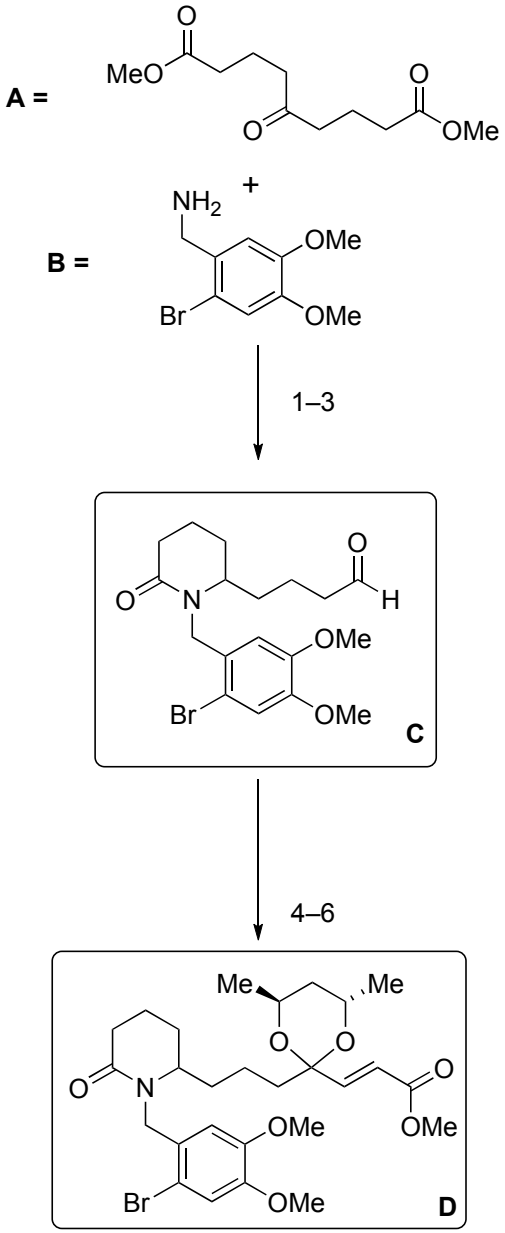
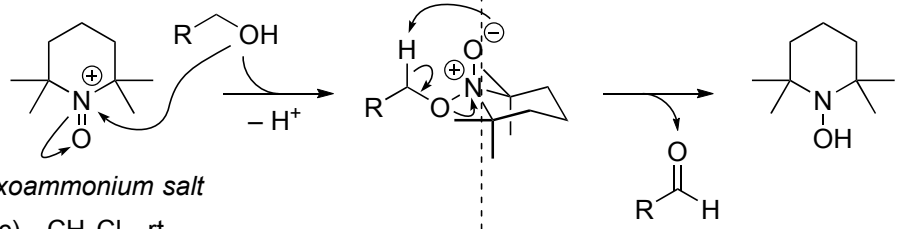
Total Synthesis of (–)-Histrionicotoxin through a Stereoselective Radical Translocation–Cyclization Reaction

Sato, M.; Azuma, H.; Daigaku, A.; Sato, S.; Takasu, K.; Okano, K.; Tokuyama, H.; *Angew. Chem. Int. Ed.* **2017**, *56*, 1087–1091.



Step 3 mechanism:

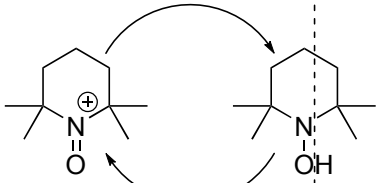
Oxidation of alcohol to aldehyde



oxoammonium salt

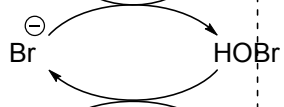
1) $NaBH(OAc)_3$, CH_2Cl_2, rt
2) K-Selectride, THF, 0 °C to rt
3) cat. TEMPO, NaOCl, KBr, $NaHCO_3$, CH_2Cl_2/H_2O, 0 °C

primary catalytic oxidant



TEMPO is oxidized to oxoammonium salt

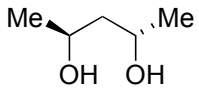
secondary catalytic oxidant

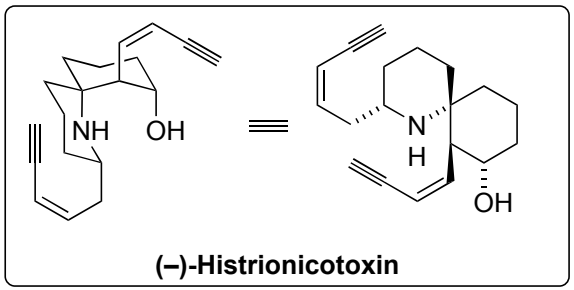


stoichiometric oxidant

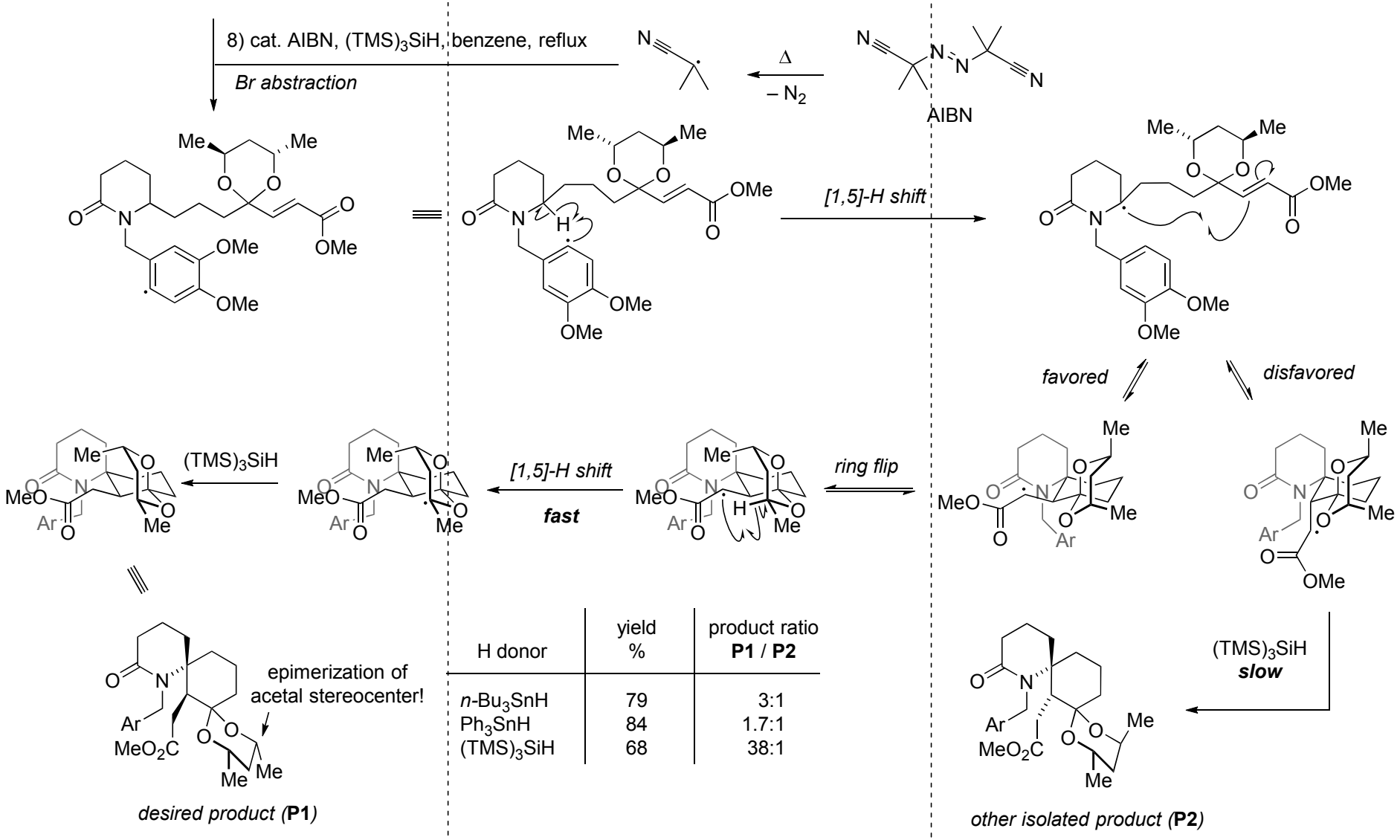
4) vinylmagnesium bromide, THF, –78 °C to 0 °C
5) methyl acrylate, cat. Grubbs II, CH_2Cl_2, reflux
6) MnO_2, CH_2Cl_2, rt
7) diol **X**, cat. TMSOTf, TMSO*i*-Pr, CH_2Cl_2, 0 °C to rt

X =





(–)-Histrionicotoxin



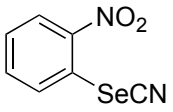
H donor	yield %	product ratio **P1** / **P2**
n-Bu_3SnH	79	3:1
Ph_3SnH	84	1.7:1
$(TMS)_3SiH$	68	38:1

Use of less active H donor $(TMS)_3SiH$ improves diastereoselectivity of radical reaction to allow [1,5]-H shift on acetal to occur before H donation to radical alpha to the ester.

Chiral acetal imparts conformational bias and determines facial selectivity of the 6-*exo* cyclization leading to desired stereochemistry (94% ee)

9–14

9) cat. $FeCl_3$, SiO_2, acetone, rt
10) Li, NH_3, *t*-BuOH/THF, –78 °C, 1 h
11) PBu_3, reagent **Y**, THF, 1 h

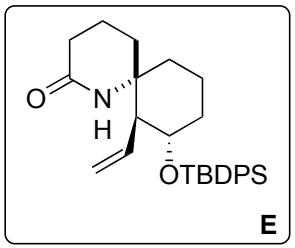
Y = 

12) *p*-TSA, toluene, reflux
13) TBDPSCl, imidazole, CH_2Cl_2, rt
14) *m*-CPBA, CH_2Cl_2, 0 °C to rt

Mechanism of step 8?
What other reagents other than $(TMS)_3SiH$ could be used? Advantages/disadvantages?

nBu_3SnH or Ph_3SnH or nBu_3GeH

Sn = toxic, more reactive and lower diastereoselectivity
Ge = more stable and less toxic, can sometimes improve yield in cyclization.
expensive



E

15–22

15) $Ti(Oi\text{-}Pr)_4$, Et_2SiH_2, THF, reflux
then cool to –78 °C, allylMgCl, cat. $ZnCl_2$
17) TBAF, THF
18) $SOCl_2$, imidazole, CH_2Cl_2, 0 °C, 1 h
19) O_3, *then* Me_2S, CH_2Cl_2/MeOH, –78 °C to rt
20) PhP_3CH_2I, KHMDS, THF, –78 °C
21) TMS-acetylene, cat. $Pd(PPh_3)_4$, cat. CuI, Et_2NH
22) $LiAlH_4$, THF, 0 °C to rt

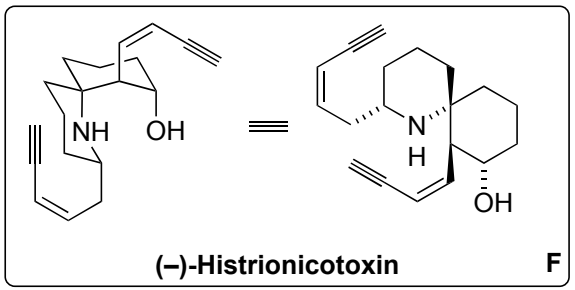
Name Reaction?
Stork-Zhao reaction
Name 3 alternative methods for the formation of this functional group (also in other stereo- and regioselectivities)

terminal E- vinyl iodide:
Takai hydrozirconation/iodination

internal vinyl iodide:

Hoveyda Ni-catalyzed hydroalumination of alkynes

beta-oxido-phosphonium reaction from aldehydes and phosphonium salt



(–)-Histrionicotoxin **F**