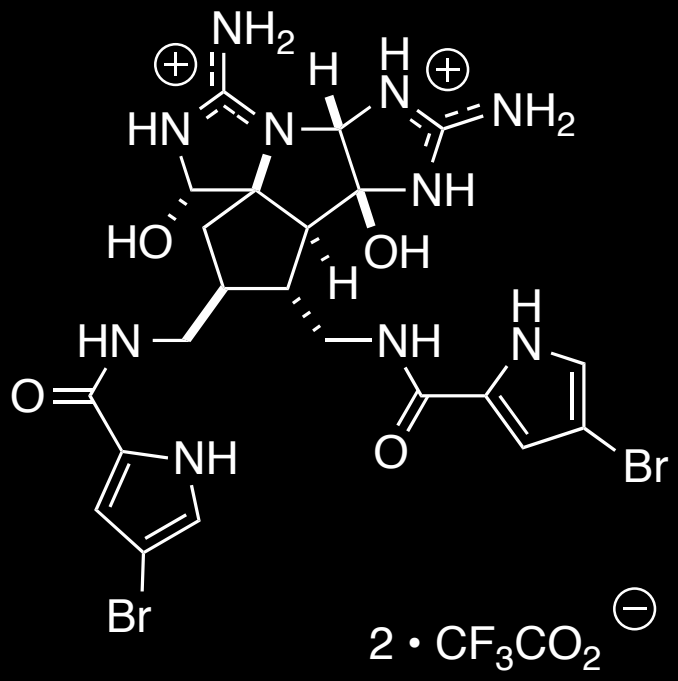
Synthetic (±)-Axinellamines Deficient in Halogen

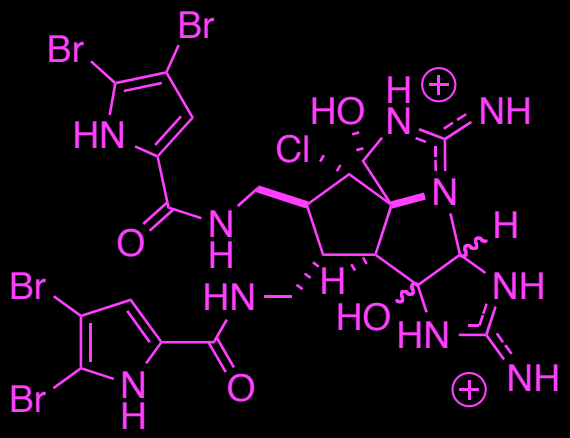
Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP



Eric E. Buck
Current Literature
March 31, 2012

Isolation and biological activity

• Axinellamines A-D were isolated from the Australian marine sponge, *Axinella sp* (pictured right).



(-)-axinellamine A (OH, H = β)

(-)-axinellamine B (OH, H = α)

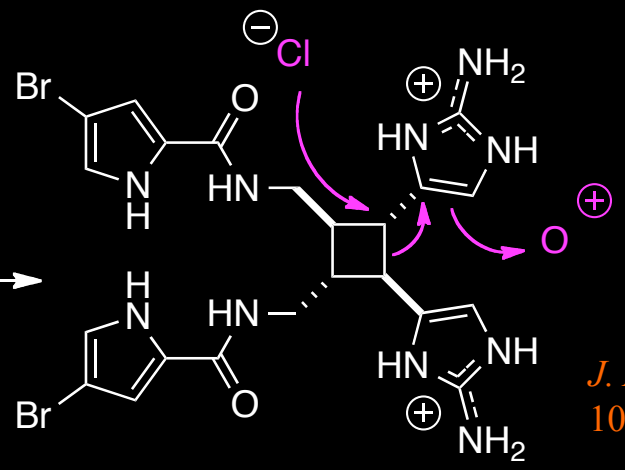
J. Org. Chem. **1999**, 64, 731-735

• Axinellamine A was not bactericidal at 1000 μM.

• Axinellamine B-D exhibited MIC for bactericidal action against *H. pylori* (a gram negative bacterium associated with peticular and gastric cancer) at 1000 μM

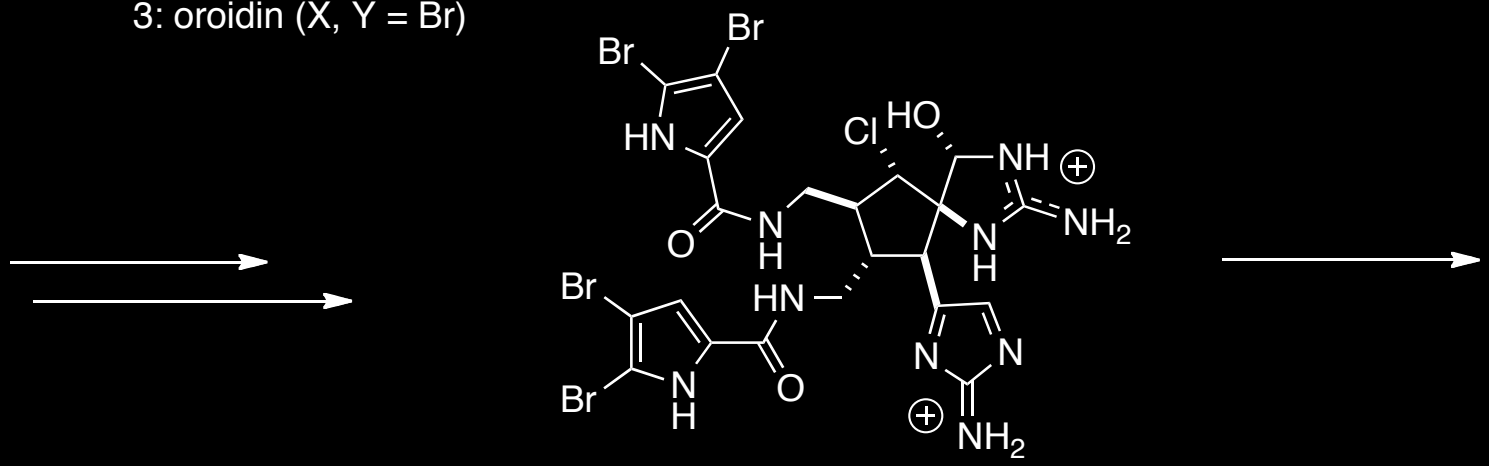
Biosynthesis

1: clathrodin (X, Y = H)
2: hymenidin (X = H, Y = Br)
3: oroidin (X, Y = Br)



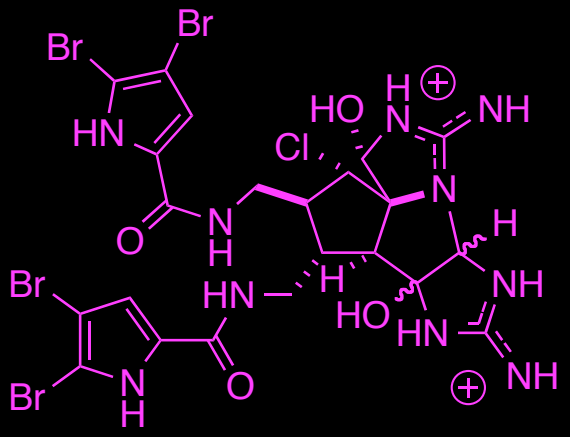
(-)-Sceptrin

J. Am. Chem. Soc. **1981**, 103, 6772-6773



pre-axinellamine

Biosynthesis

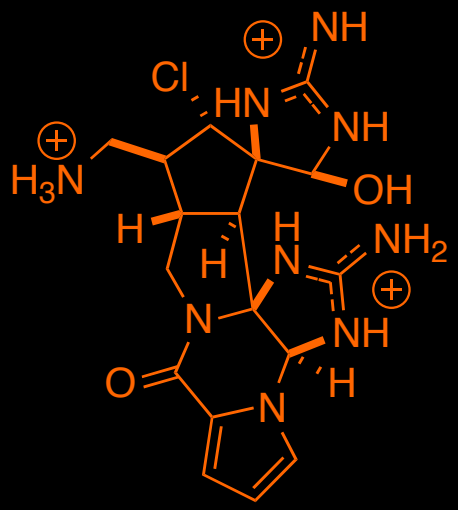


(-)-axinellamine A (OH, H = β)

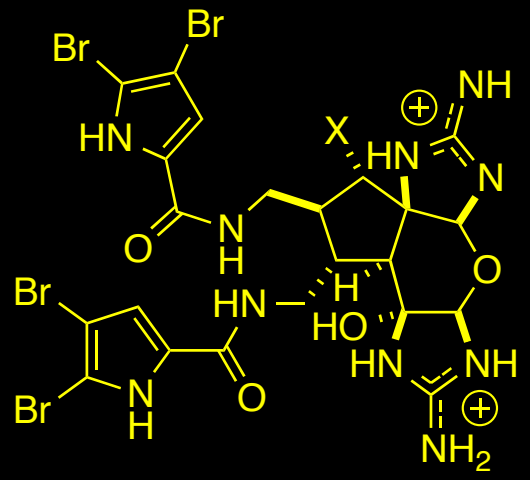
(-)-axinellamine B (OH, H = α)

J. Org. Chem. **1999**, 64, 731-735

J. Am. Chem. Soc. **1993**, 115, 3376-3377 (12,17-epi-13)



(-)-palau'amine



(-)-massadine (X = OH)

(-)-massadine chloride (X = Cl)

Org. Lett. **2003**, 5, 2255-2257

Synthetic efforts towards pyrrole-imidazole alkaloids

- Synthesis of 1,9-Dideoxy-pre-axinellamine

Yamaguchi, J.; Seiple, I. B.; Young, I. S.; O'Malley, D. P.; Maue, M.; Baran, P. S. *Angew. Chem. Int. Ed*. **2008**, 47, 3578-3580

- Total syntheses of (±)-massadine and massadine chloride

Su, S.; Seiple, I. B.; Young, I. S.; Baran, P. S. *J. Chem. Soc*. **2008**, 130, 16490-16491

- Total synthesis of (-)-palau'amine

Seiple, I. B.; Su, S.; Young, I. S.; Lewis, C. A.; Yamaguchi, J.; Baran, P. S. *Angew. Chem. Int. Ed*. **2010**, 49, 1095-1098

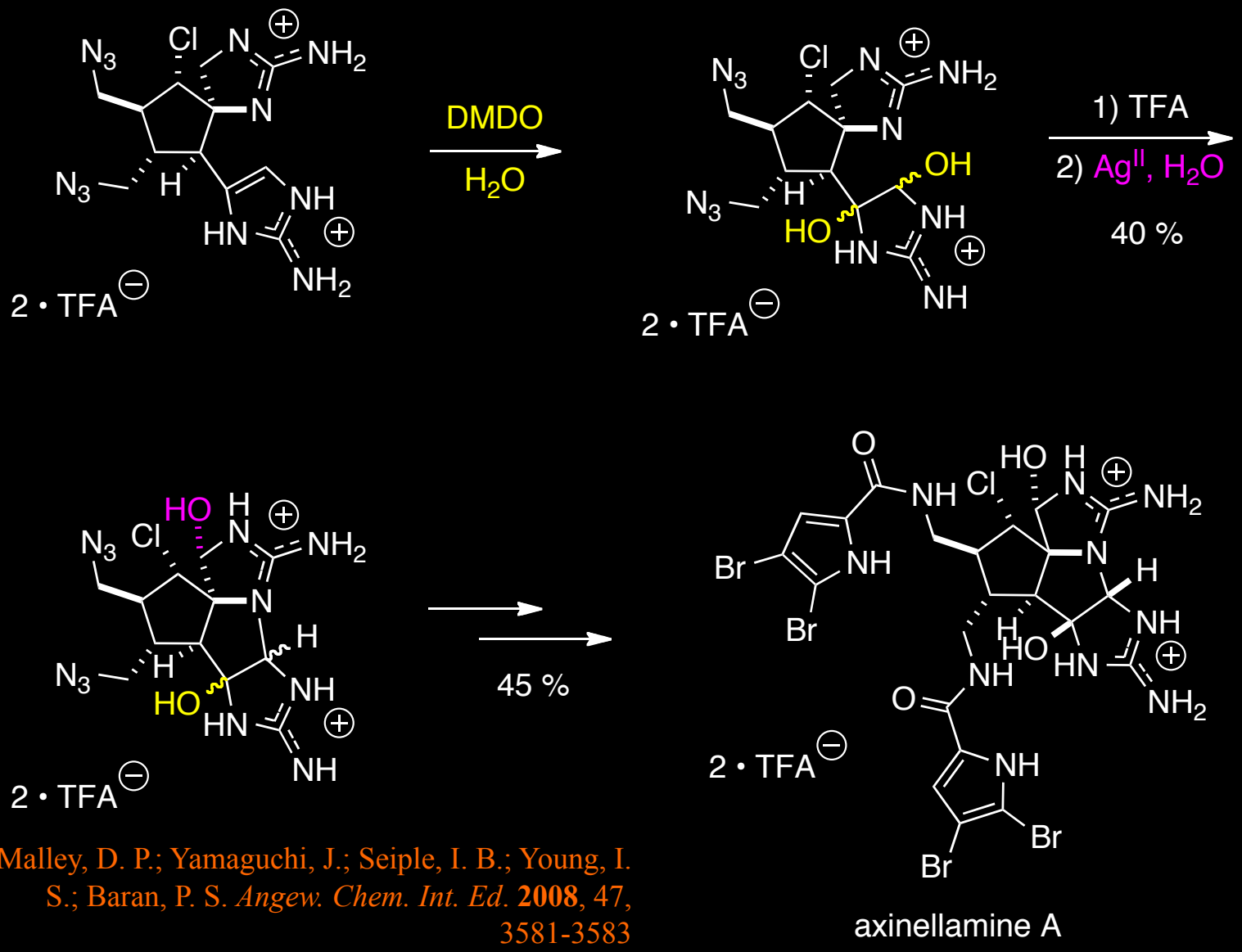
- The Baran Group's full paper detailing their efforts towards (-)-palau'amine, (-)-axinellamines, and massadines.

J. Chem. Soc. **2011**, 133, 14710-14726

- A review on the biosynthesis, assymetric synthesis, and pharmacology of pyrrole-2-aminoimidazole alkaloids.

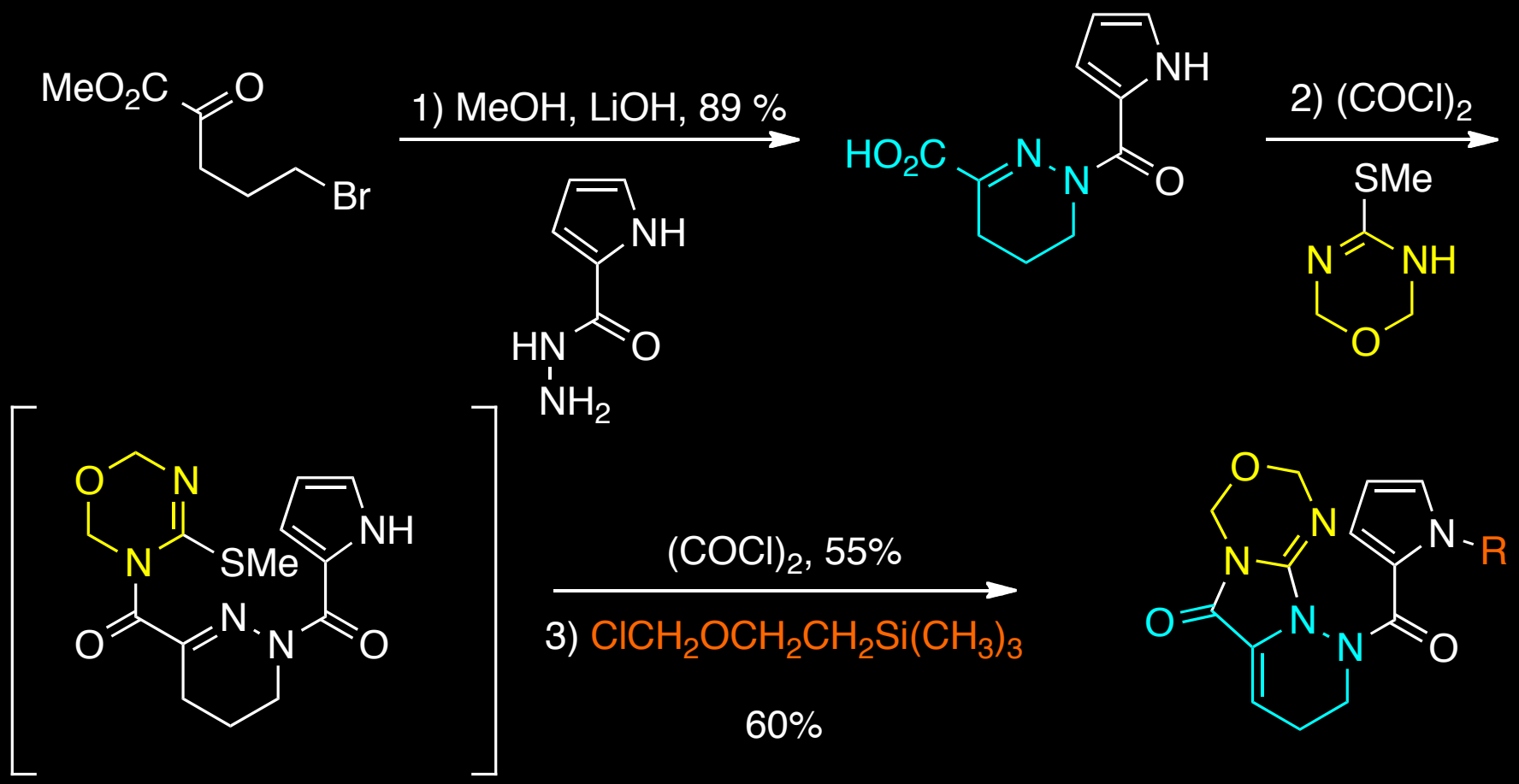
Al-Mourabit, A.; Zancanella, M, A.; Tilvi, S.; Romo, D. *Nat. Prod. Rep*., **2011**, 28, 1229-1260

The Baran Group's synthesis of (±)-axinellamines



O'Malley, D. P.; Yamaguchi, J.; Seiple, I. B.; Young, I. S.; Baran, P. S. *Angew. Chem. Int. Ed.* **2008**, 47, 3581-3583

Title paper: Two new ring systems



Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

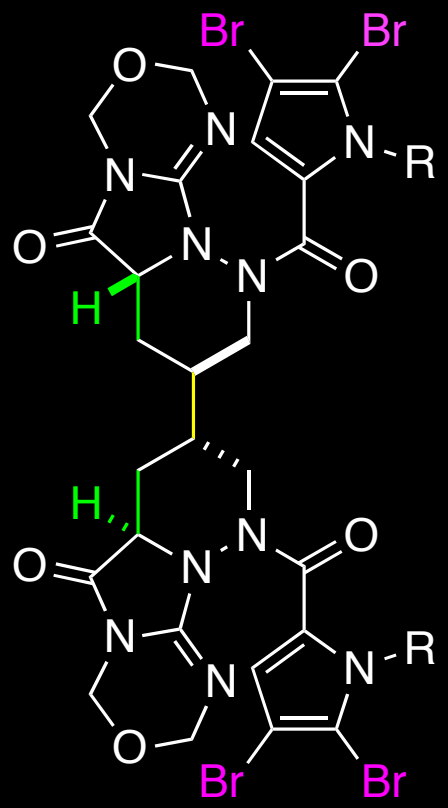
Title paper: Oxidative enolate coupling

1) [(*i*PrCp)$_2$TiCl$_2$], KHMDS

Cu(OTf)$_2$, 55 %, d.r. = 1.2:1

2) Rh[1], H$_2$, 600 psi, 3 d, 67%

3) NBS, 57%

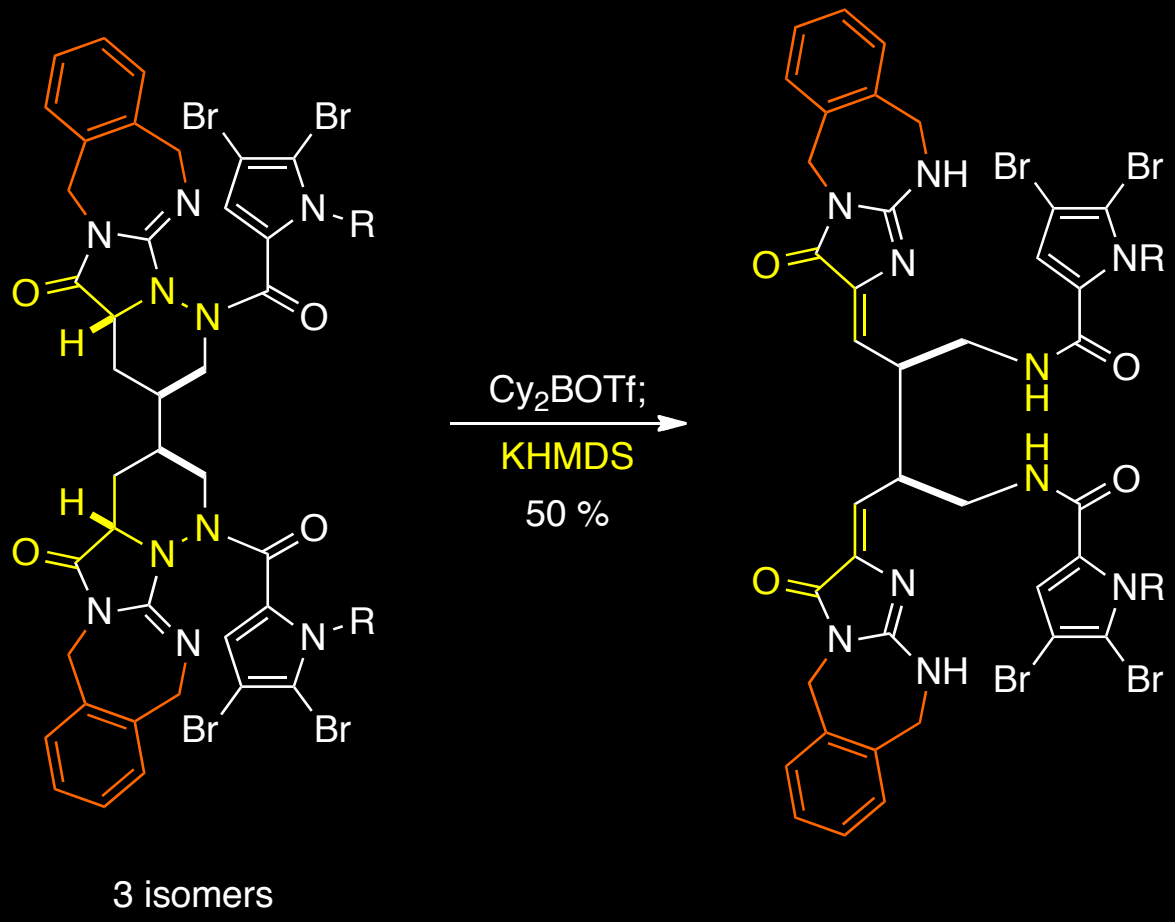


Note: [(CF$_3$CH$_2$O)V(O)Cl$_2$] "Livinghouse reagent" only other oxidant tried that provided comparable yield and regioselectivity to Cu(OTf)$_2$

Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

Ryter, K.; Livinghouse, T. *J. Am. Chem. Soc.* **1998**, 120, 2658-2659

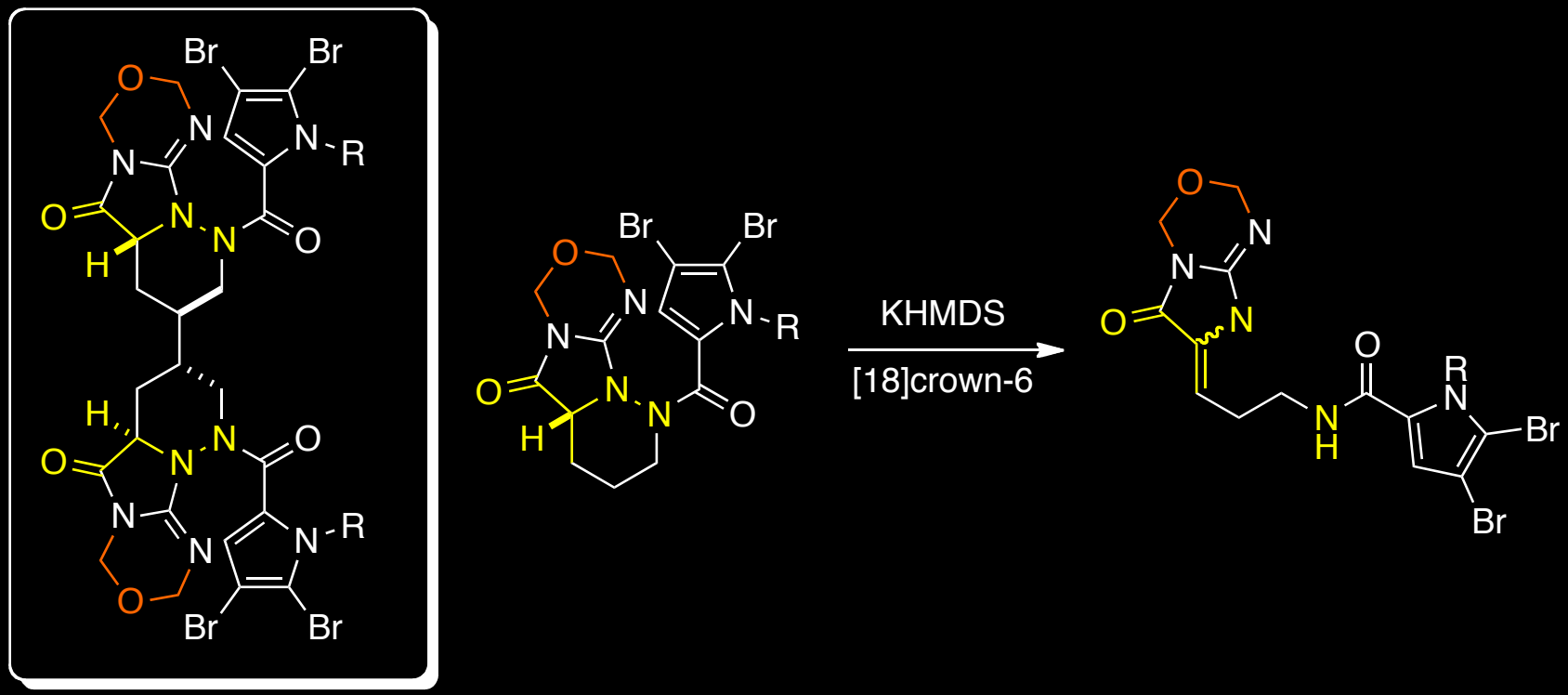
Exploring Symmetry-Based Logic for a synthesis of Palau'amine



3 isomers

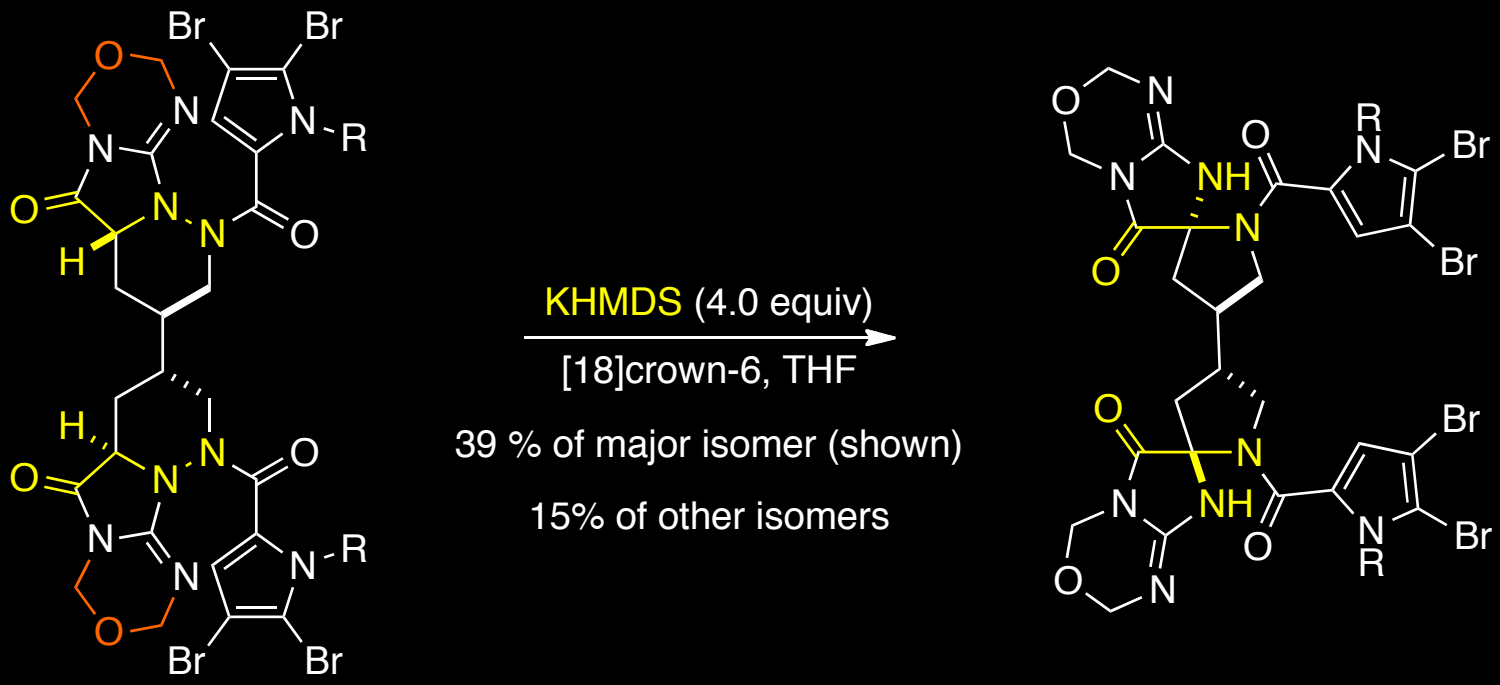
Li, Q.; Hurley, P.; Ding, H.; Roberts, A. G.; Akella, R.; Harran, P. G. *J. Org. Chem.* **2009**, 74, 5909-5919

Monomer forms targeted alkylidene



Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

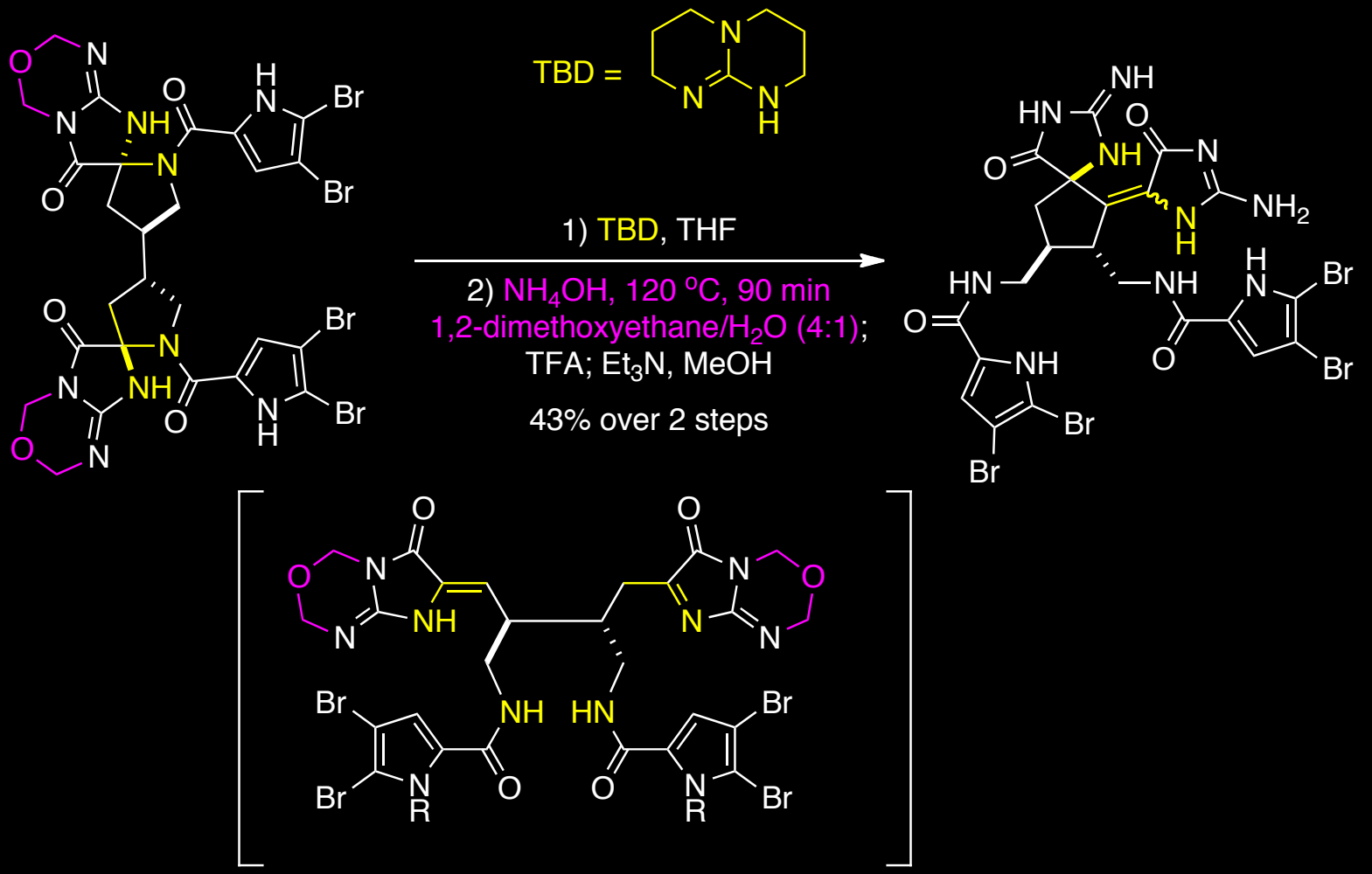
Title paper: unexpected spiroaminal formation



Note: Major isomer (shown) was treated with TFA and the corresponding salt was recrystalized. Relative stereochemistry was based on corresponding X-ray.

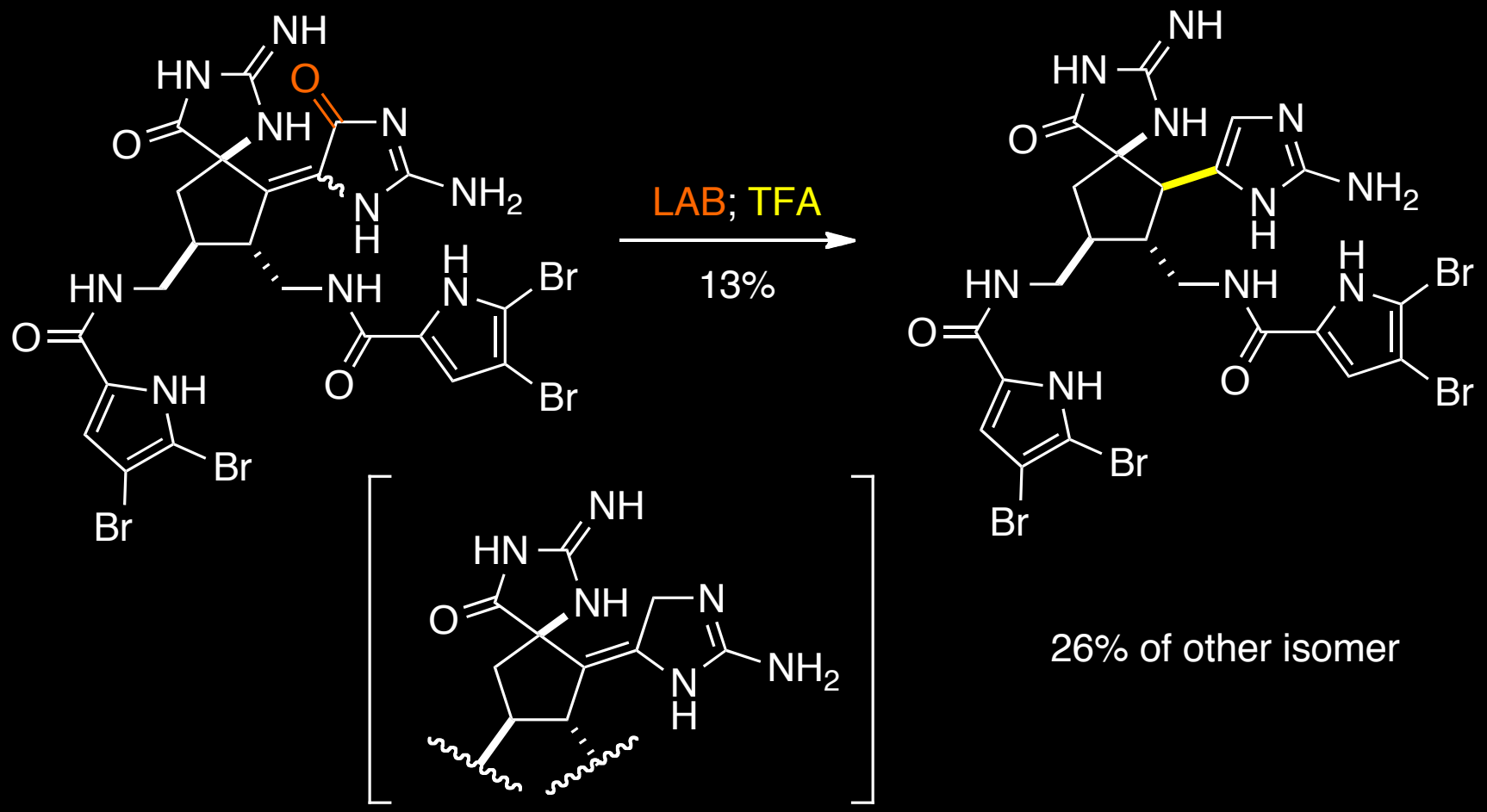
Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

Title paper: Isomerization to monoalkylidene-containing spirocycles



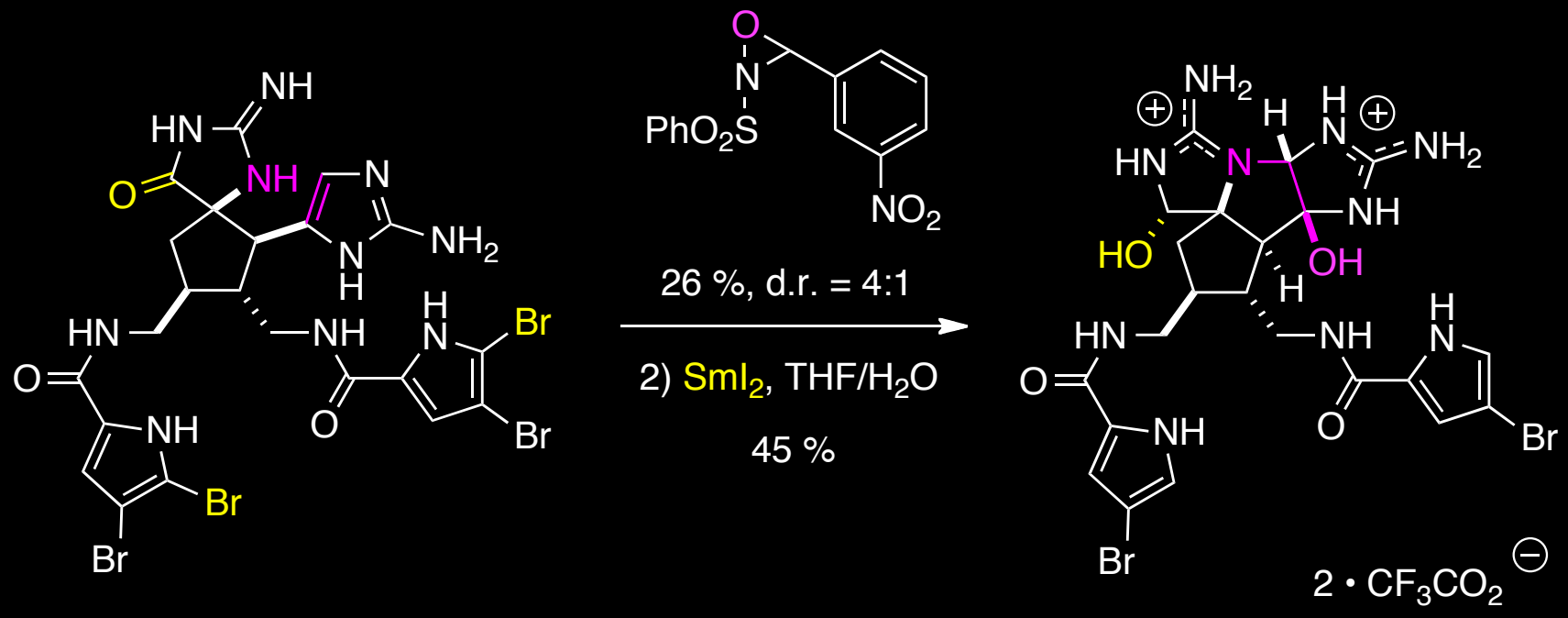
Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

Title paper: Deoxygenation and isomerization



Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

Title paper: Oxidation and reduction



Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed.* **2012**, 51, ASAP

SmI_2 preparation

- Water, oxygen, and peroxide content in THF have little influence on the synthesis of SmI_2
- Most problems associated with SmI_2 preparation are due to "inactive" samarium metal
- "inactive" samarium metal can be activated by dry stirring under argon (similar to activating magnesium).
- Solutions of SmI_2 can be stored, however the solution should be stirred for 1 hr prior to use.

Szostak, M.; Spain, M.; Procter, D. J. *J. Org. Chem*. **2012**, ASAP

Final thoughts

• The synthesis of 2.0 mg of nonchlorinated (±)-Axinellamines was achieved in 13 steps in 0.016 % yield.

• Interesting formation of spiroaminals and their base-mediated isomerization into monoalkylidene spriocycles.

• The Haran Group mentions that there interest lie in synthesizing several halogenated analogs through this method and determine there impact on biological activity.

• Essential to achieving their above goal is the refinement of spiroaminal formation and isomerization.

Ding, H.; Roberts, A. G.; Harran, P. G. *Angew. Chem. Int. Ed*. **2012**, 51, ASAP