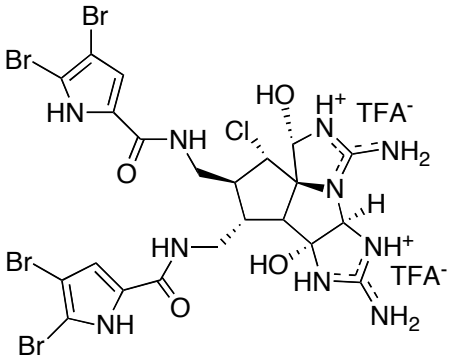
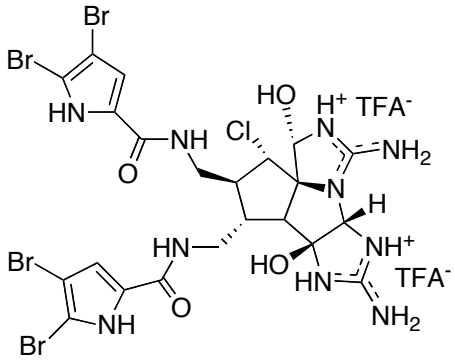


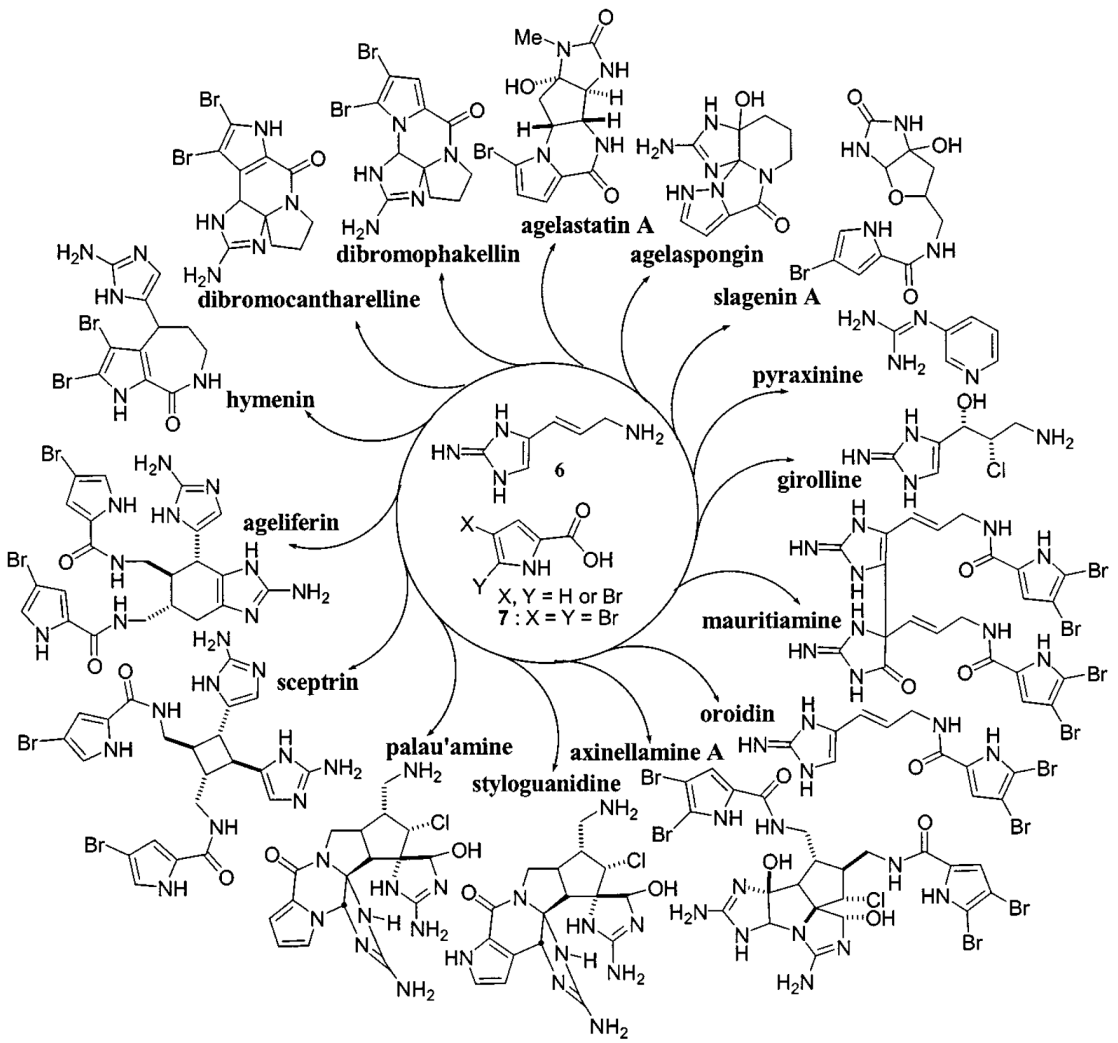


Scalable, Stereocontrolled Total Synthesis of (±)-Axinellamines A and B

Shun Su, Rodrigo A. Rodriguez, Phil S. Baran

J. Am. Chem. Soc. **2011**, *ASAP*

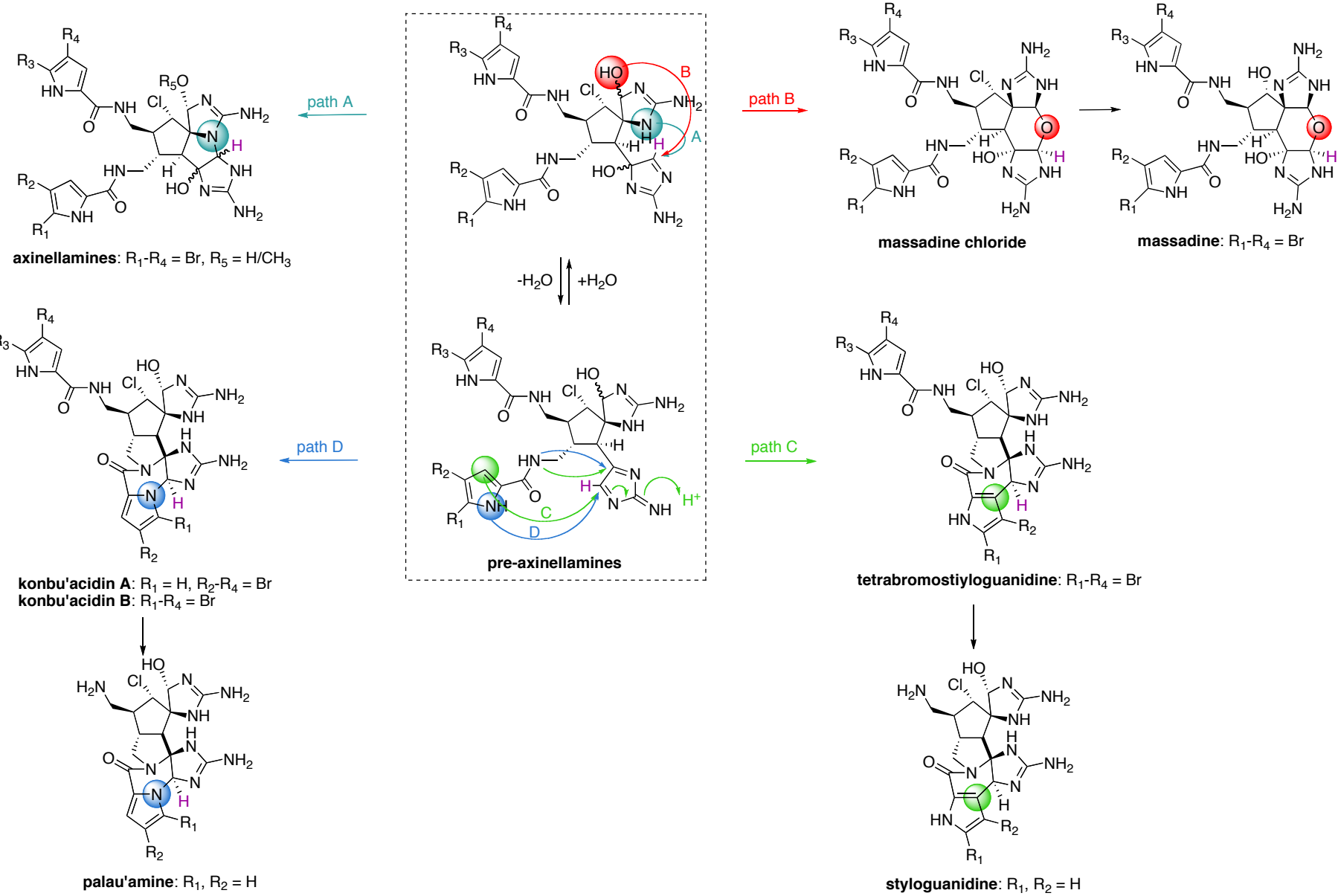
Pyrrole-Imidazole Alkaloid Diversity



3 Representative structural groups

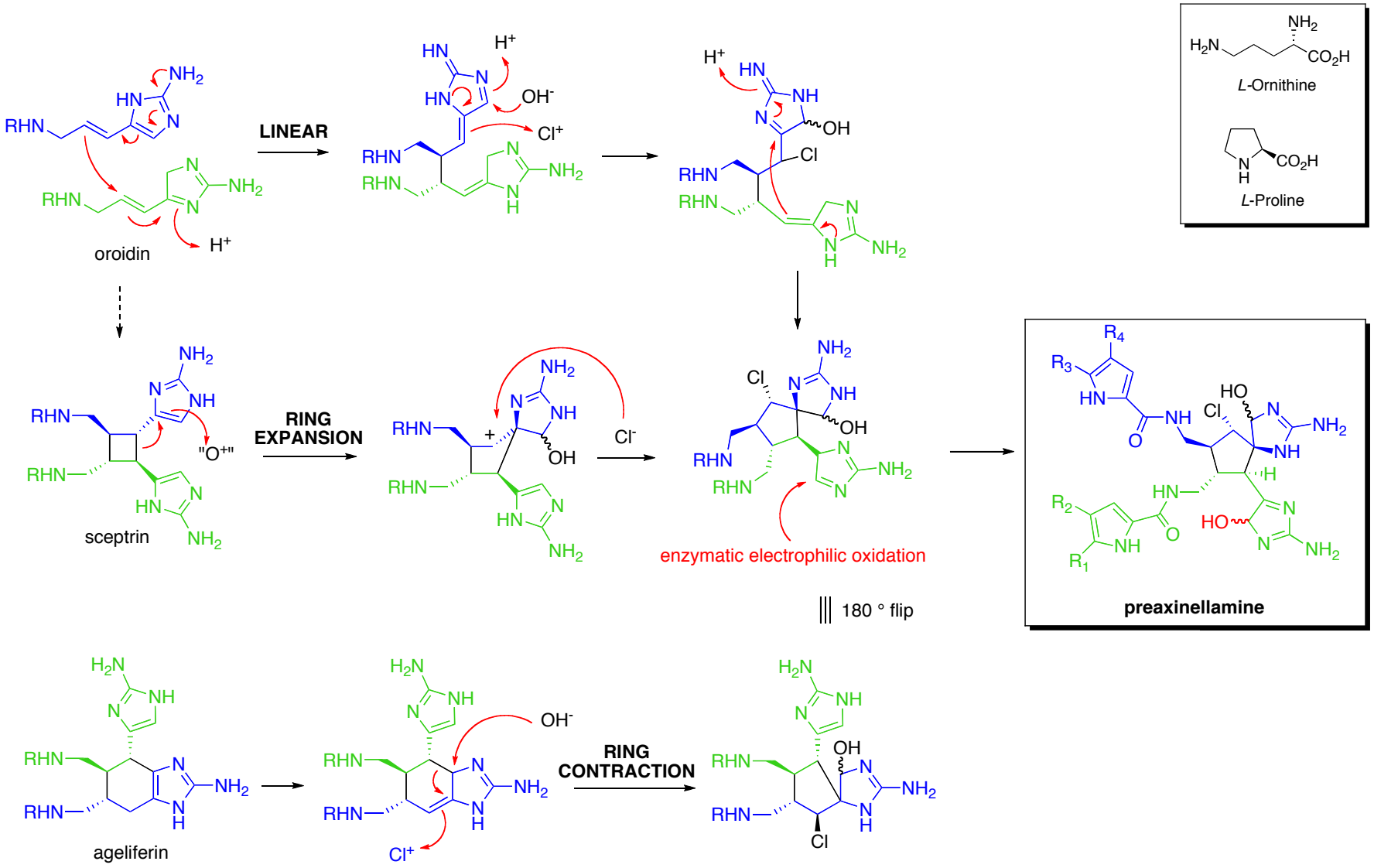
Taken from: Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.

Axinellamines and Other Pyrrole-Imidazole Alkaloids in Nature



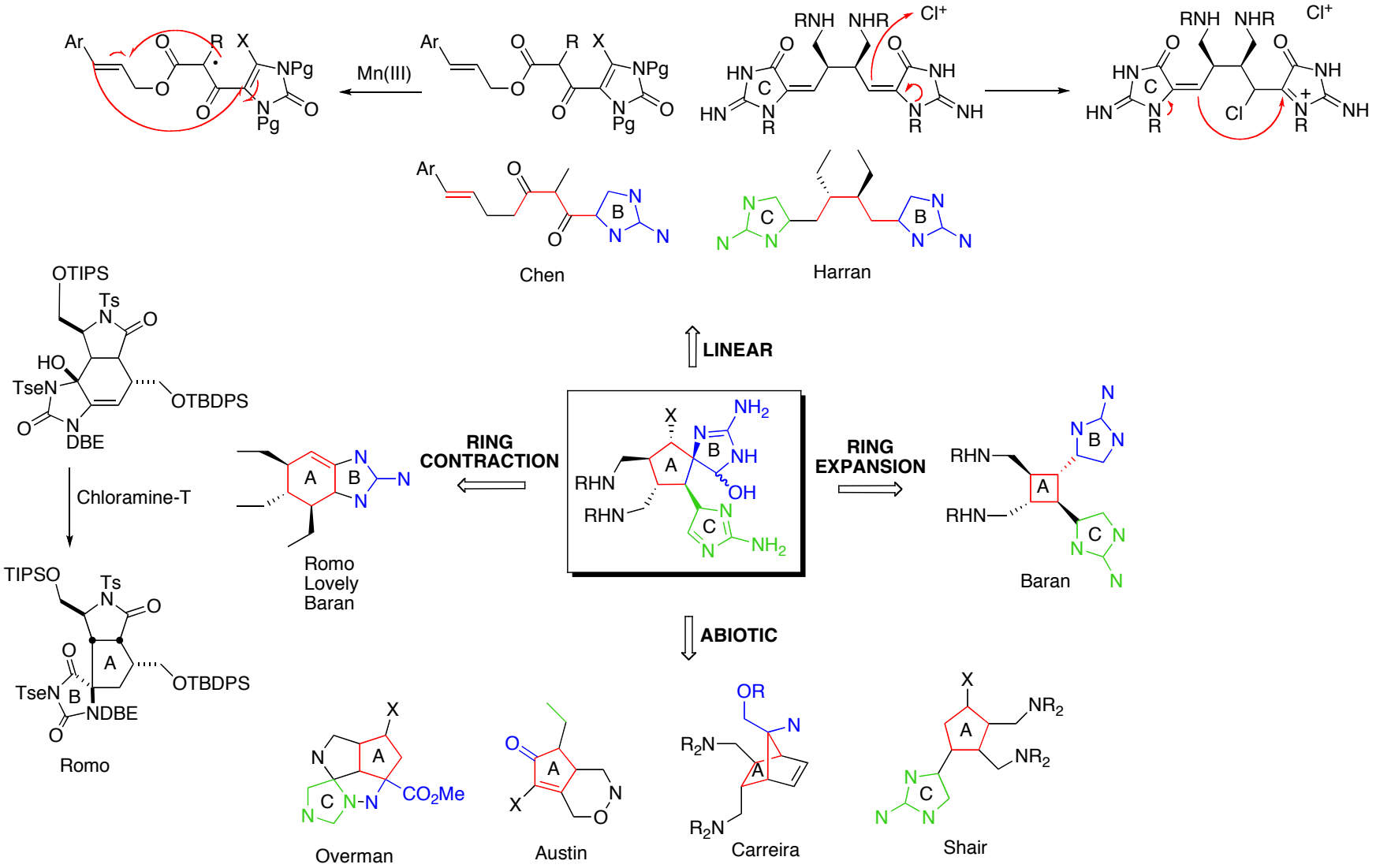
For review, see: a) Köck, M.; Graube, A.; Seiple, I.B.; Baran, P.S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586. b) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237. c) Forte, B.; Malgesini, B.; Piutti, C.; Quartieri, F.; Scolaro, A.; Papeo, G. *Mar. Drugs* **2009**, *7*, 705.

Three Hypotheses for the Origin of "Pre-axinellamine"



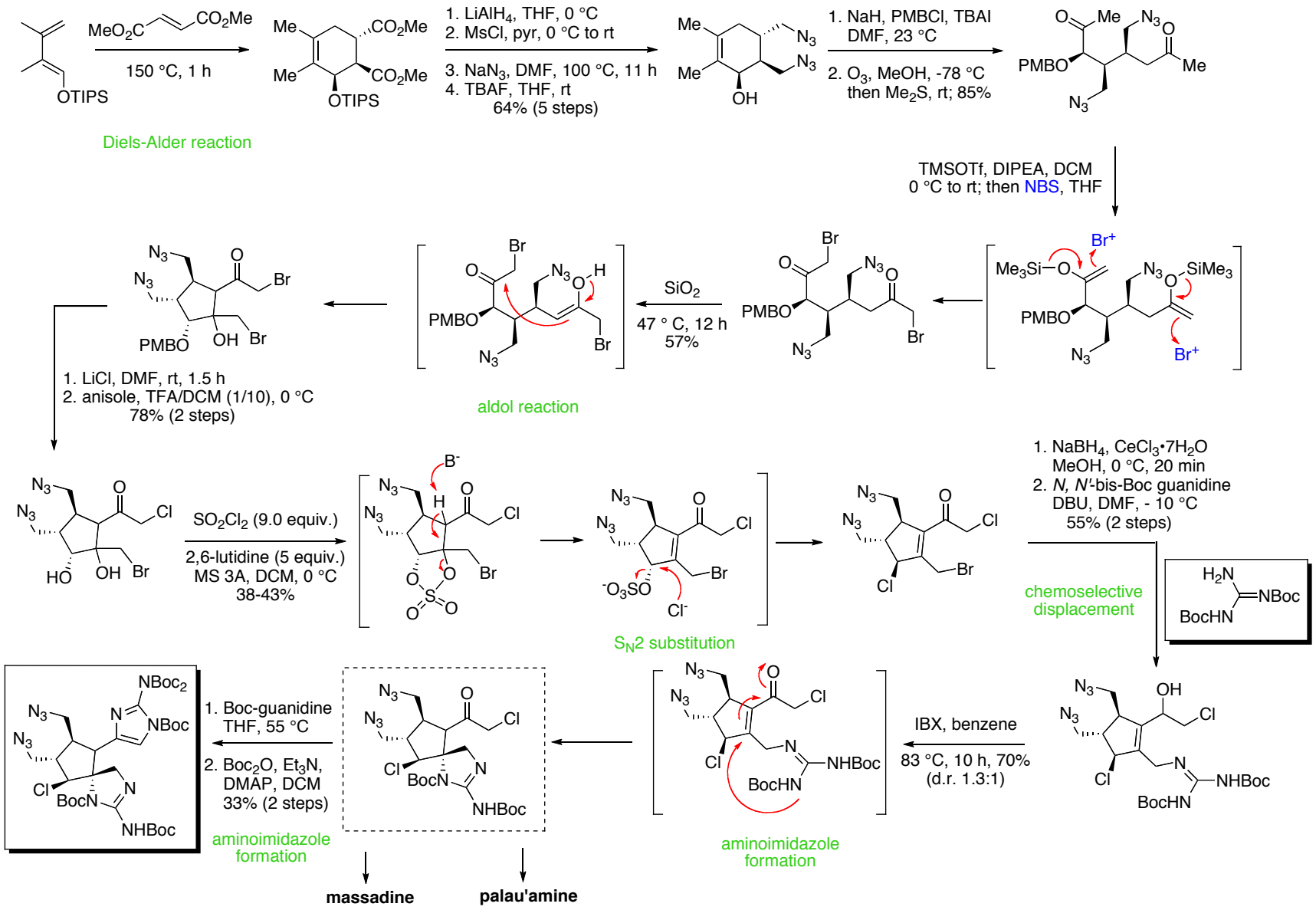
1) Köck, M.; Graube, A.; Seiple, I.B.; Baran, P.S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586. 2) Al Mourabit, A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237. 3) Kinnel, R.B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P.J. *J. Org. Chem.* **1998**, *63*, 3281. 4) Poupon, E.; Nay, B. *Biomimetic Organic Synthesis*; Wiley-VCH: Weinheim, 2011.

Synthetic Approaches toward the Cyclized Pyrrole-Imidazole Alkaloids



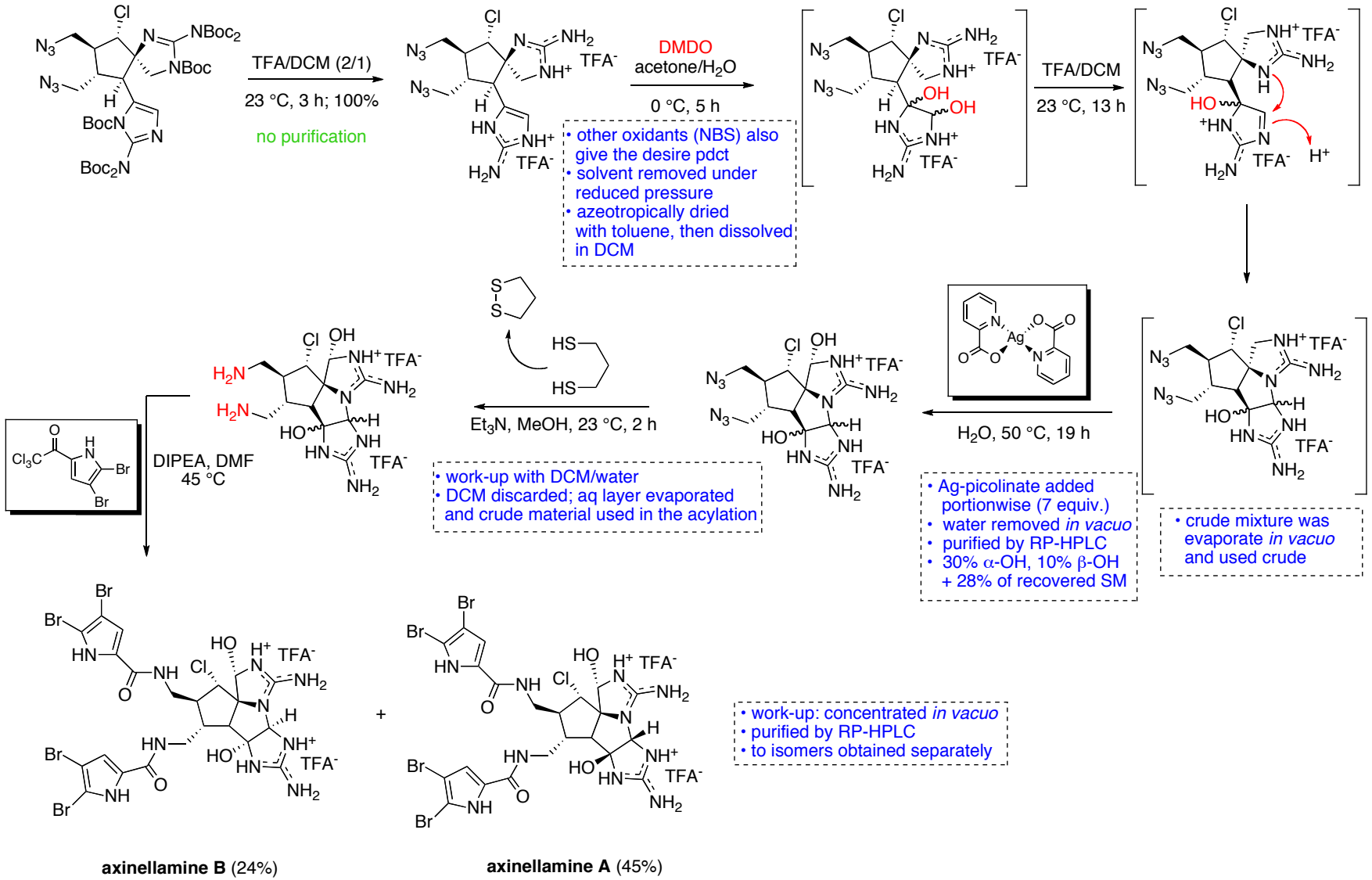
1) Köck, M.; Graube, A.; Seiple, I.B.; Baran, P.S. *Angew. Chem. Int. Ed.* **2007**, *46*, 6586. 2) Tan, X.; Chen, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 4345. 3) Garrido, H. –H.; Nakadai, M.; Vimolratana, M.; Li, Q.; Doundoulakis, T.; Harran, P.G. *Angew. Chem. Int. Ed.* **2005**, *44*, 765. 4) Wang, S.; Dilley, A.S.; Poullenec, K.G.; Romo, D. *Tetrahedron* **2006**, *62*, 7155. 5) Du, H.; He, Y.; Sivappa, R.; Lovely, C.J. *Synlett* **2006**, 695. 6) O'Malley, D.P.; Li, K.; Maue, M.; Zografos, A.L.; Baran, P.S. *J. Am. Chem. Soc.* **2007**, *129*, 4762. 7) Overman, L.E.; Rogers, B.N.; Tellew, J.E.; Trenkle, W.C. *J. Am. Chem. Soc.* **1997**, *119*, 7159. 8) Koenig, S.G.; Miller, S.M.; Leonard, K.A.; Lowe, R.S.; Chen, B.C.; Austin, D.J. *Org. Lett.* **2003**, *5*, 2203.; 9) Starr, J.T.; Koch, G.; Carreira, E.M. *J. Am. Chem. Soc.* **2000**, *122*, 8793.

Total Synthesis of Axinellamines A and B - First Approach, Part 1



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

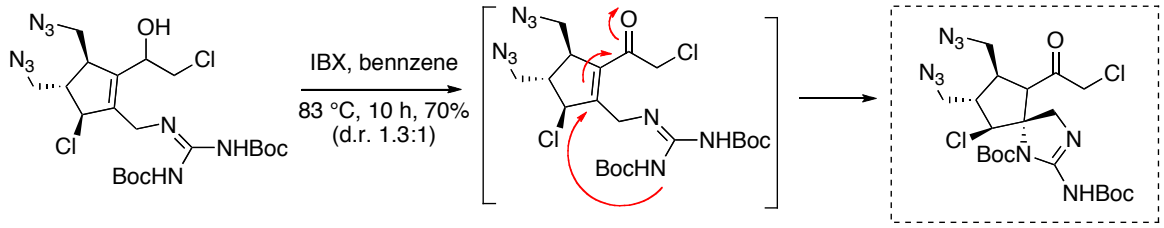
Total Synthesis of Axinellamines A and B - First Approach, Part 2



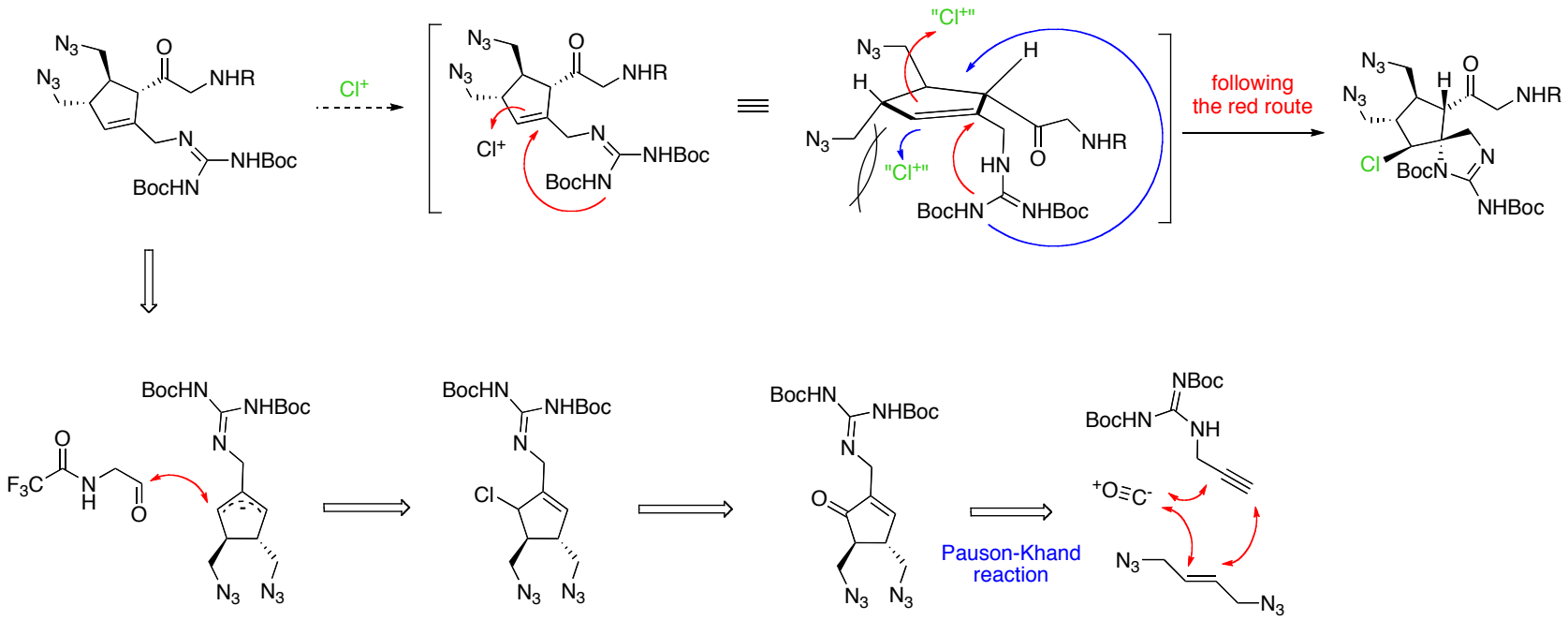
1) O'Malley, D.P.; Yamaguchi, J.; Young, I.S.; Seiple, I.B.; Baran, P.S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3581. 2) for Ag picolinate, see: a) Fowles, G. W. A.; Matthews, R.W.; Walton, R.A. *J. Chem. Soc. A* **1968**, 1108. b) Clarke, T.G.; Hampson, N.A.; Lee, J.B.; Morley, J.R.; Scanlon, B. *J. Chem. Soc. C* **1970**, 815. c) Lee, J.B.; Parkin, C.; Shaw, M.J. *Tetrahedron* **1973**, *29*, 751. 3) for propanedithiol, see: Bayley, H.; Stardring, D.N.; Knowels, J.R. *Tetrahedron Lett.* **1978**, *19*, 3633.

Total Synthesis of Axinellamines – New Approach (Scalable & Stereocontrolled)

previous route to Axinellamines:

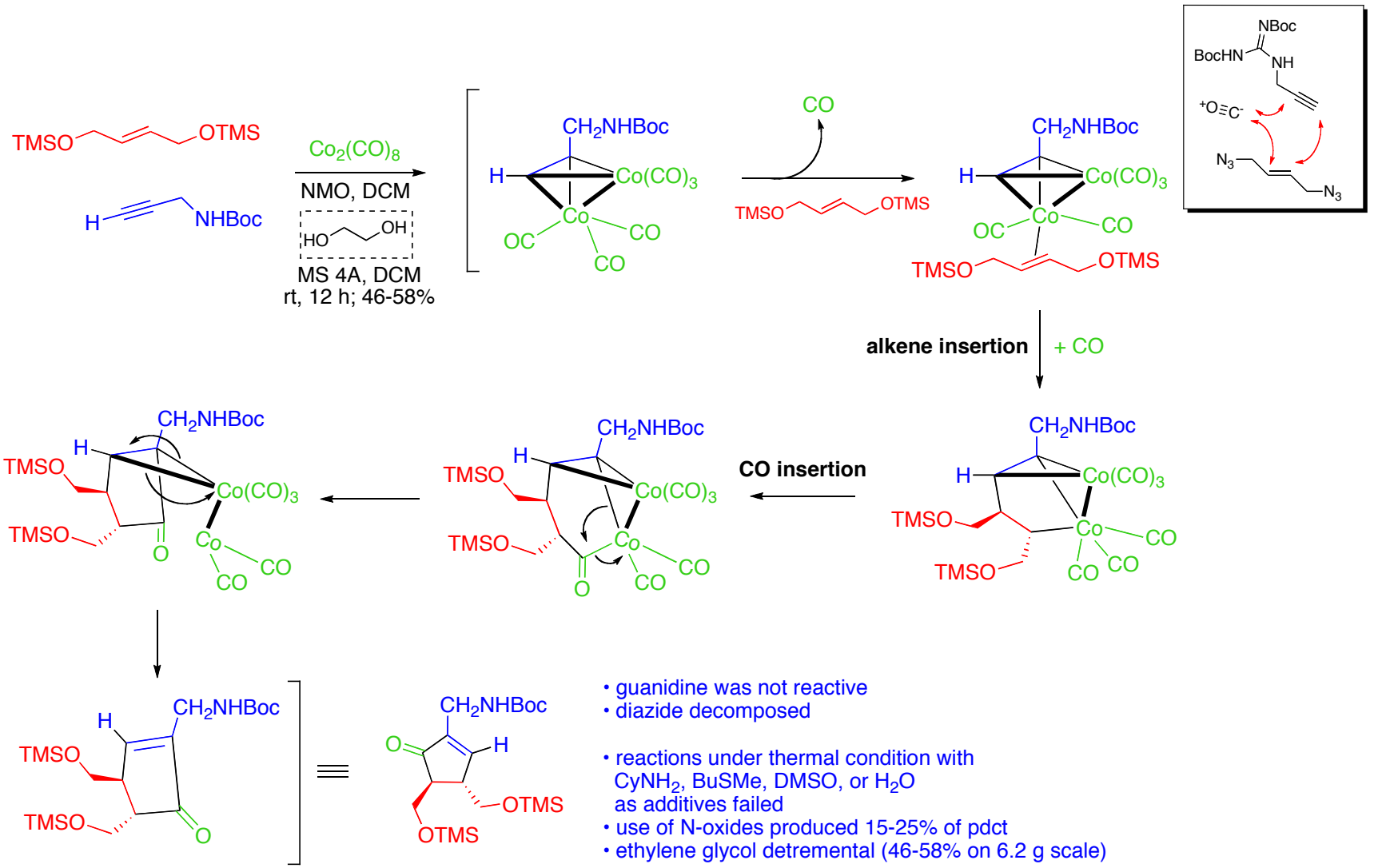


this work:



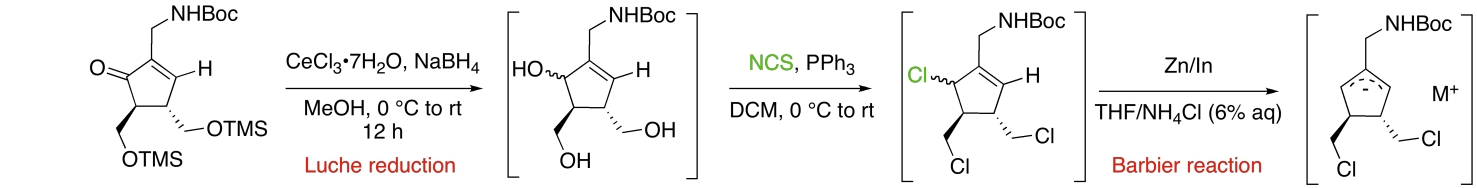
1) O'Malley, D.P.; Yamaguchi, J.; Young, I.S.; Seiple, I.B.; Baran, P.S. *Angew. Chem. Int. Ed.* **2008**, *47*, 3581. 2) Su, S.; Rodriguez, R.A.; Baran, P.S. *J. Am. Chem. Soc.* **2011**, ASAP.

Pauson-Khand Reaction – Initial Forays toward Axinellamines



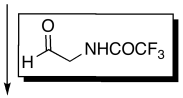
1) Su, S.; Rodriguez, R.A.; Baran, P.S. *J. Am. Chem. Soc.* **2011**, ASAP. 2) Kurti, L; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, MA, USA, 2005.; 3) for NMO in Puson-Khand, see: Shambayati, S.; Crowe, W.E.; Schreiber, S.L. *Tetrahedron Lett.* **1990**, *31*, 5289.

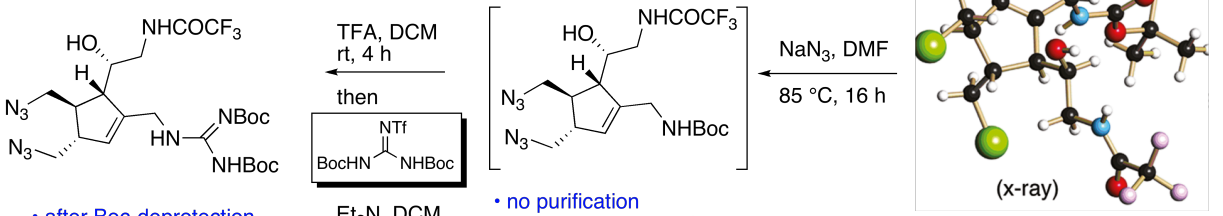
Stereocontrolled, Gram-Scale Synthesis of the Axinellamines – Spirocycle Synthesis



- 1,2-reduction and DESILYLATION
- crude mixture diluted with EtOAc
- filtered through silica-plug
- used crude (1:1 d.r.)

- diluted with hexanes
- loaded onto SiO_2
- flushed with 25% EA/hexanes
- used crude (2:1 d.r.)





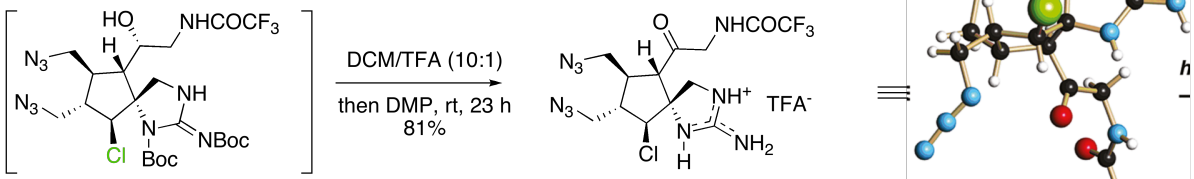
- after Boc-deprotection solvent removed and redissolved in DCM
- purification on SiO_2 (3.2 g obtained)

- no purification
- filtration through SiO_2 plug

- amide and trichloride mixed together
- add In, Zn, then NH_4Cl (6% aq)
- purification by SiO_2-chromatography
- single diastereomer

- In, Sn, Fe alone - do not work

$TfNH_2$ (0.25 equiv.), DCM, 0 °C
then *t*-BuOCl, 0 °C, 30 min



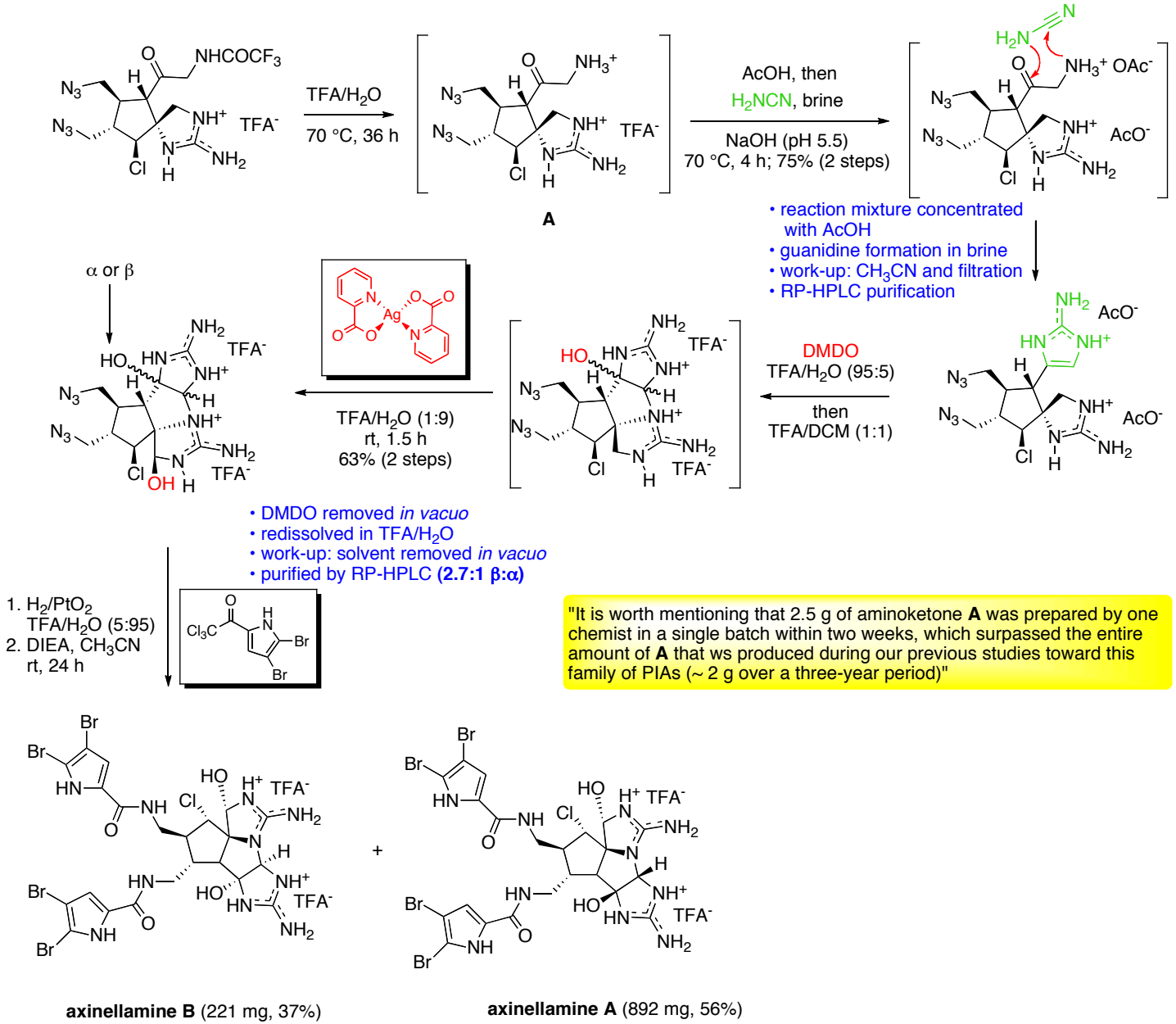
- work-up: dried on high vacuum and used crude

- detrimental effect of $TfNH_2$
- no formation of TfNHCl with t-BuOCl (^{19}F NMR)

- solvent removed *in vacuo*
- redissolved in $MeCN/H_2O$ and filtered through a fritted funnel
- RP HPLC purification

1) Su, S.; Rodriguez, R.A.; Baran, P.S. *J. Am. Chem. Soc.* **2011**, ASAP. 2) for Barbier reaction and the use of NH4Cl, see:: Breton, G.W.; Shugart, J.H.; Hughey, C.A., Conard, B.P.; Perala, S.M. Molec*ules* **2001**, *6*, 655.

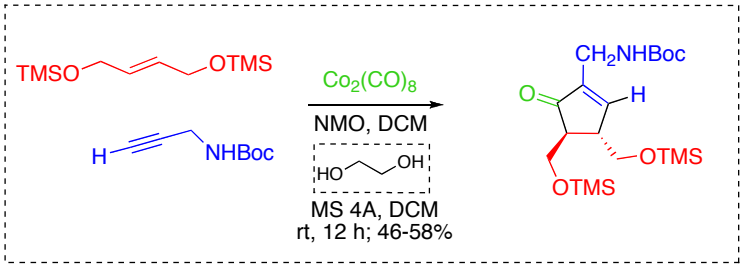
Stereocontrolled, Gram-sale Sytnehsis of Axinellamines – Accomplishing the Mission

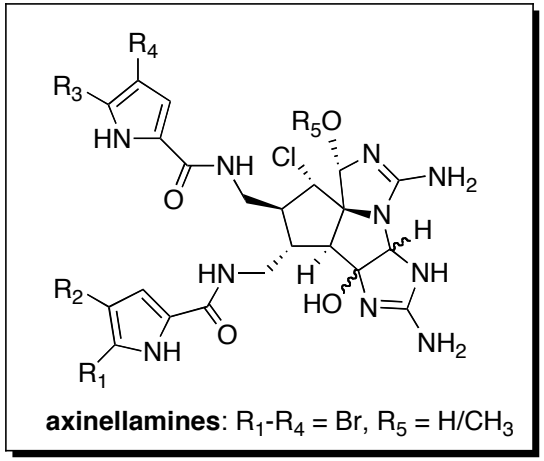


1)) Su, S.; Rodriguez, R.A.; Baran, P.S. *J. Am. Chem. Soc.* **2011**, ASAP.

Conclusions

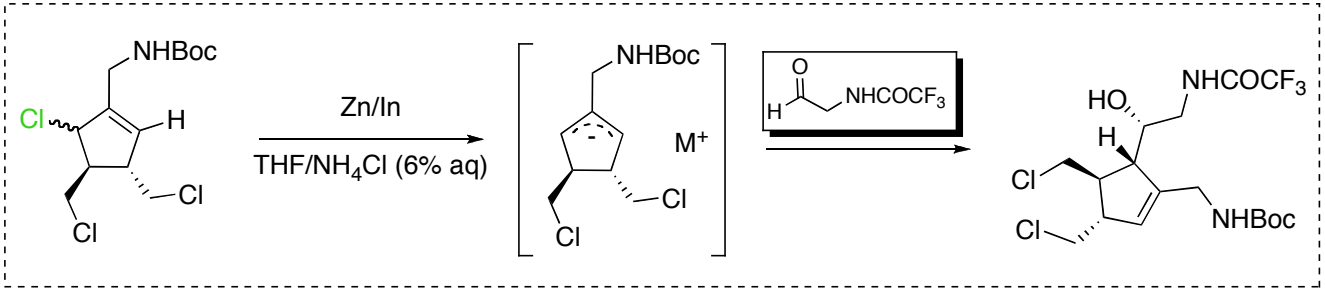
- robust, simple and practical route to Axinellamines, despite the sheer complexity
- all steps conducted on a gram scale
- no cryogenic temperature required
- minimum purification
- ethylene-glycol assisted Pauson-Khand reaction





axinellamines: R_1-R_4 = Br, R_5 = H/CH_3

- chemoselective In/Zn-mediated Barbier reaction



- novel chlorination/spirocyclization method