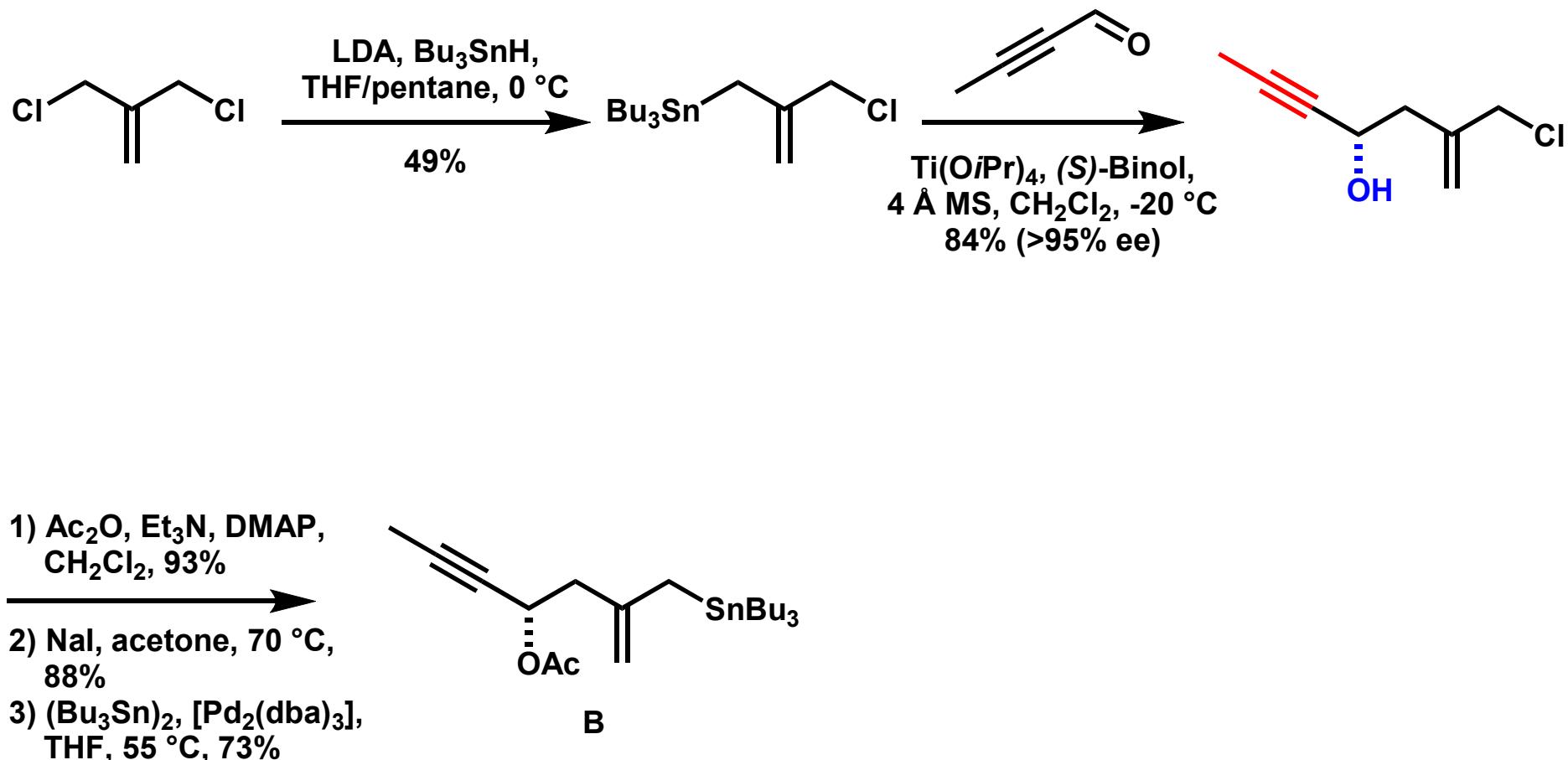
Synthesis of fragment A(1)



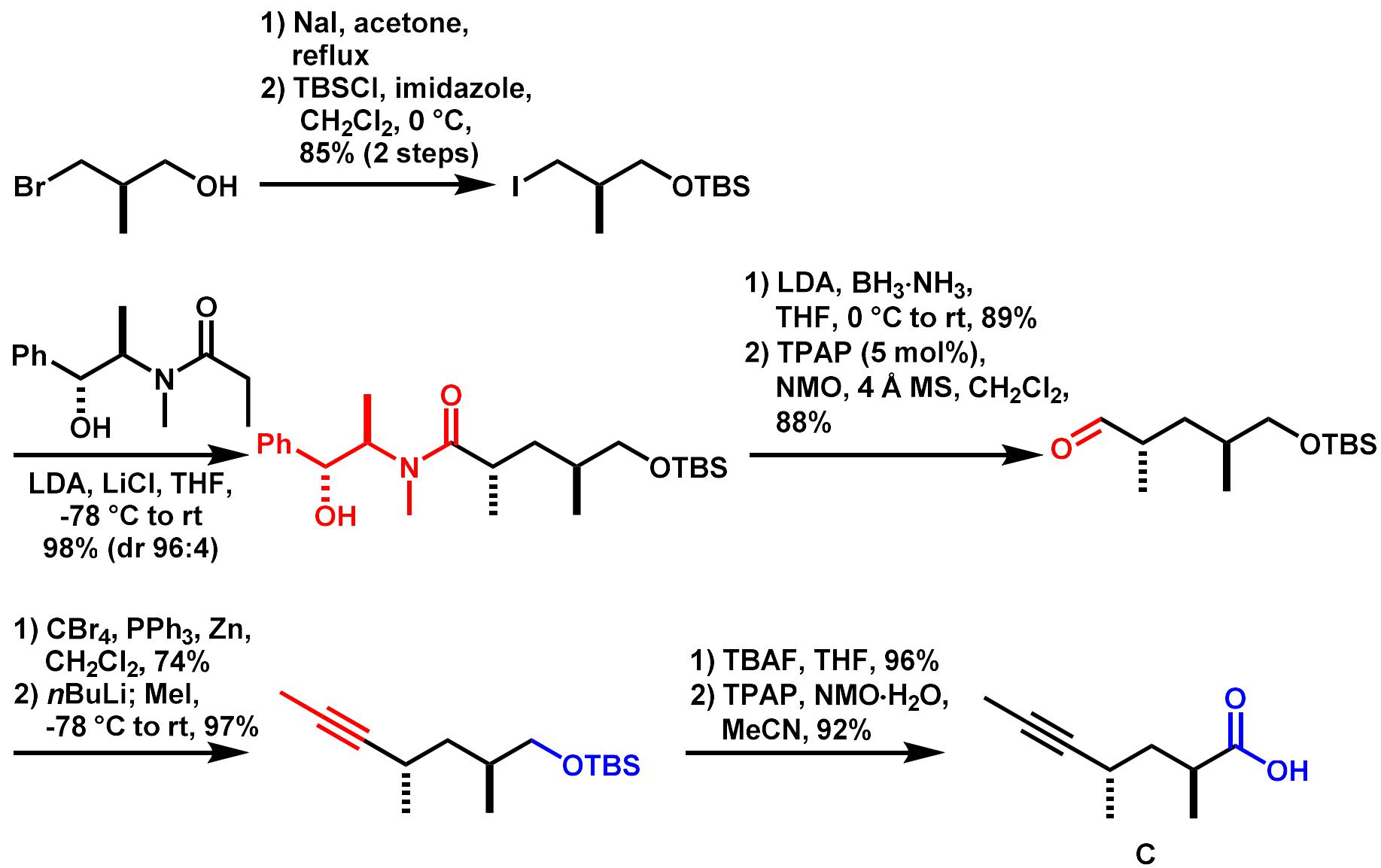
Synthesis of fragment A (2)



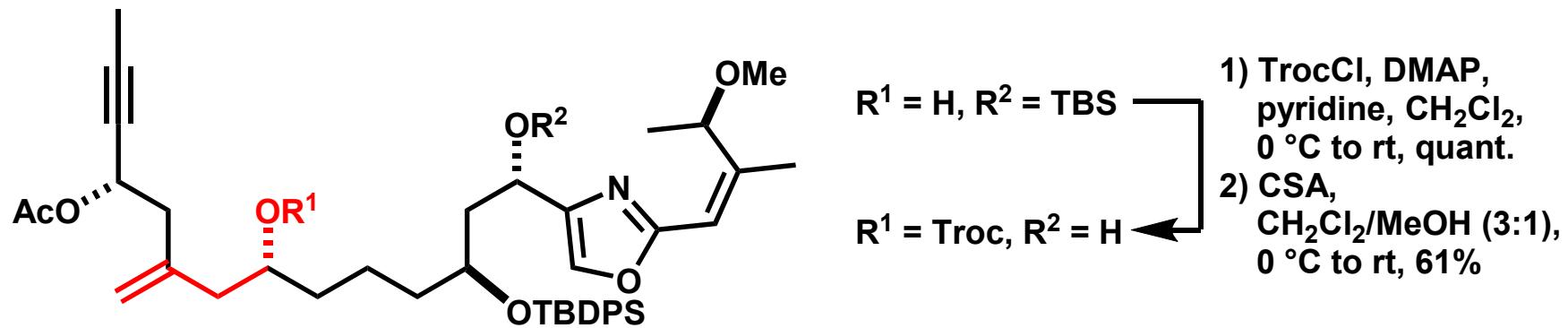
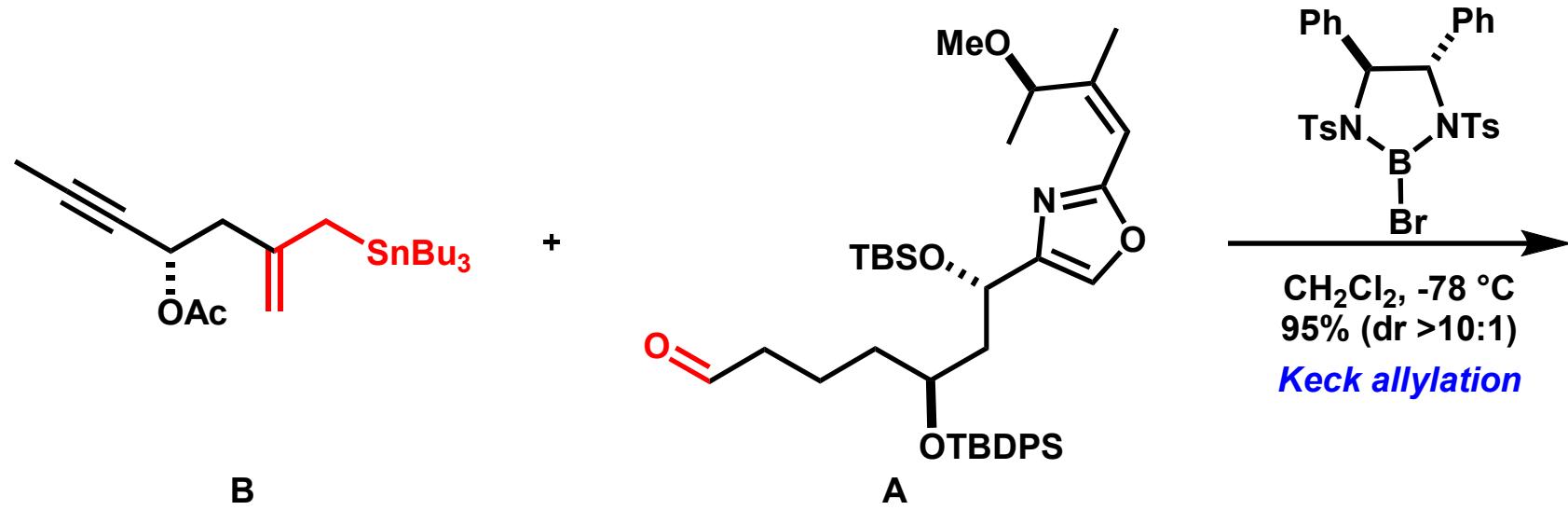
Synthesis of fragment B



Synthesis of fragment C

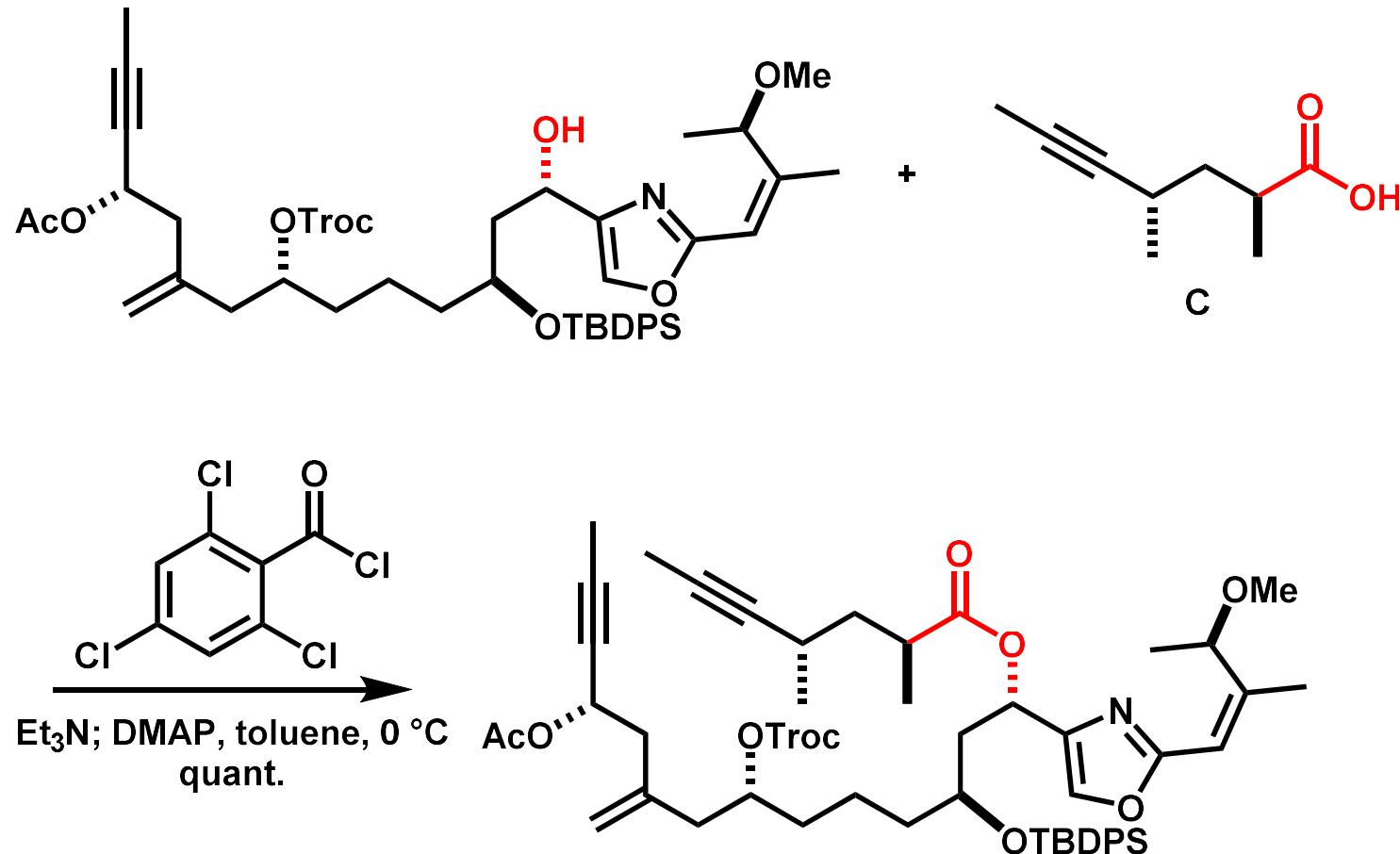


Fragments Connection (1)

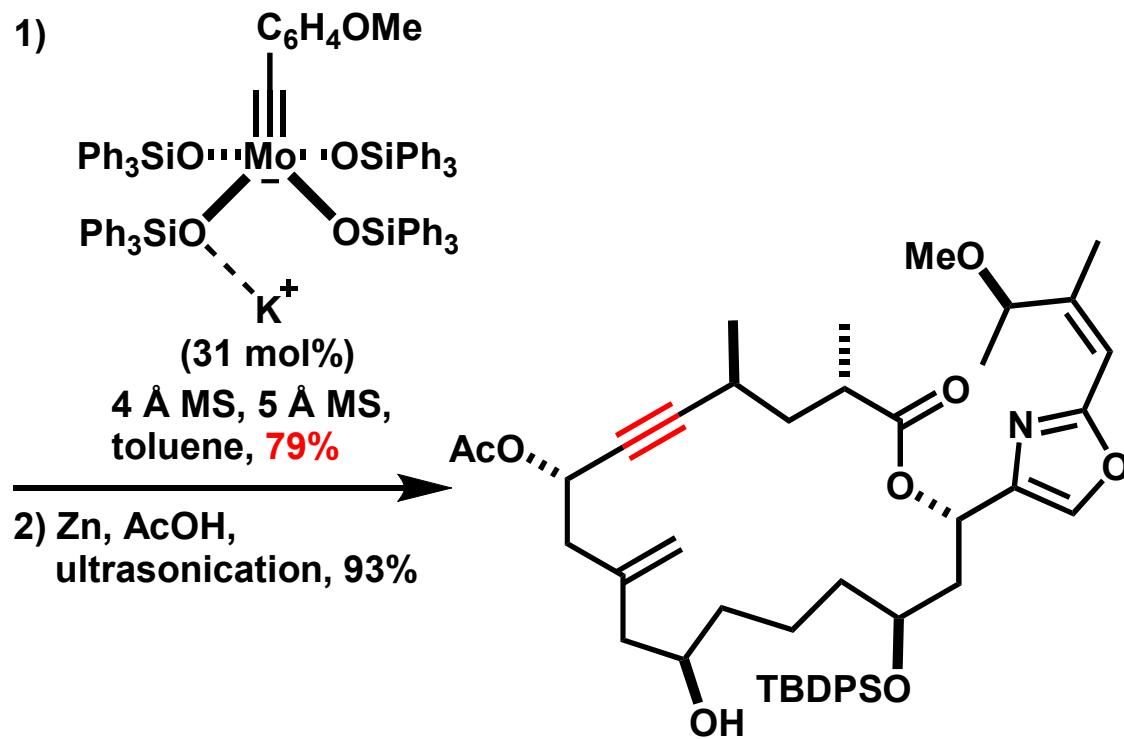
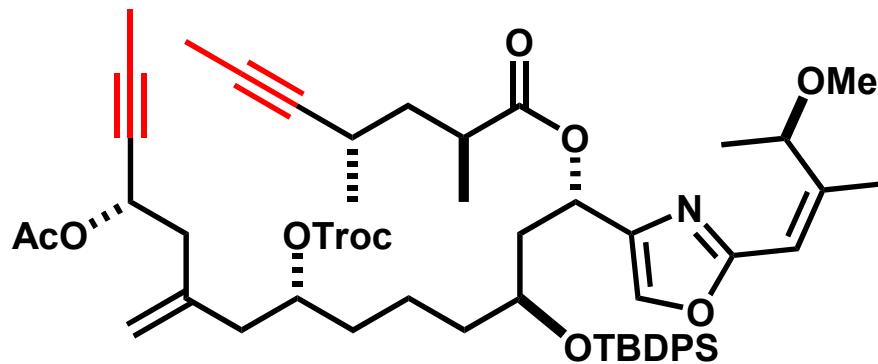


1. Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *111*, 5495

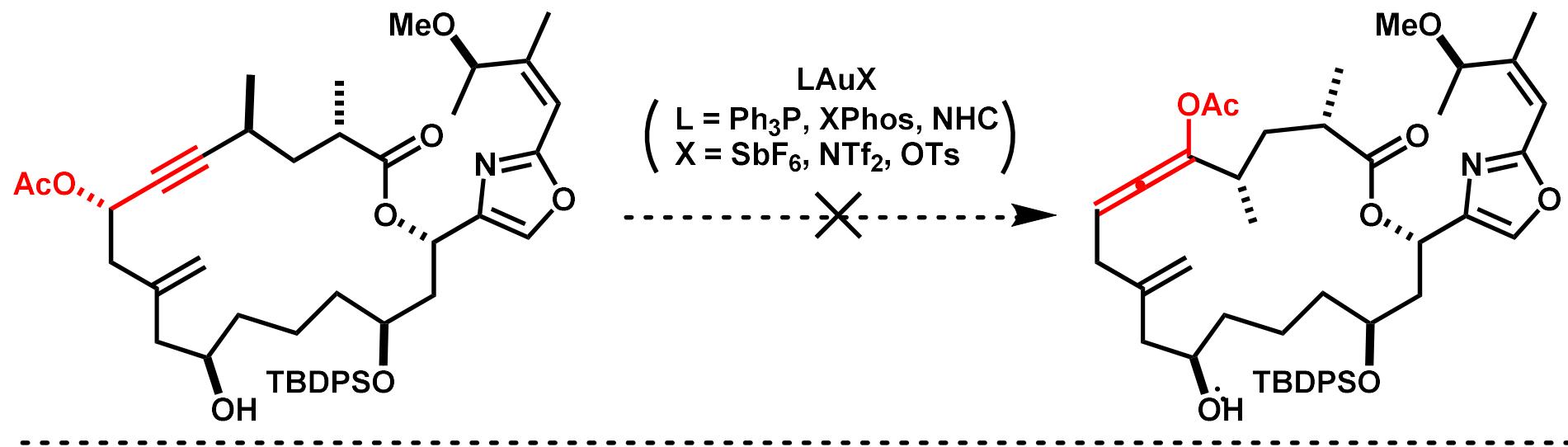
Fragments Connection (2)



Ring-Closing Alkyne metathesis (RCAM)

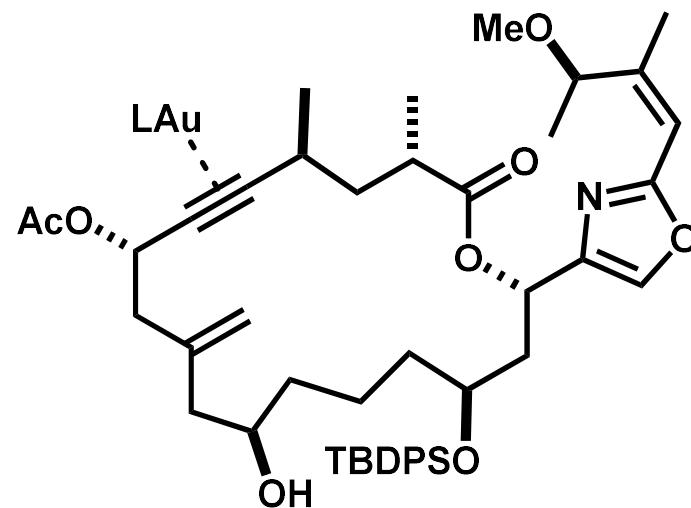


Attempt at [3,3]-sigmatropic rearrangement

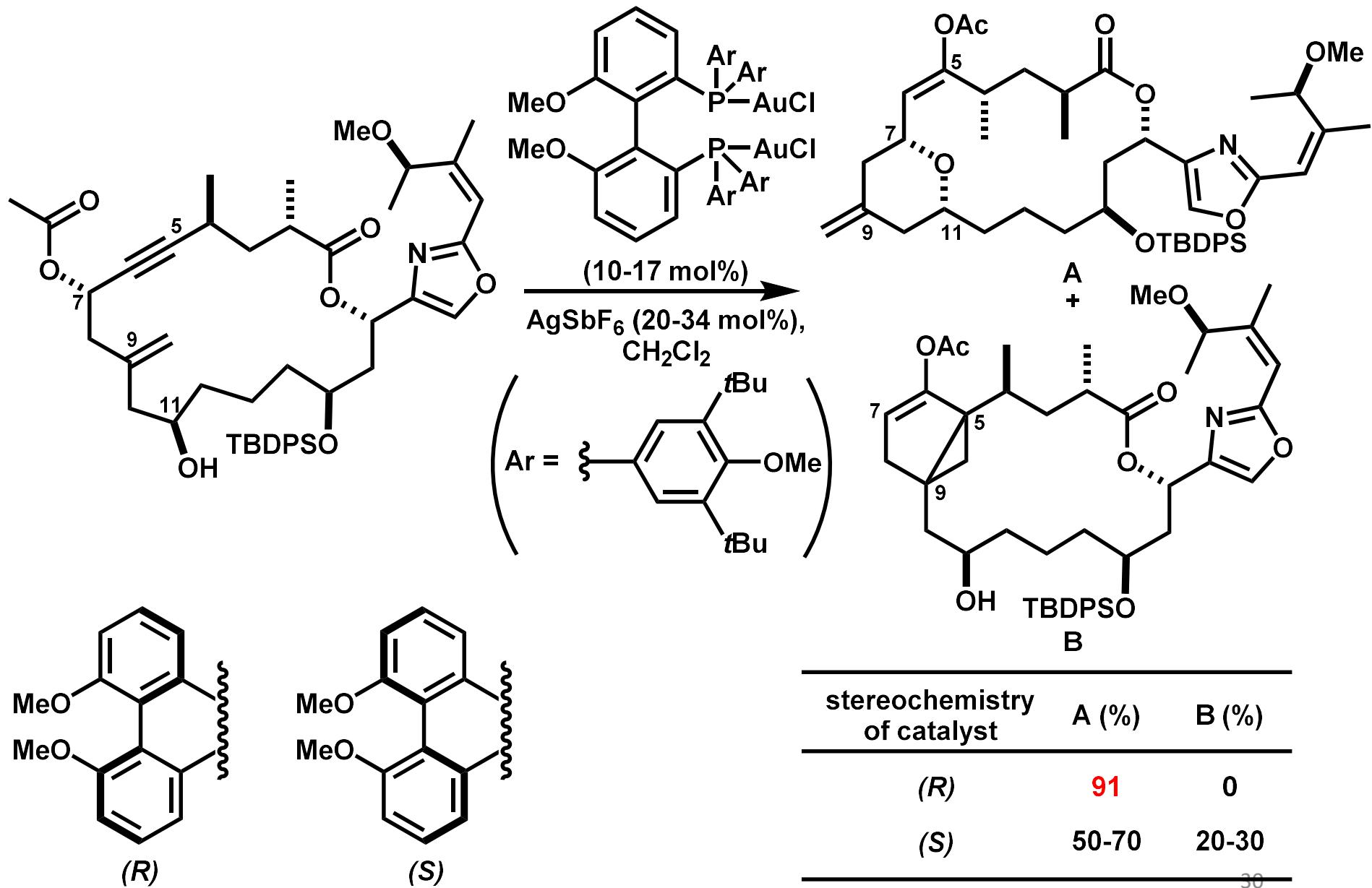


Author's hypothesis

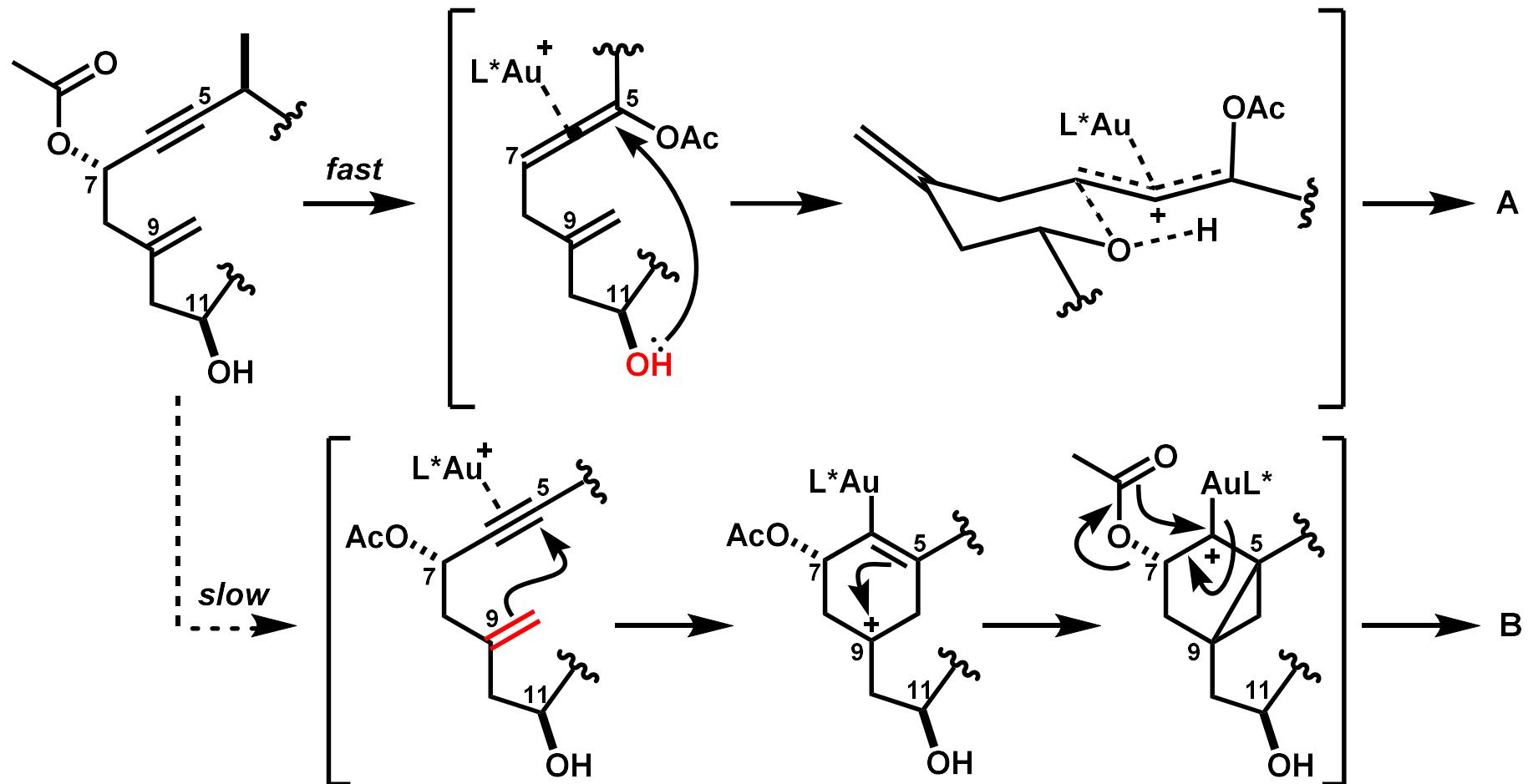
- The initial complex is diastereomeric.
- There is Match / mismatch problem between substrate and catalyst.
- Chiral ligands are needed.



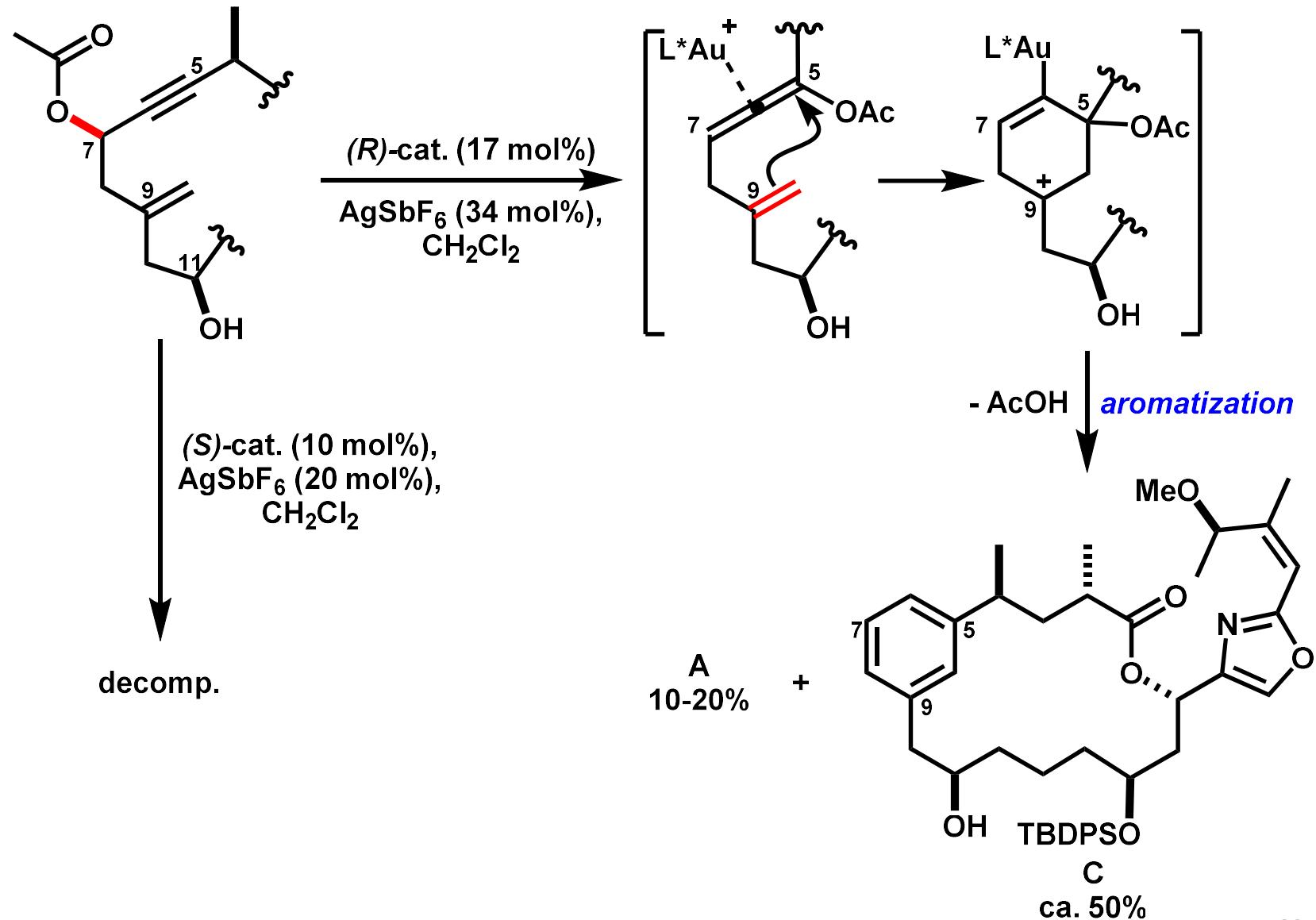
Effect on stereochemical pairing (1)



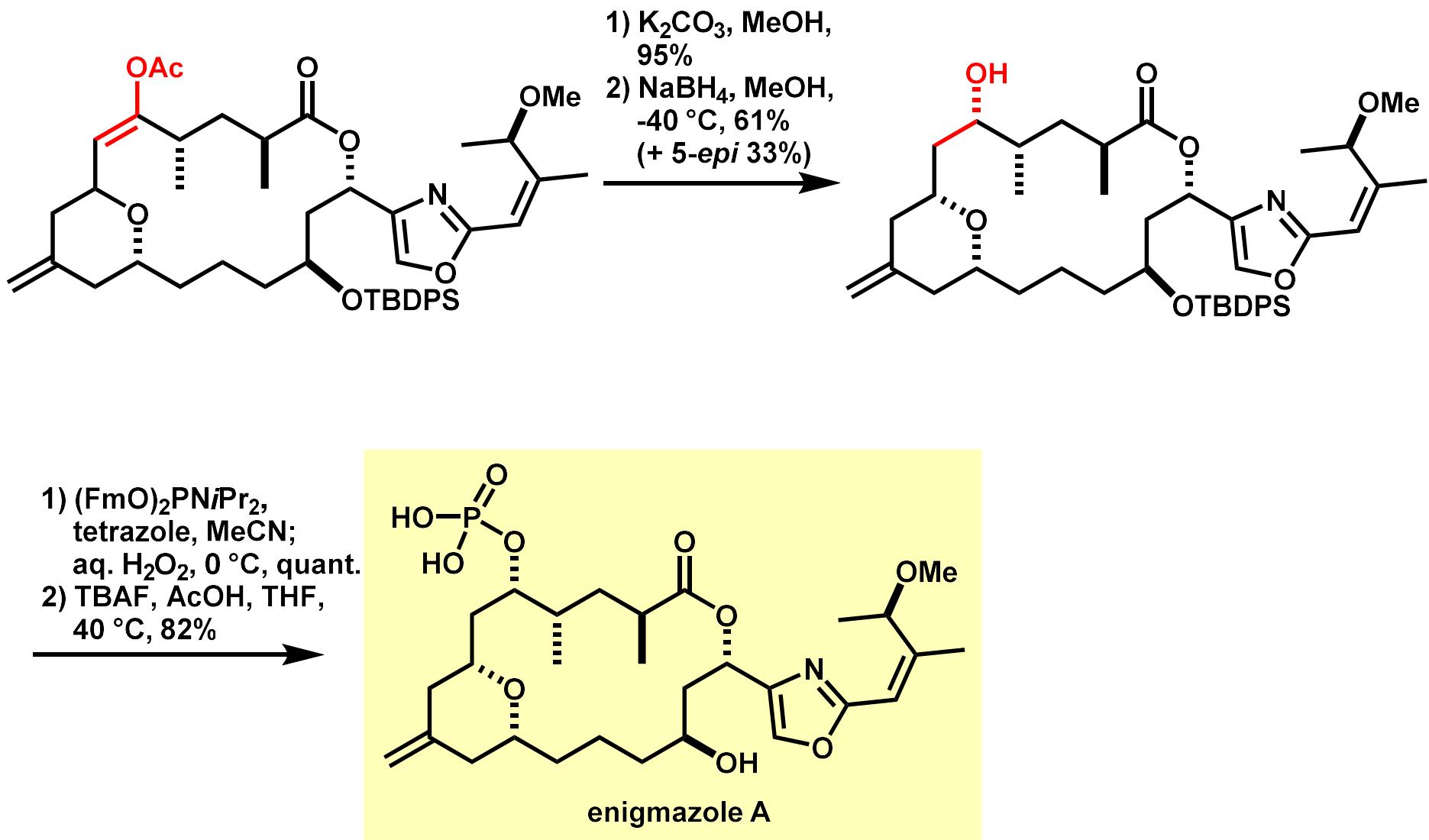
Mechanism of producing A and B



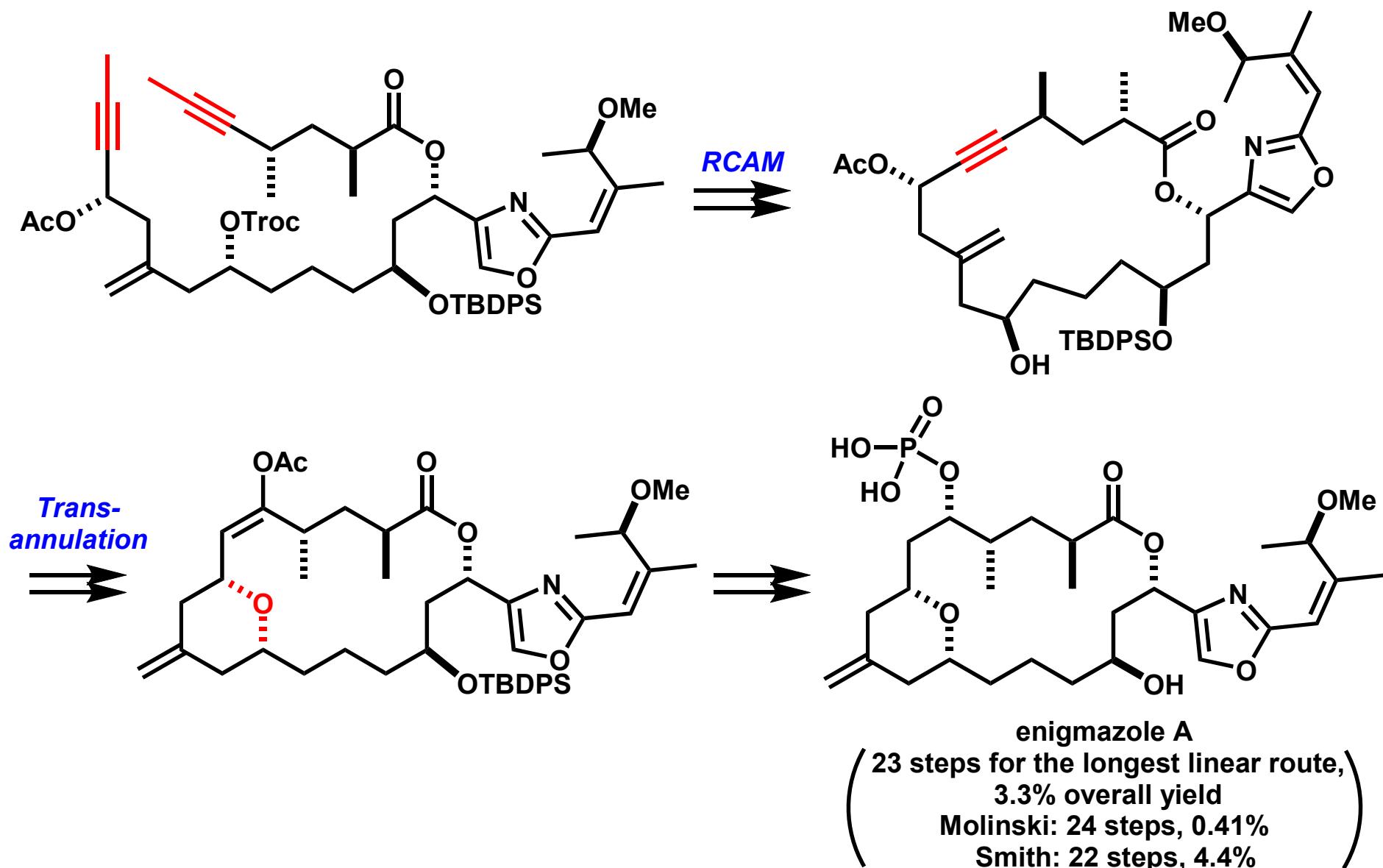
Effect on stereochemical pairing (2)



Completion of total synthesis

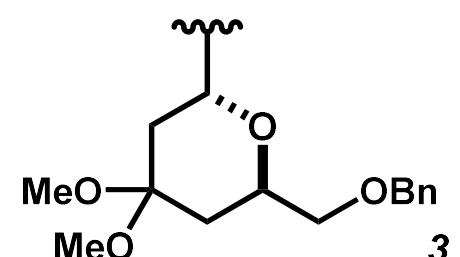
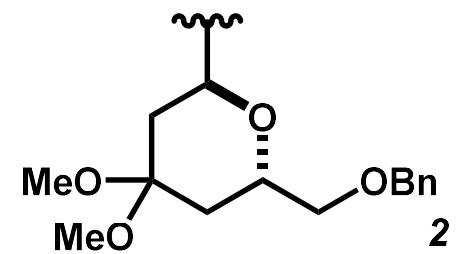
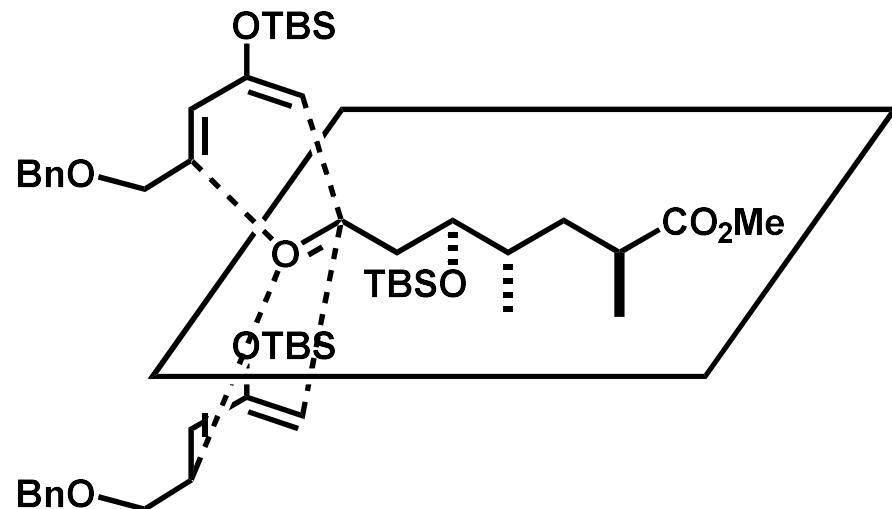
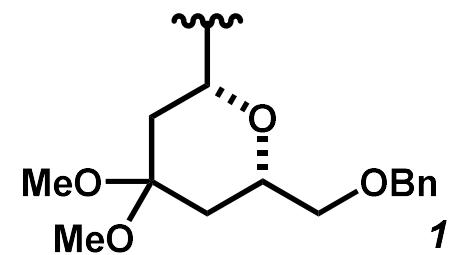
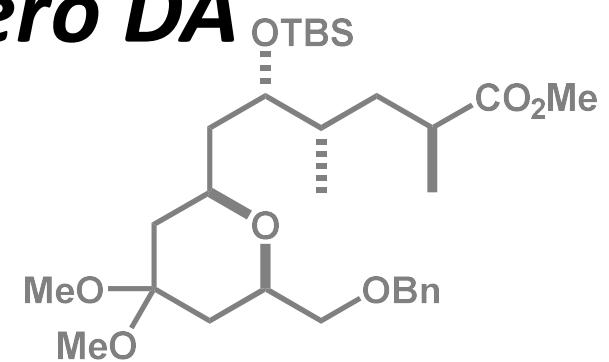
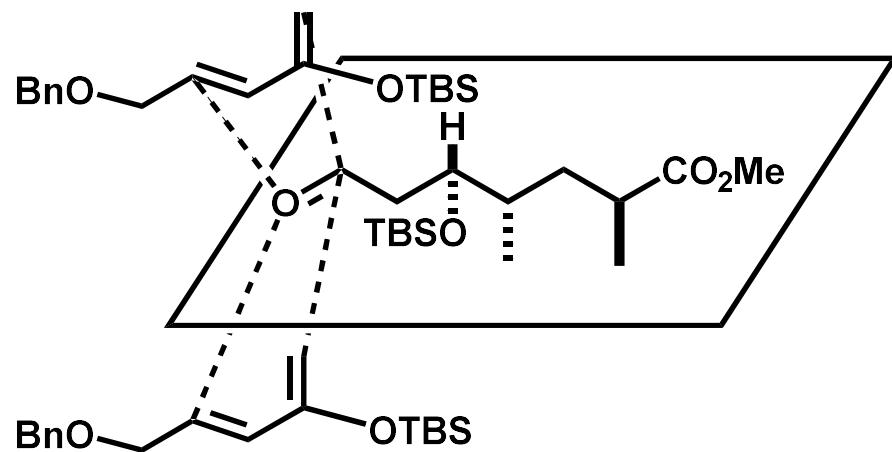


Summary

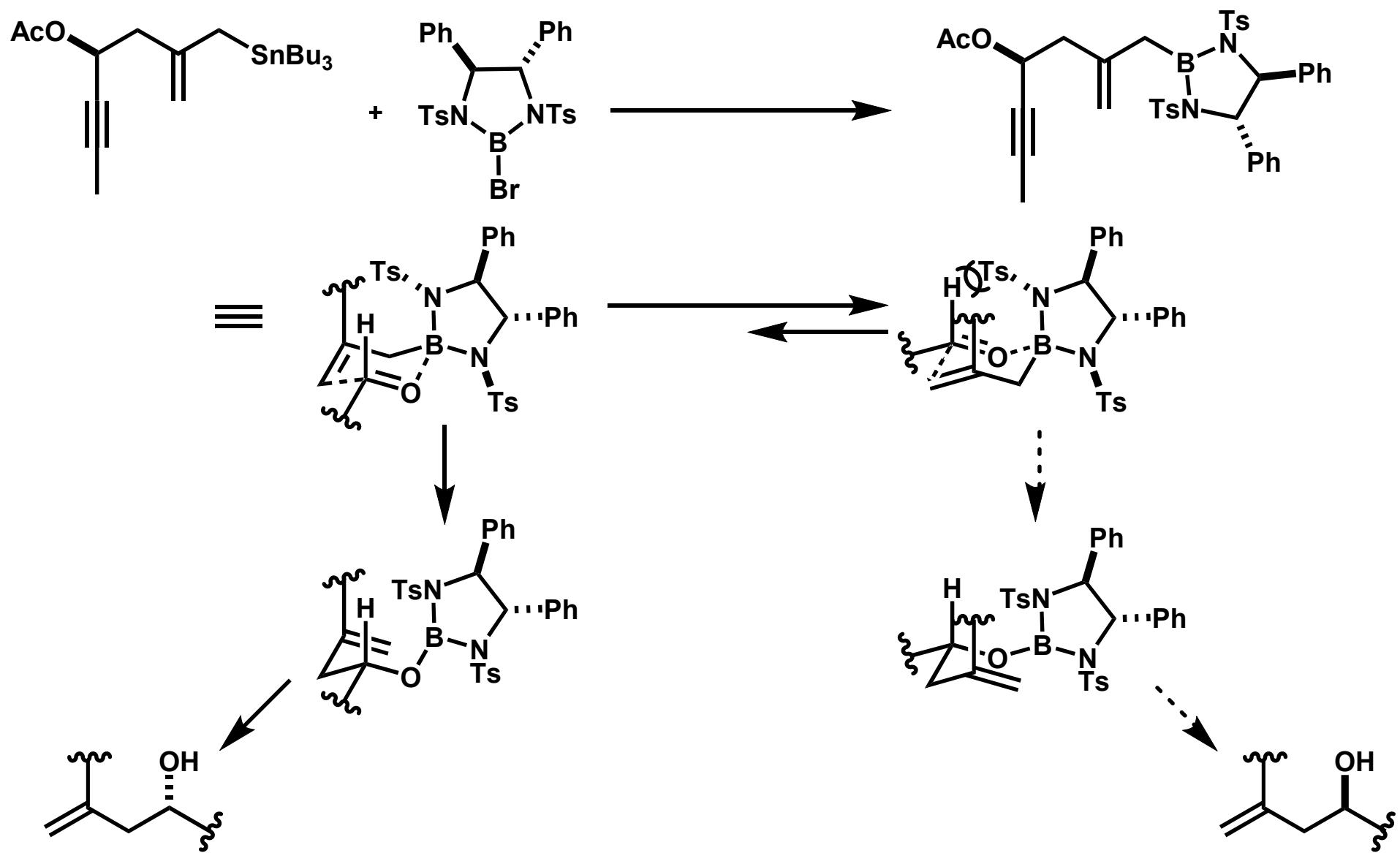


Appendix

Stereoselectivity at Hetero DA



Stereoselectivity at Keck allylation



X-ray crystal Structure of Mo catalyst

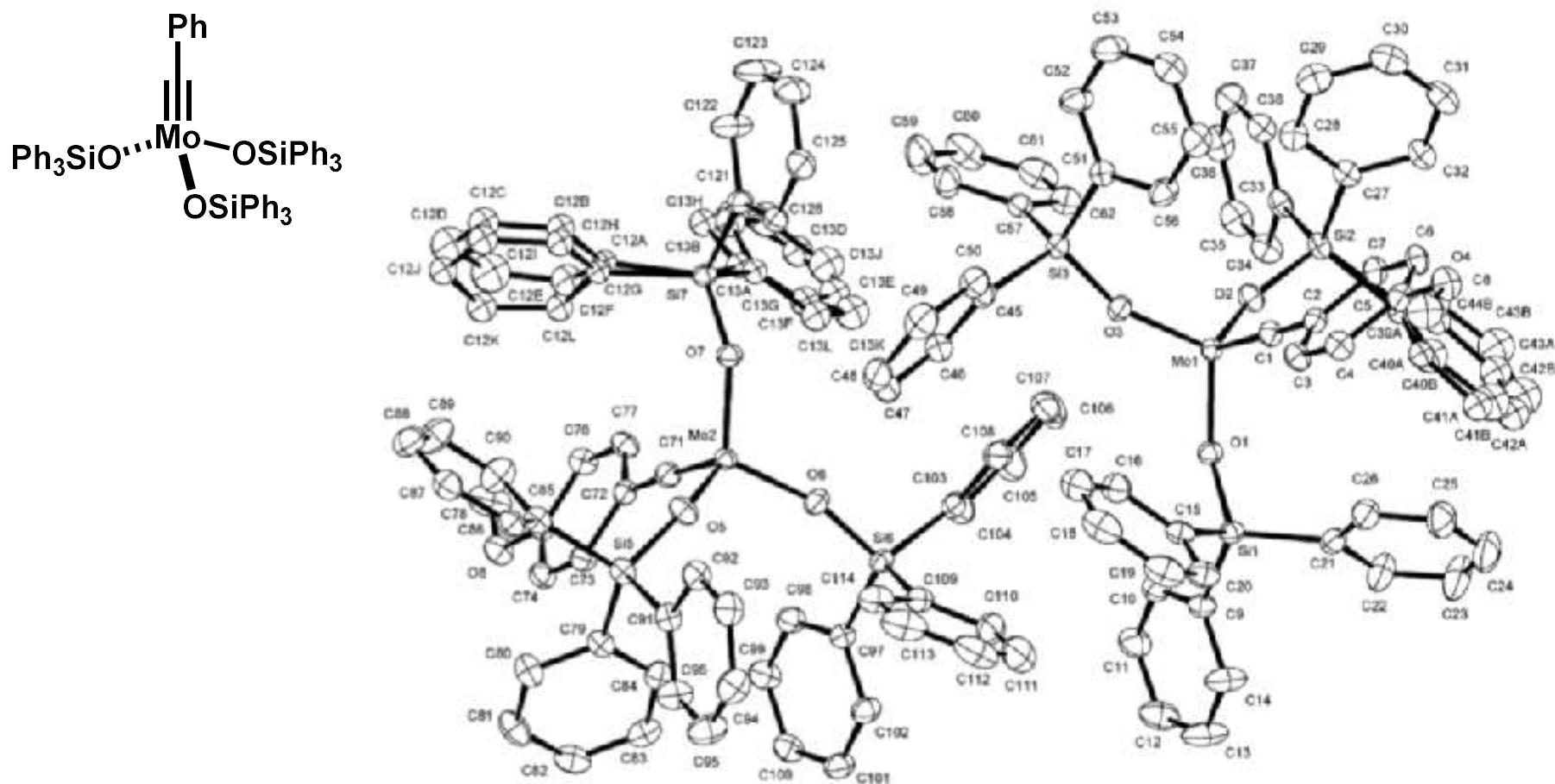


Figure 5. Structure of the two independent molecules of the donor-free alkylidyne complex **32** in the solid state. Selected bond lengths [Å] and angles [°]: Mo1—C1 1.745(1), Mo2—C71 1.747(1), C2-C1-Mo1 175.8(1), C72-C71-Mo2 175.3(1), Si1-O1-Mo1 141.3(1), Si2-O2-Mo1 147.7(1), Si3-O3-Mo1 159.5(1), Si5-O5-Mo2 149.9(1), Si6-O6-Mo2 162.9(1), Si7-O7-Mo2 142.5(1).

Heppekausen, J.; Stade, R.; Kondoh, A.; Seidei, G.; Goddard, R.; Fürstner, A. *Chem. Eur. J.* **2012**, *18*, 10281