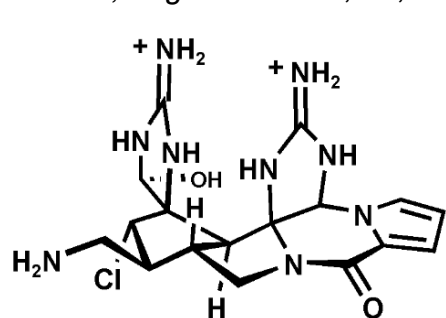


Enantioselective Total Synthesis of (+)-KB343

C. Bi, Y. Wang, C. He, P. S. Baran, *J. Am. Chem. Soc.* **2023**, *145*, 7753.

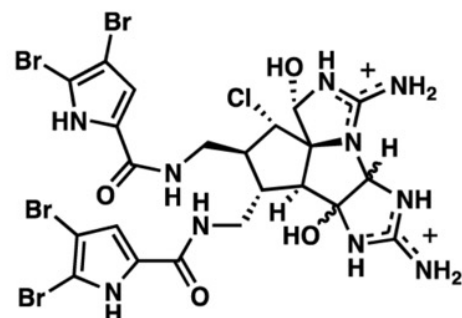
(+)-KB343, complex guanidinium toxin, was isolated in 2018 from a zoantharian “*epizoanthus illoricatus*”, off the coast of the republic of Palau.

R. Sakai, *Org. Lett.* **2018**, *20*, 3039.



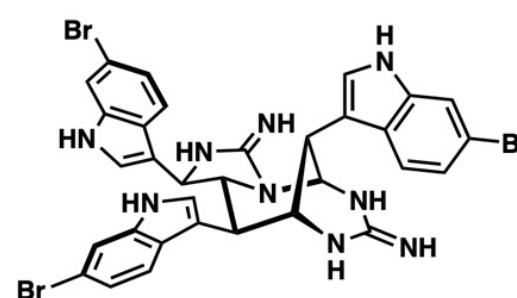
Palau' amine

P. S. Baran,
Angew. Chem. Int. Ed. **2010**, *49*, 1095.
J. Am. Chem. Soc. **2011**, *133*, 14710.



Axinellamine

P. S. Baran,
J. Am. Chem. Soc. **2011**, *133*, 13922.
2014, *136*, 15403.



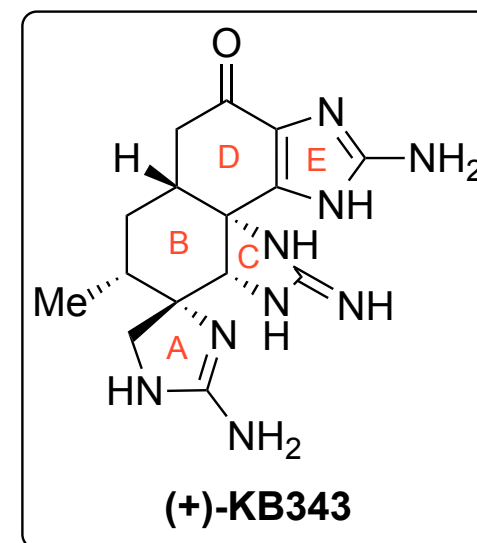
Araisamine C

P. S. Baran,
J. Am. Chem. Soc. **2016**, *138*, 14234.



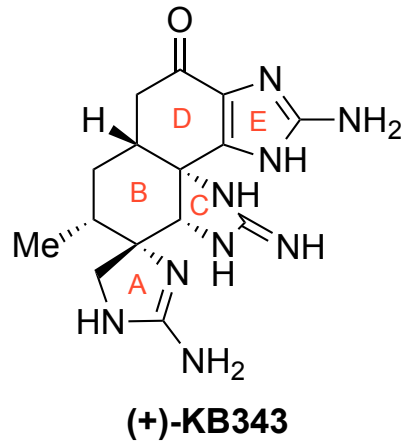
Baran group shows long-standing fascination towards the synthesis of guanidine-containing alkaloids, which drew their attention to **KB343**.

KB-343 contains 3 cyclic guanidines (A, C, E) annealed onto a decalin core (B, D).



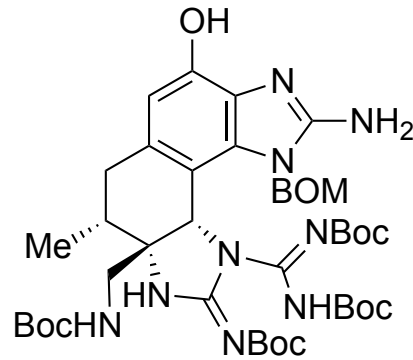
(+)-KB343

Retrosynthetic Analysis



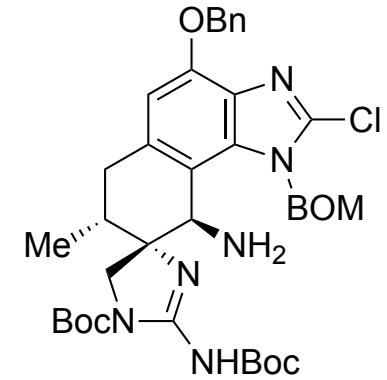
*Dearomative
Cyclization
& Guanidine Dance*

3 steps

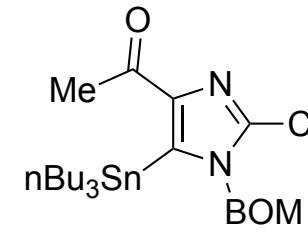


*Amine Redox
Epimerization
& Guanidine Dance*

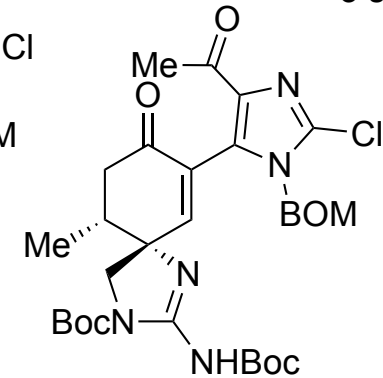
3 steps



*Aldol condensation
& Dehydration
& Rearomatization*
3 steps

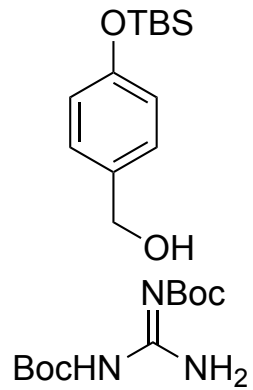


*α-Iodination
& Stille
Coupling*
2 steps



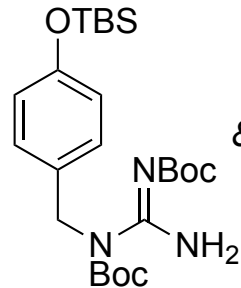
*Dearomative cyclization,
guanidine dance, and amine
redox epimerization as key steps*

Racemic Synthesis Route



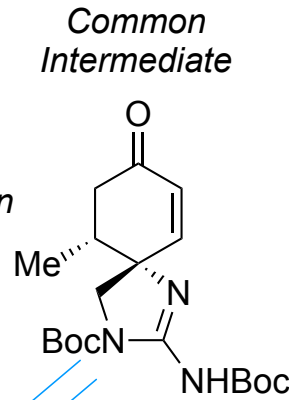
Mitsunobu

1 steps

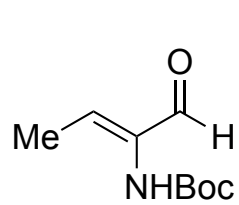


*Dearomative
Spirocyclization
& Conjugate Addition*

2 steps

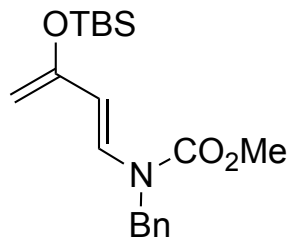


Enantioselective Synthesis Route

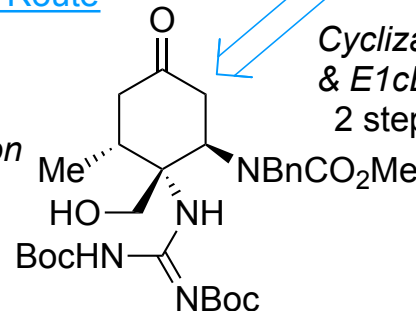


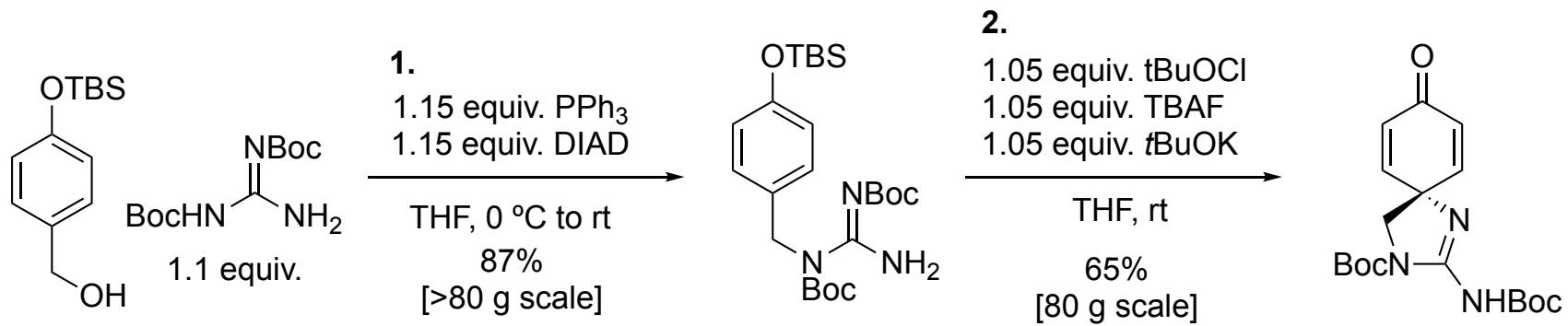
*Enantioselective
Diels-Alder
& FG Interconversion*

3 steps



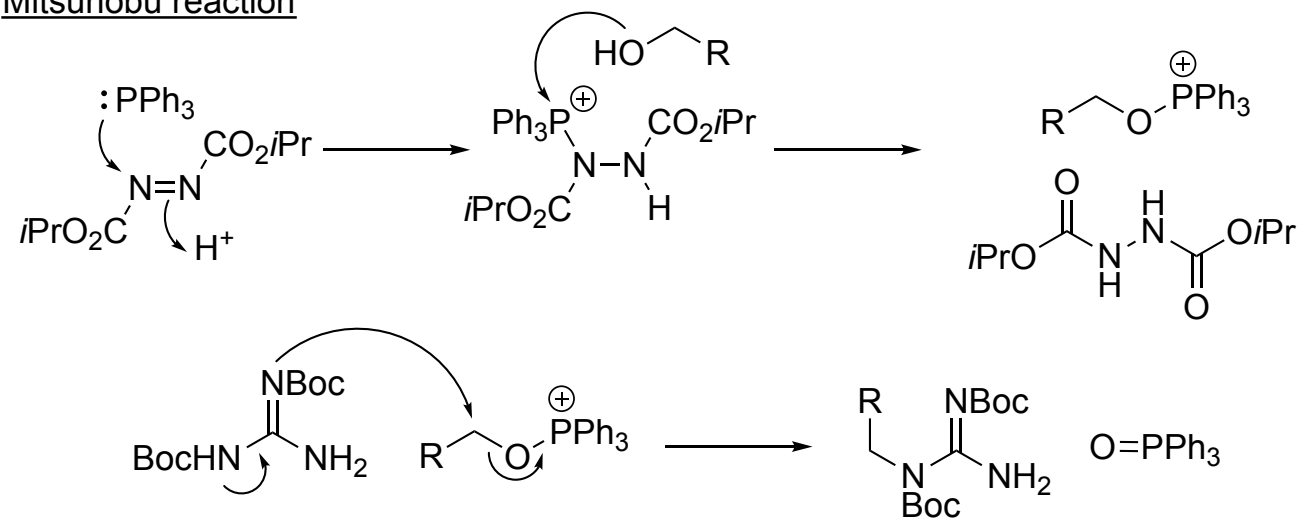
*Cyclization
& E1cB*
2 steps



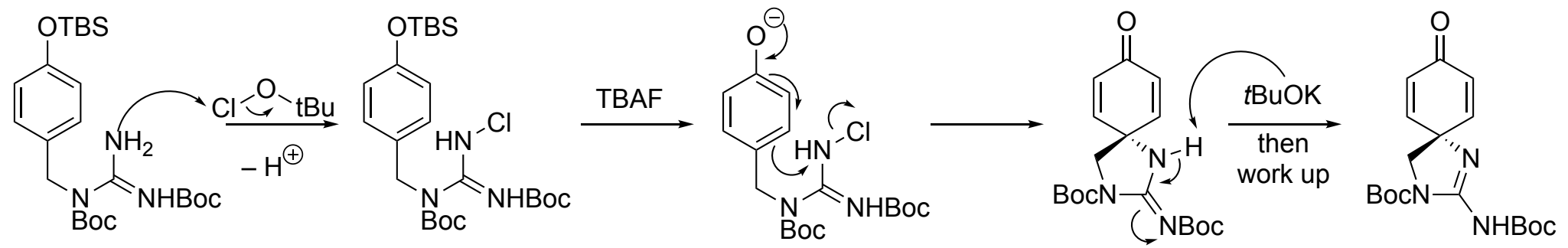


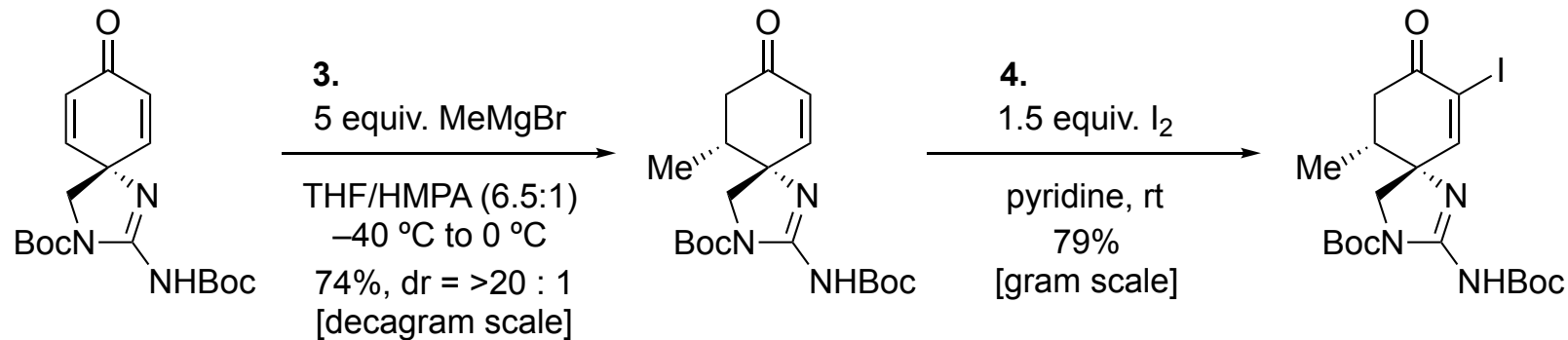
For scalability, an electrophilic guanidine route was deployed

Mitsunobu reaction



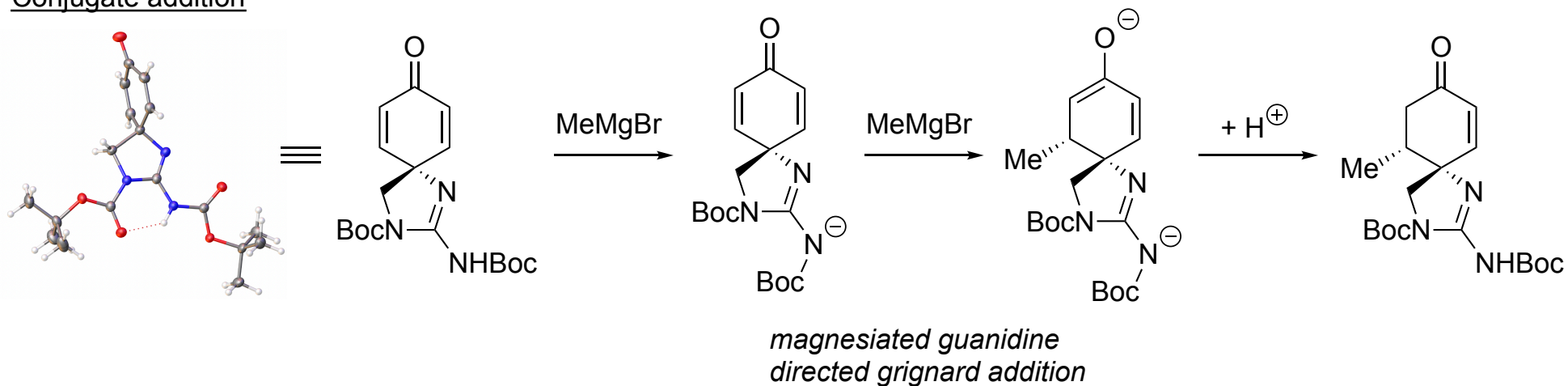
Dearomative spirocyclization (Electrophile: guanidine)



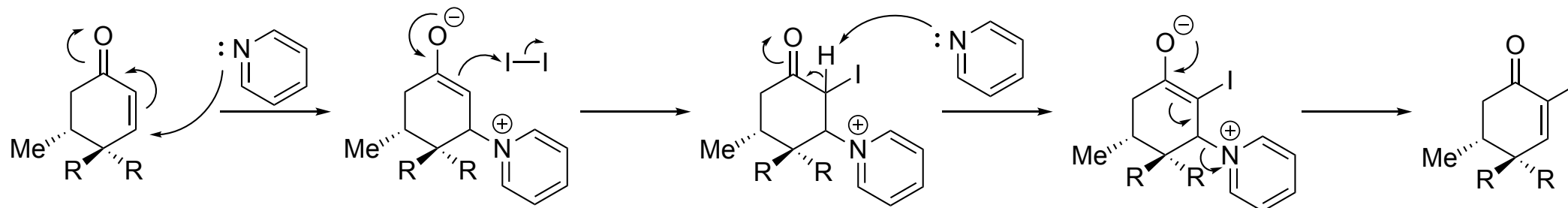


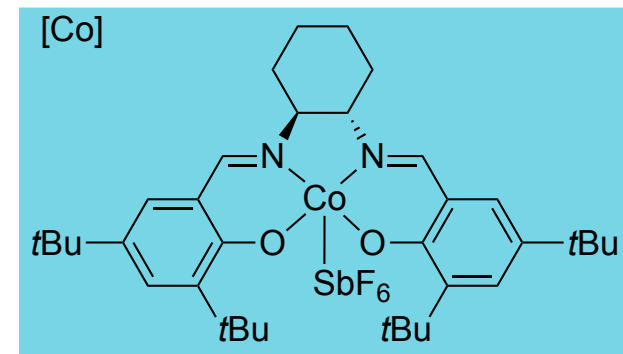
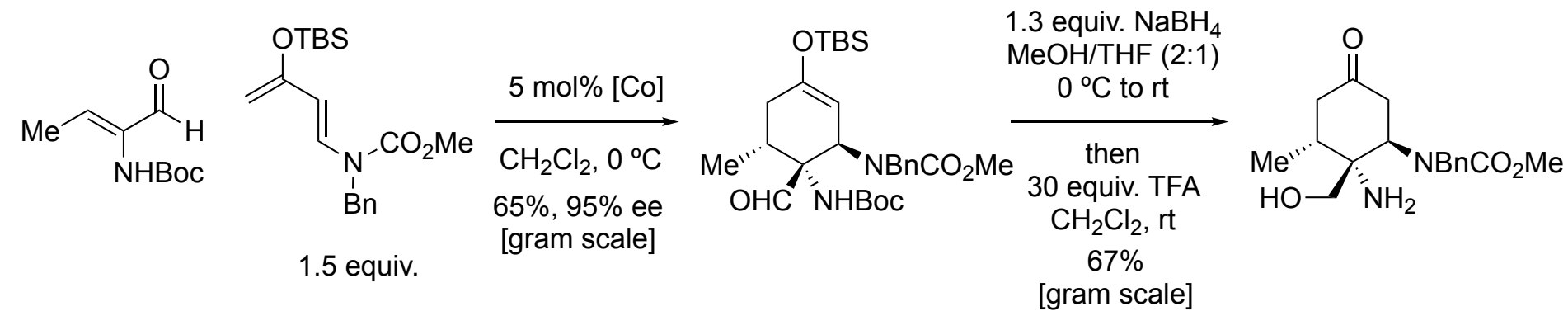
*Enantioselective
conjugate addition:
Unsuccessful
Different route was used
to access this precursor
for enantioselective synthesis*

Conjugate addition

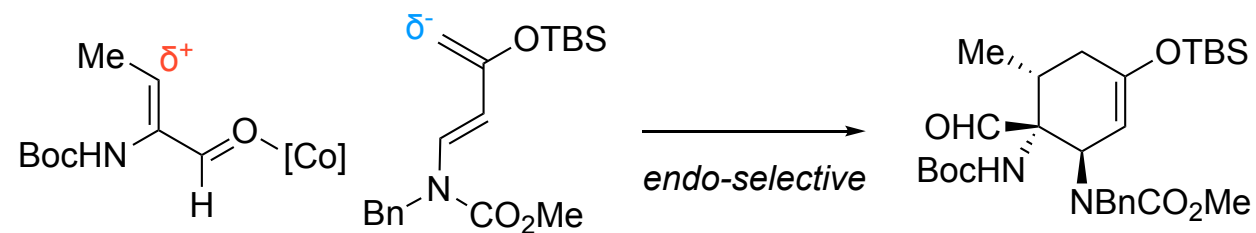


α -iodination

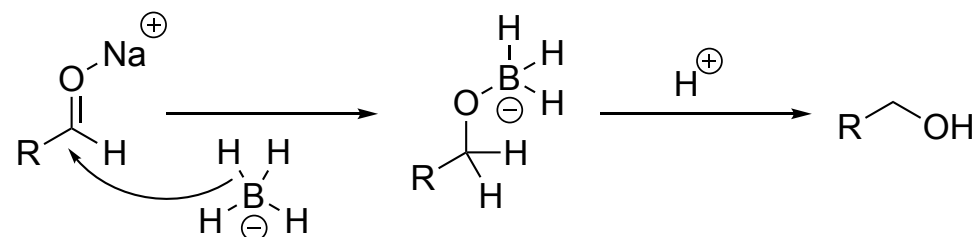




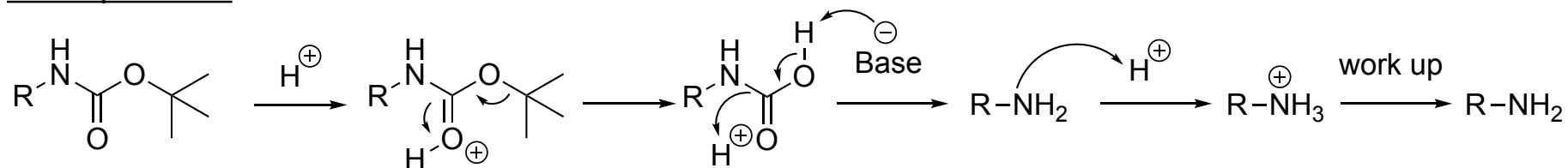
Enantioselective Diels Alder

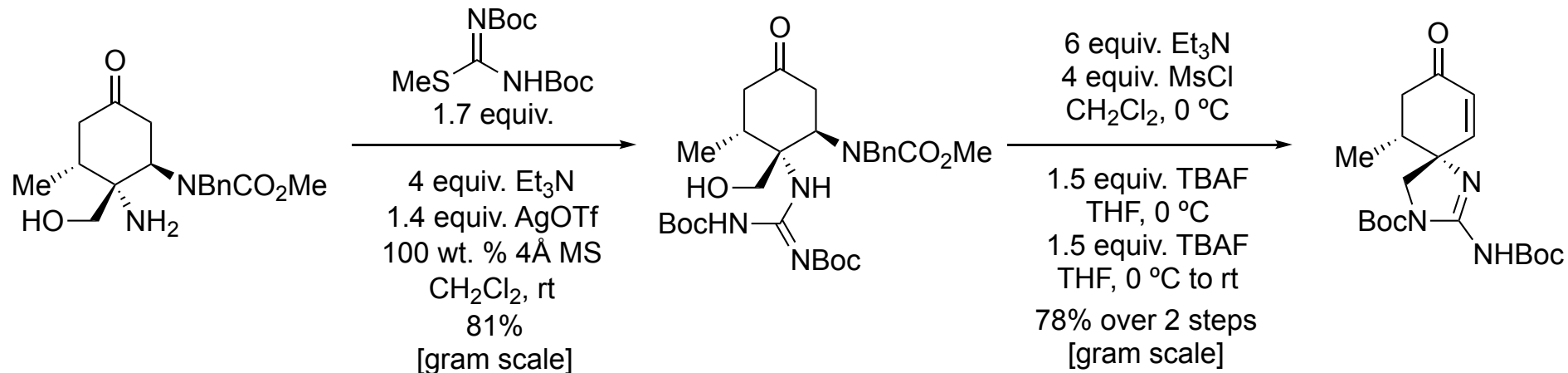


NaBH₄ reduction

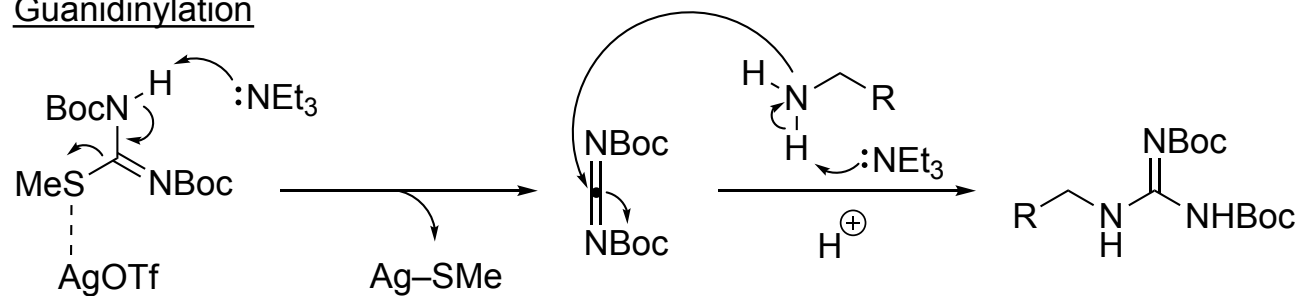


Boc deprotection

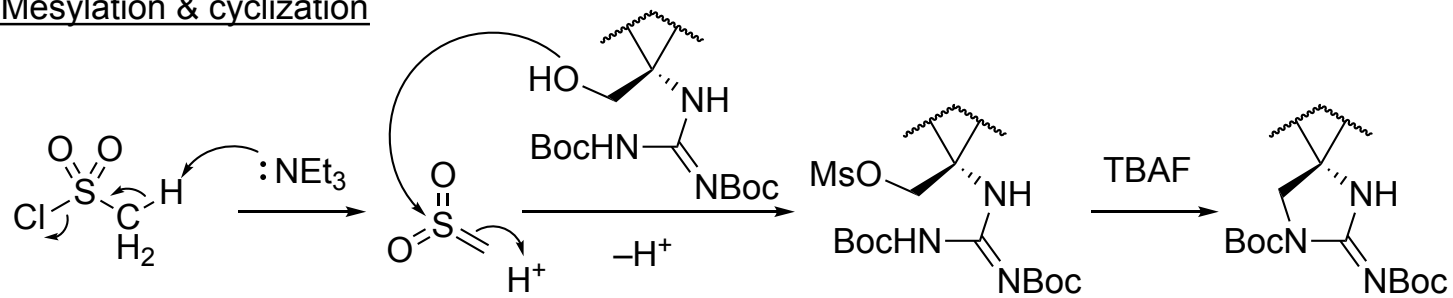




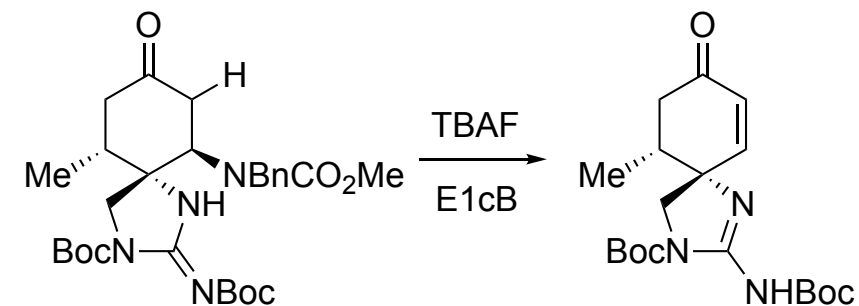
Guanidinylation

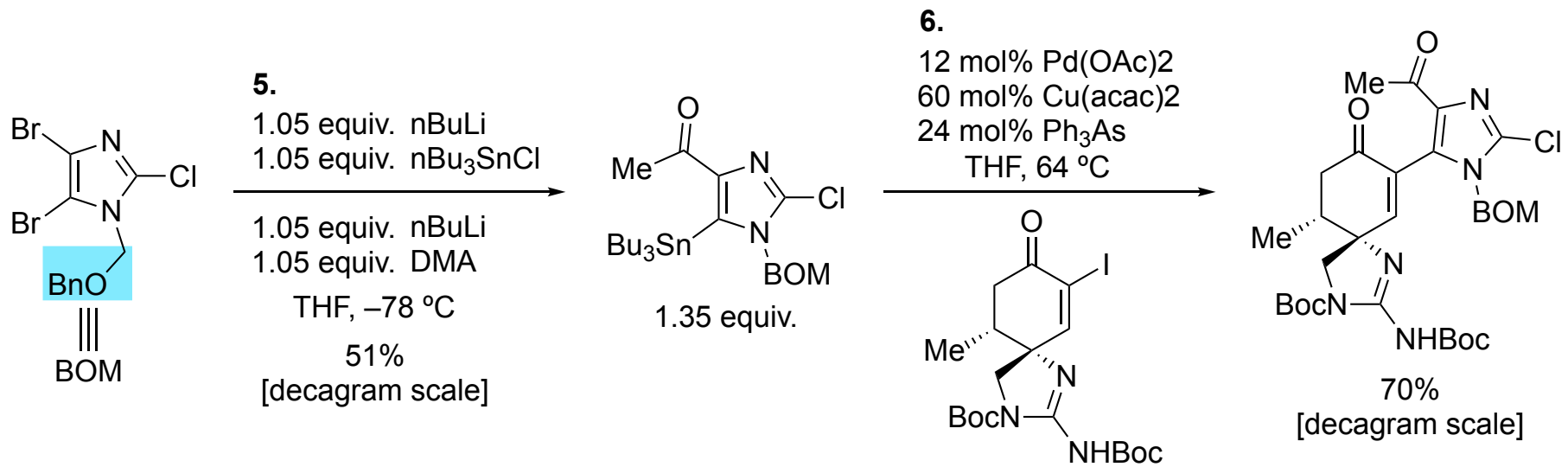


Mesylation & cyclization

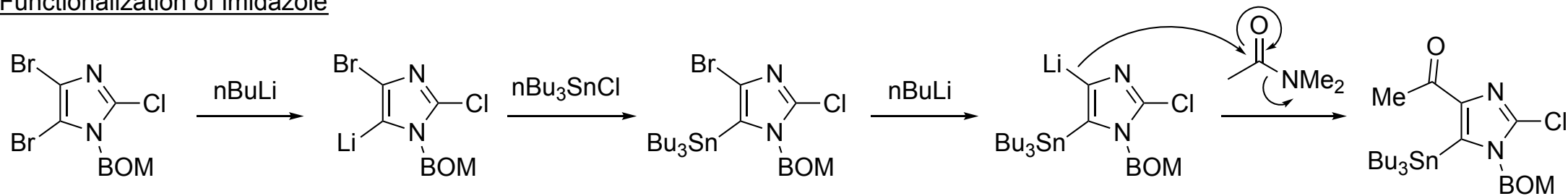


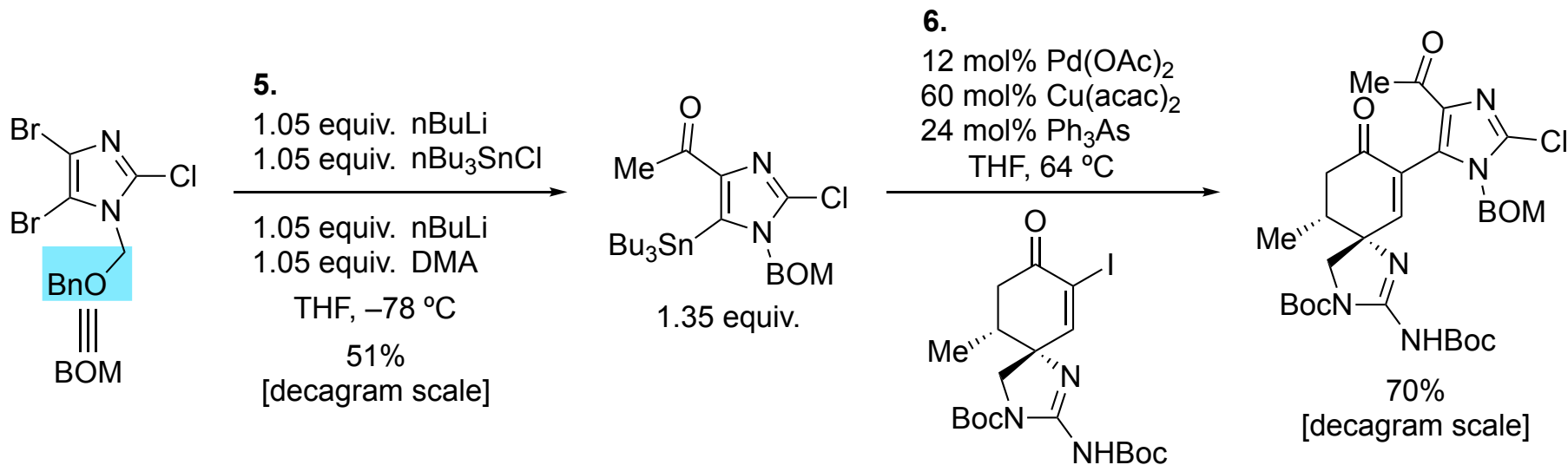
E1cB elimination





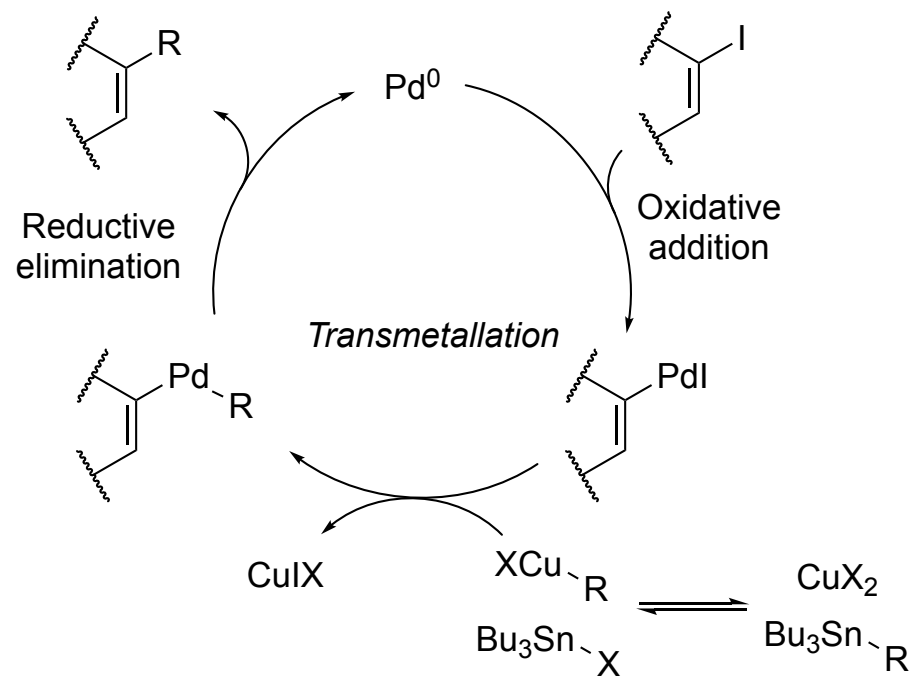
Functionalization of imidazole

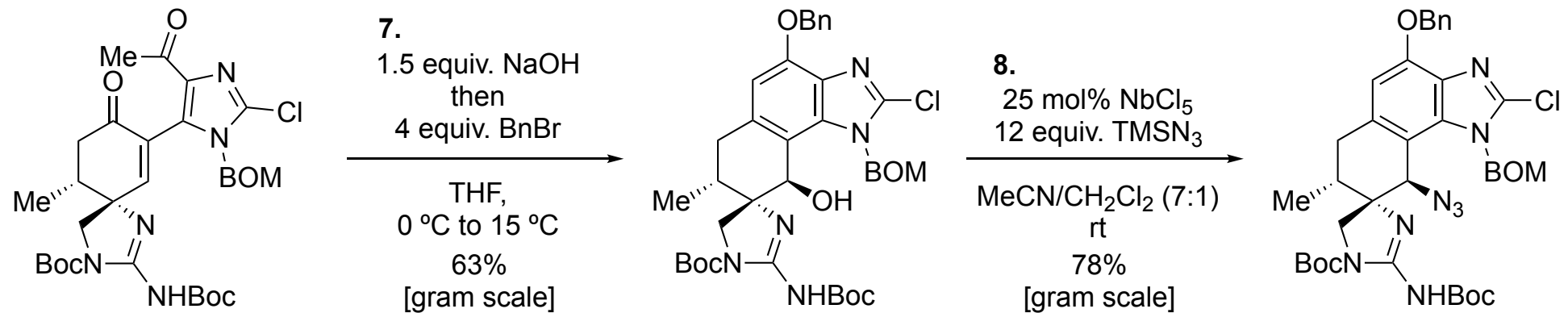




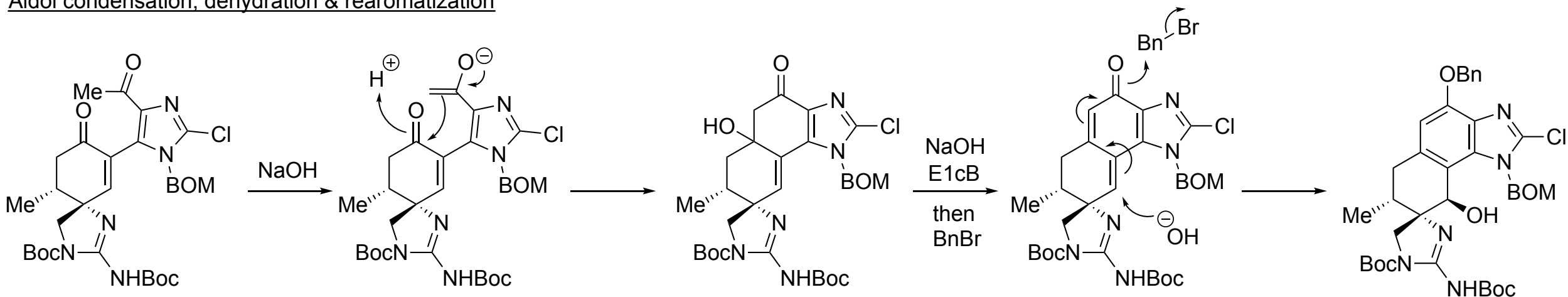
“Stille coupling proved to be the only viable cross-coupling for this pivotal C-C bond forming step”

Stille Coupling

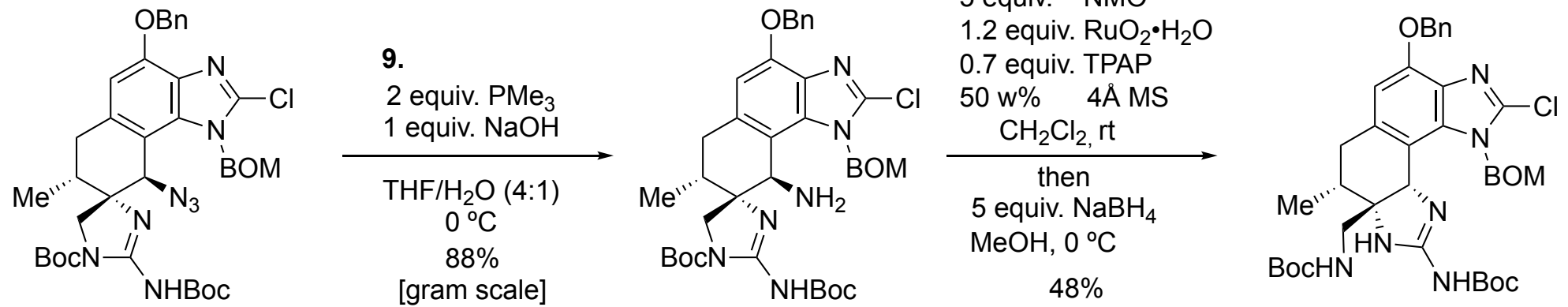




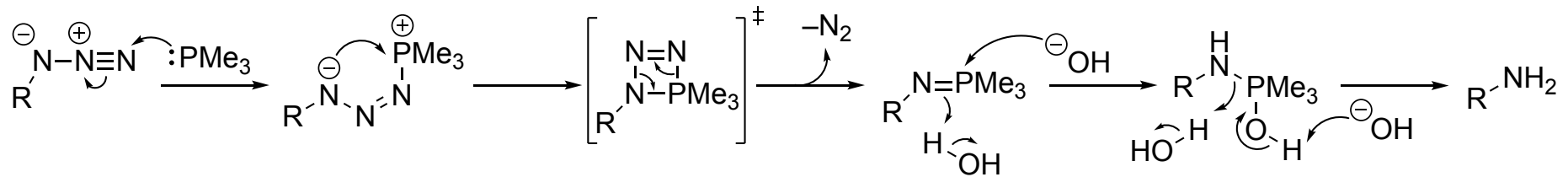
Aldol condensation, dehydration & rearomatization

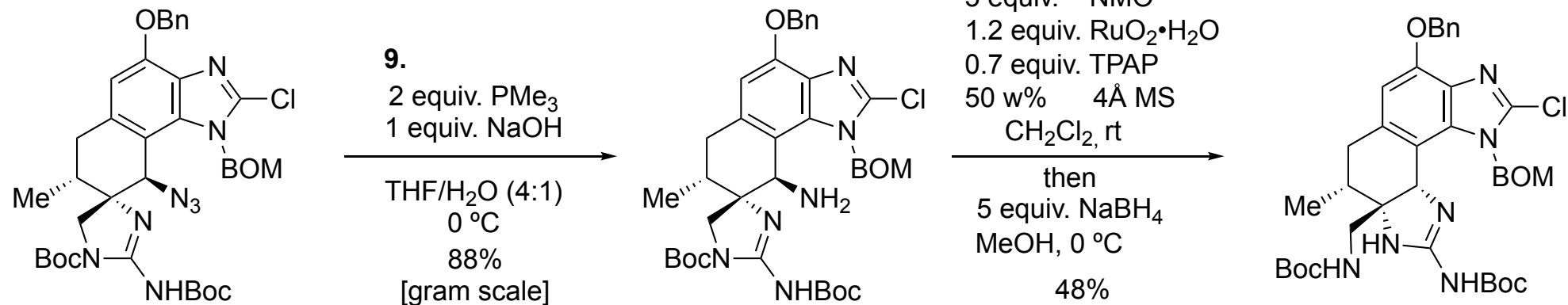


*Attack of N-based Nu for aromatization: Unsuccessful
Only attack from unwanted top face was observed*

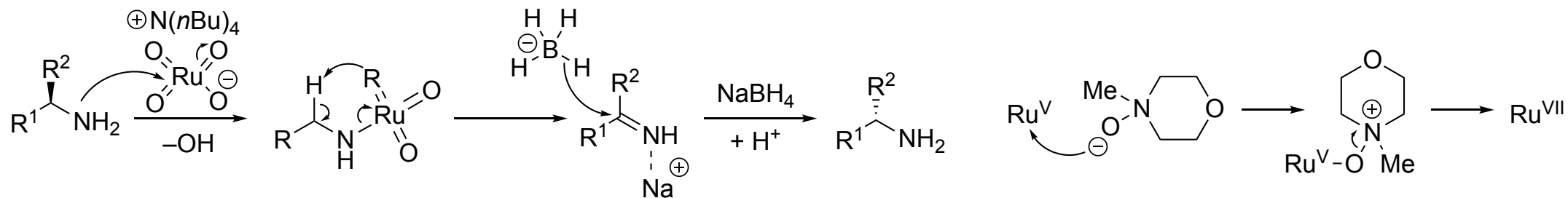


Staudinger reaction





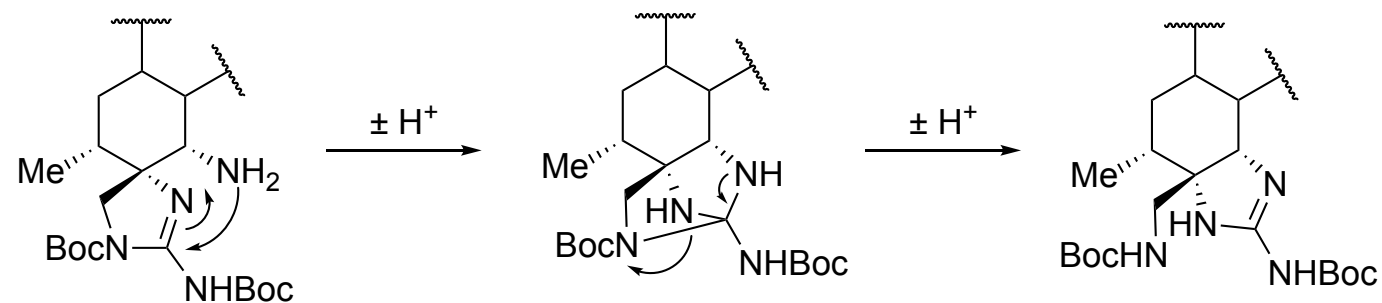
Amine redox-epimerization

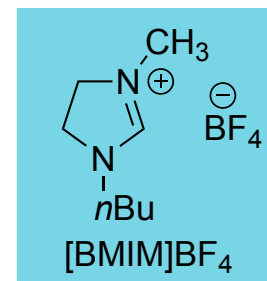
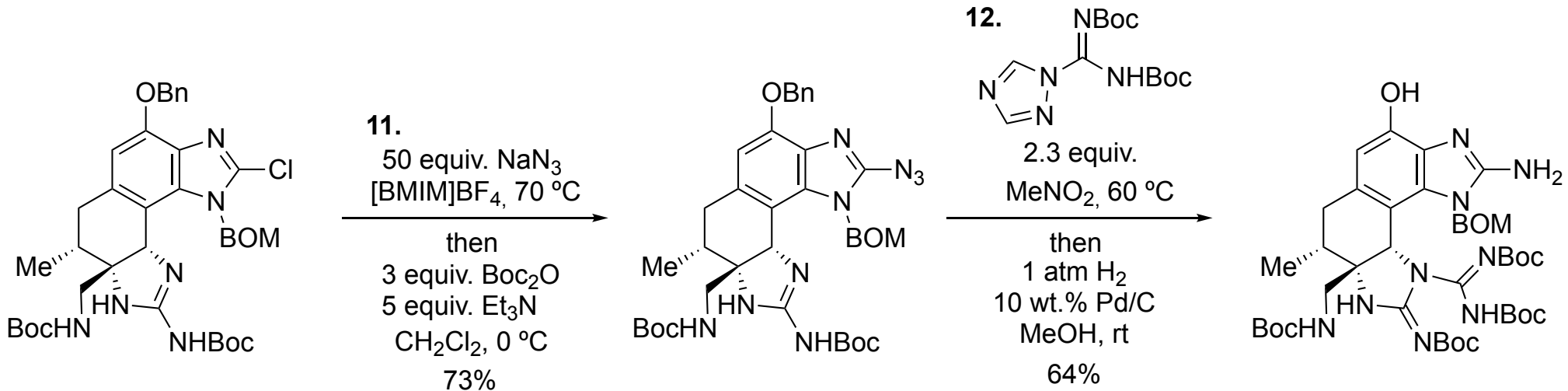


For TPAP/NMO oxidation of amine: A. Goti, *Tetrahedron Lett.* **1994**, 35, 6567.

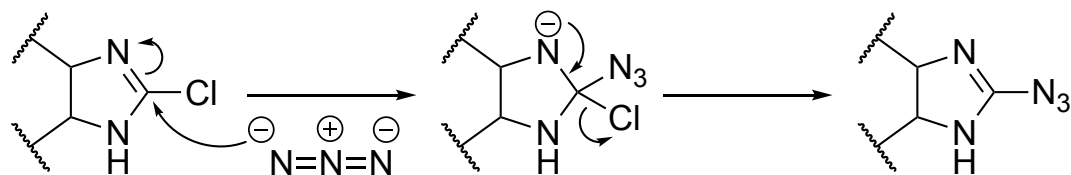
For amine redox-epimerization: M. S. Sherburn, *J. Am. Chem. Soc.* **2022**, 144, 19695.

First guanidine dance



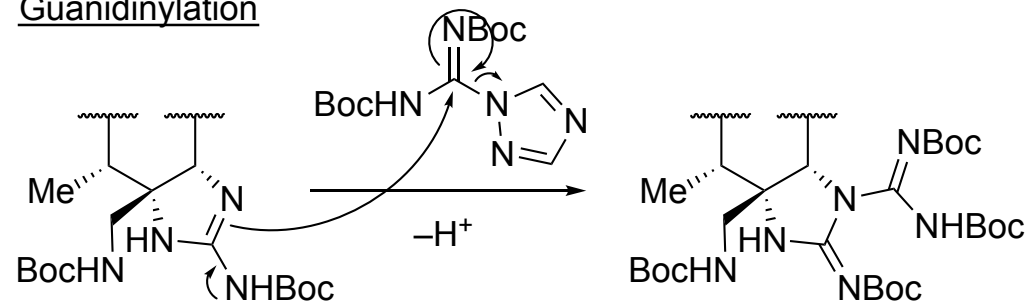


$\text{S}_{\text{N}}\text{Ar}$ azidation

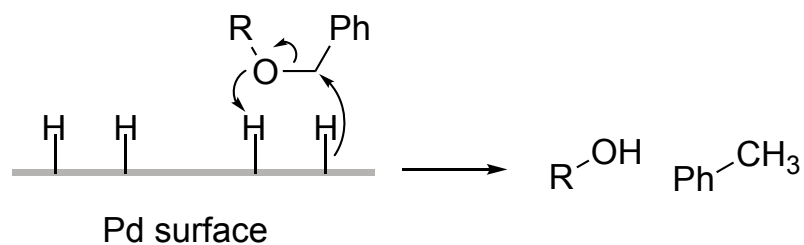


For review of $[\text{BMIM}]\text{BF}_4$: B. Banerjee, *ChemistrySelect* **2017**, 2, 8362.
 For the use of ionic liquid for $\text{S}_{\text{N}}\text{Ar}$ azidation:
 F. D'Anna, R. Noto, *J. Org. Chem.* **2008**, 73, 6224.

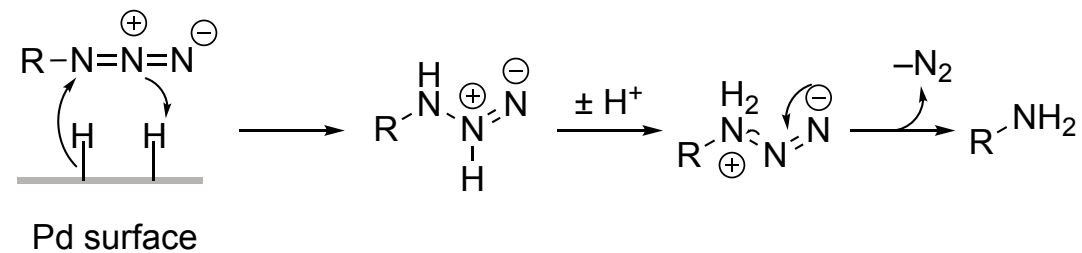
Guanidinylation



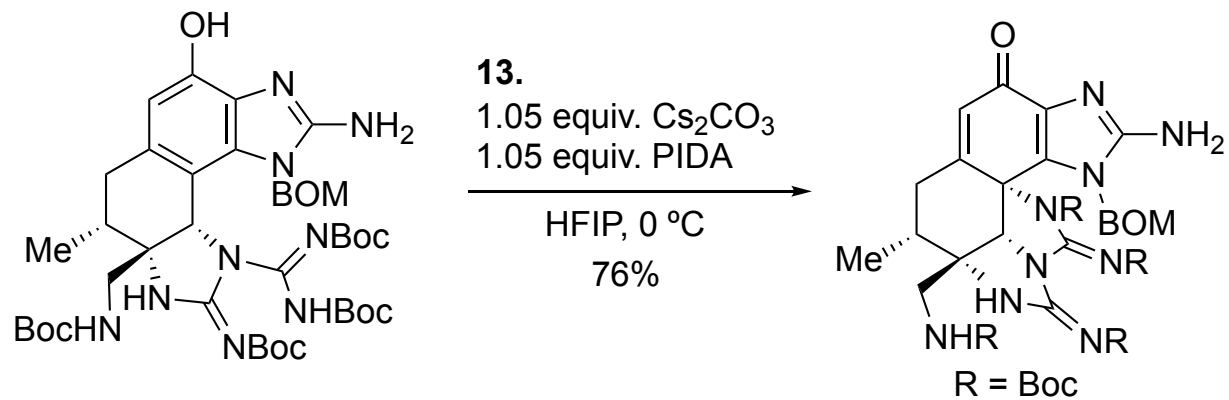
Hydrogenolysis of benzyl alcohol



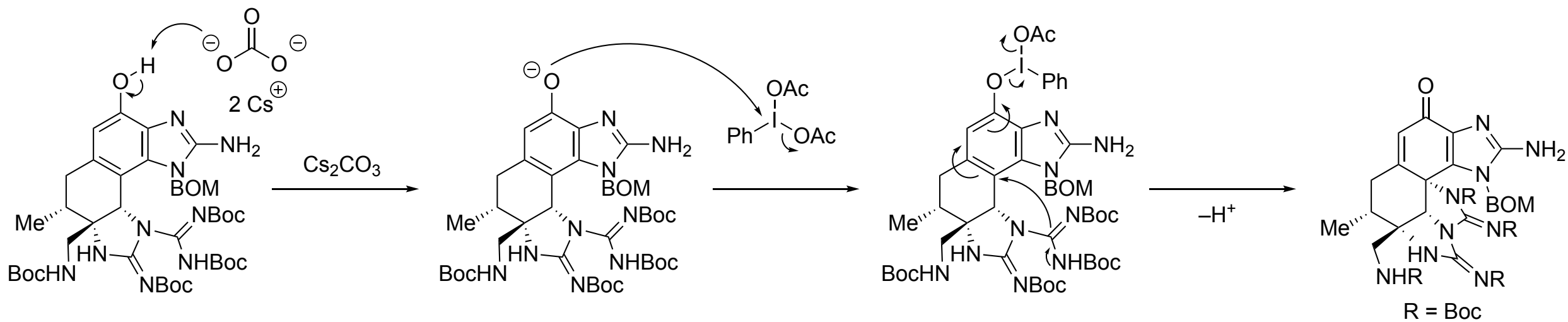
Hydrogenolysis of azide

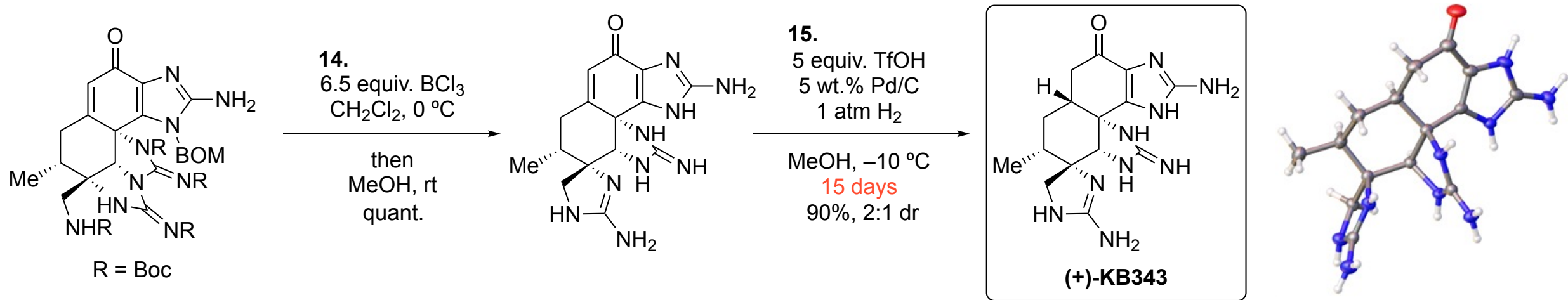


H. Göksu, *New J. Chem.*, **2016**, 40, 9550.

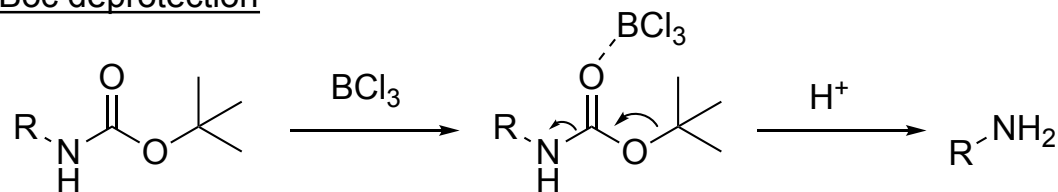


Dearomative cyclization (Nucleophile: guanidine)

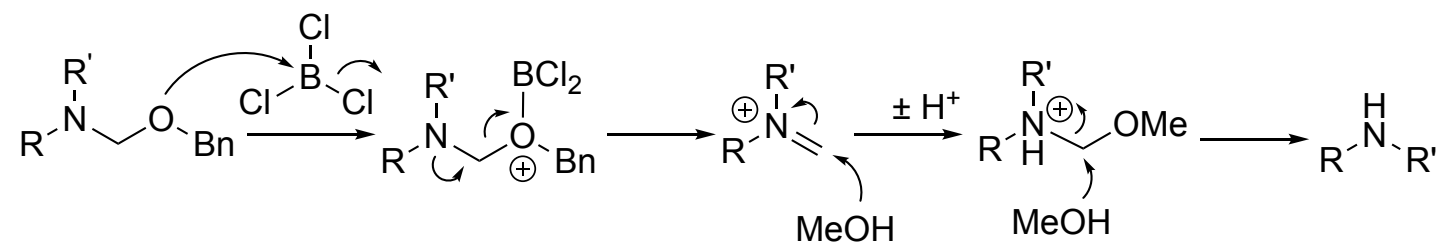




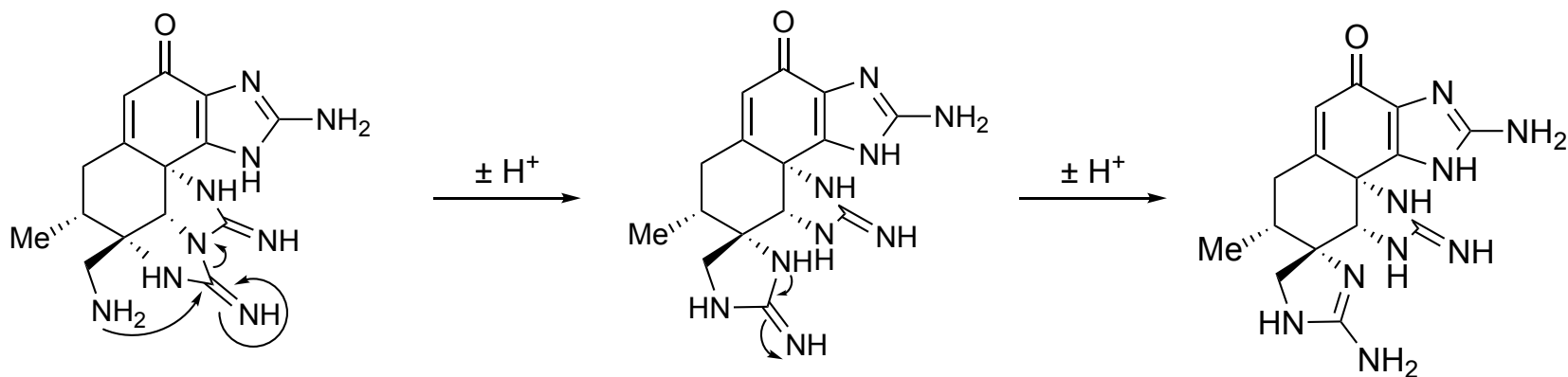
Boc deprotection

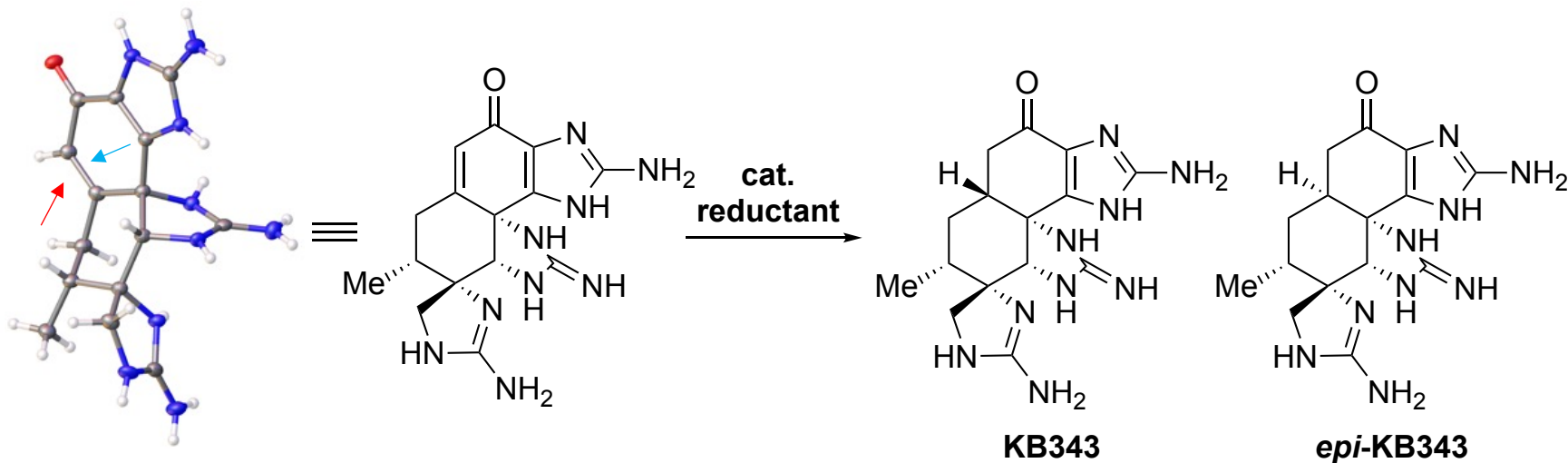
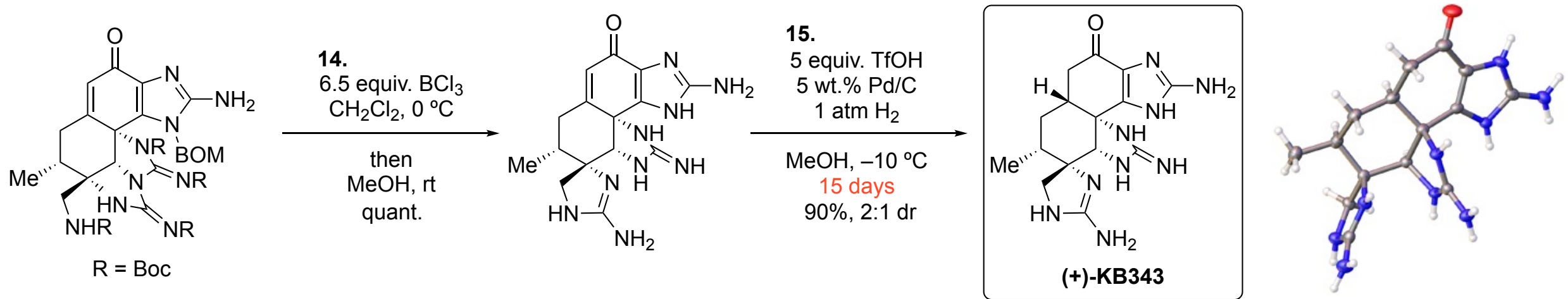


BOM deprotection



Second guanidine dance





cat.	reductant	temp.	A:B (dr)
$\text{Fe}(\text{acac})_3$	PhSiH_3	rt	<1 : 20
$\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$	NaBH_4	-78 °C	1 : 2.2
Pd/C	H_2	rt	1 : 2.6
Pd/C with AgOTf	H_2	rt	1.1 : 1
Pd/C with TfOH	H_2	-10 °C	2 : 1

Top: Wanted, unfavored side
 Bottom: Unwanted, favored side