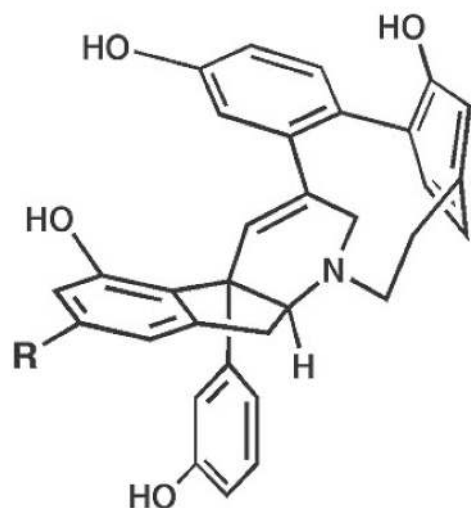


Total Synthesis of (\pm)-Haouamine A



R = H; haouamine A (**1**)
R = OH; haouamine B (**2**)

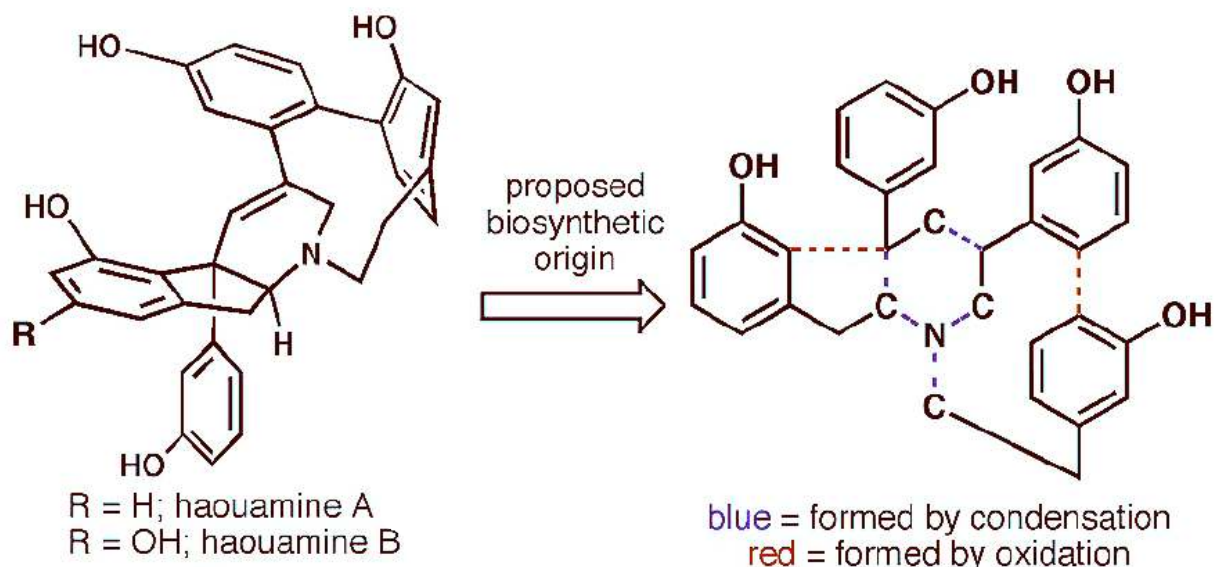
Noah Z. Burns and Phil S. Baran

Department of Chemistry, The Scripps Research Institute

J. Am. Chem. Soc. **2006**, *128*, 3908.

Juan Arredondo

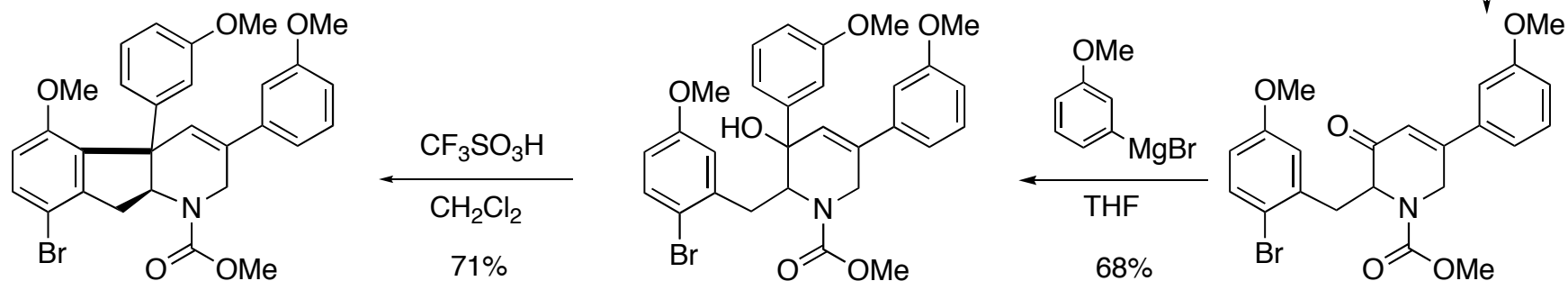
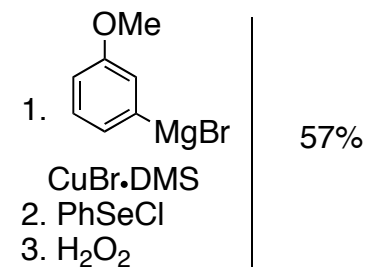
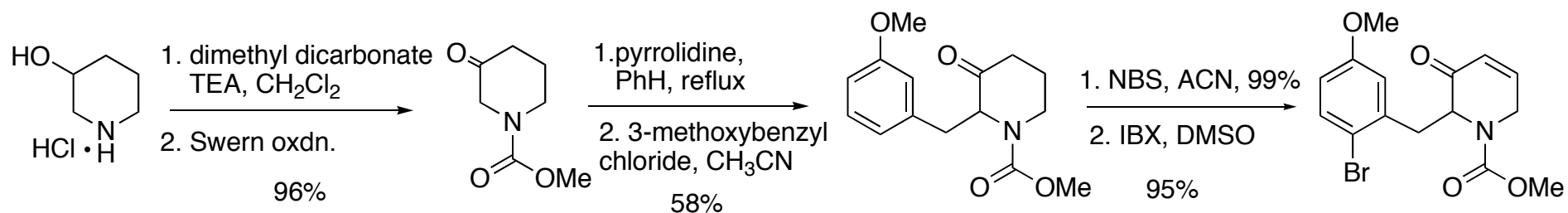
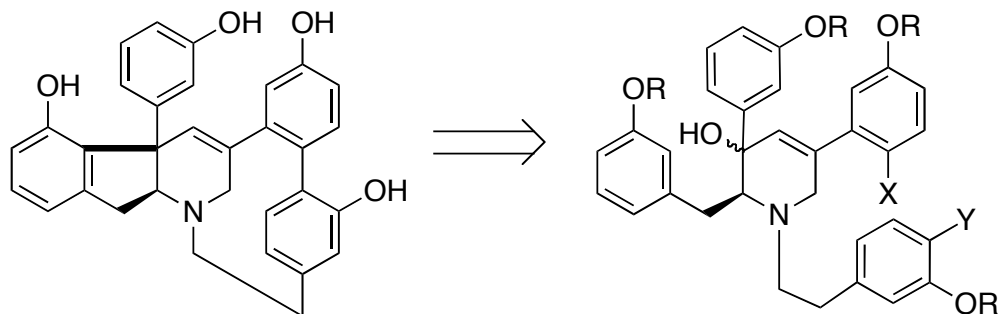
April 1, 2006



- ❖ Isolated from a tunicate *Aplidium haouarianum* off Tarifa Island (Cádiz, Spain).
- ❖ Exists as an inseparable mixture of two interconverting isomers haouamine A and B.
- ❖ Haouamine A exhibits high and selective cytotoxic activity against human colon carcinoma HT-29 cell line with $IC_{50} = 0.1 \mu\text{g/mL}$. Haouamine B is less cytotoxic, $IC_{50} = 5 \mu\text{g/mL}$ against the mice endothelial cells MS-1.
- ❖ Unprecedented class of alkaloids characterized by two constrained ring systems, the indeno-tetrahydropyridine (left half) and the aza-paracyclophane (right half).

Garrido, L.; Zubía, E.; Ortega, M. J.; Salvá, J. *J. Org. Chem.* **2003**, 68, 293. Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, 7, 4309.

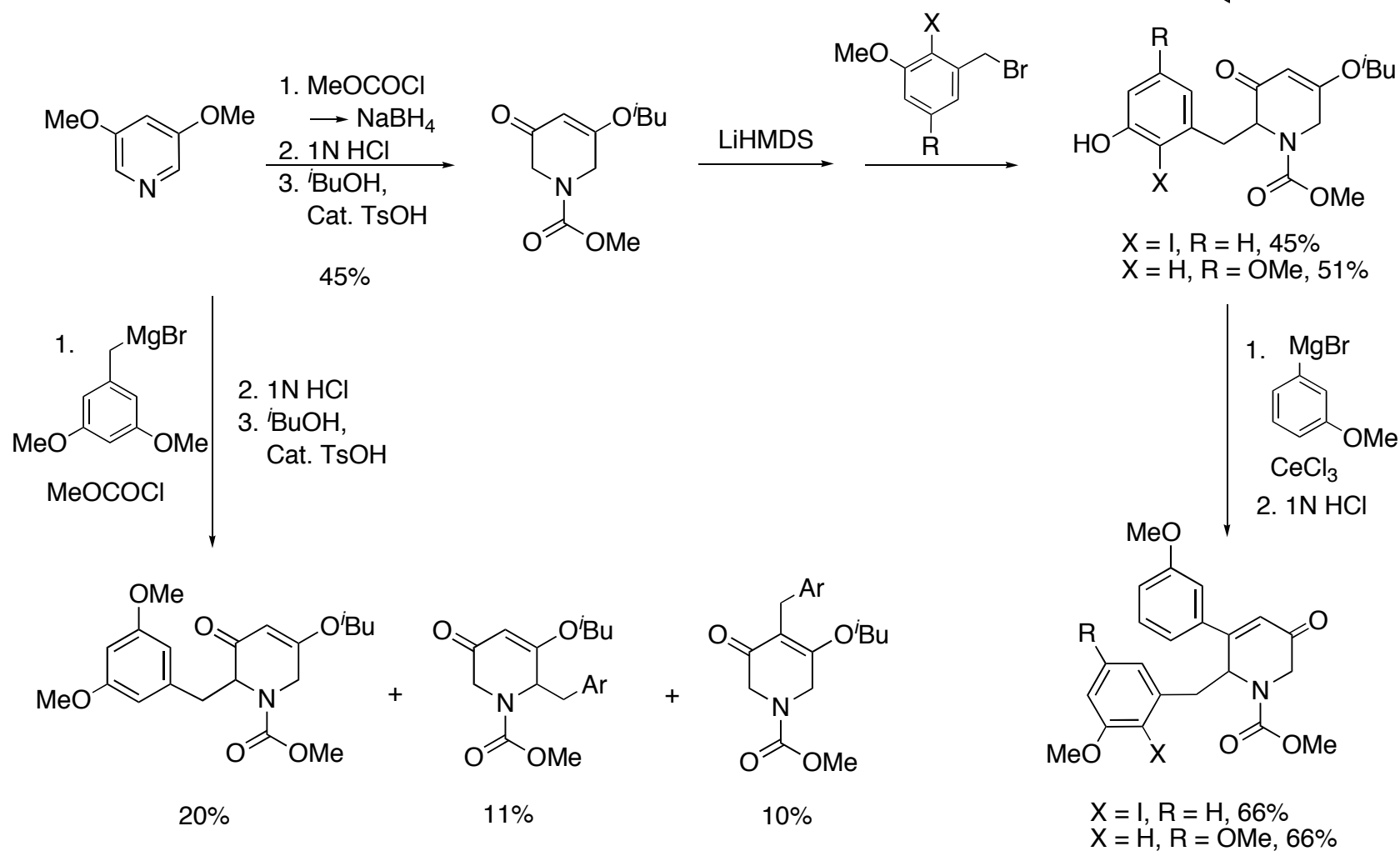
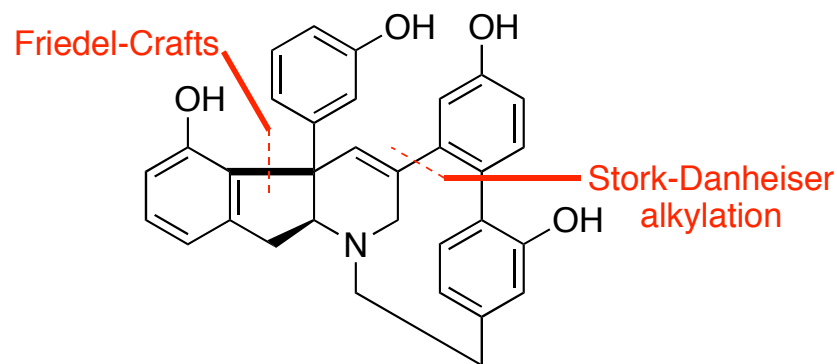
Rawal's Approach



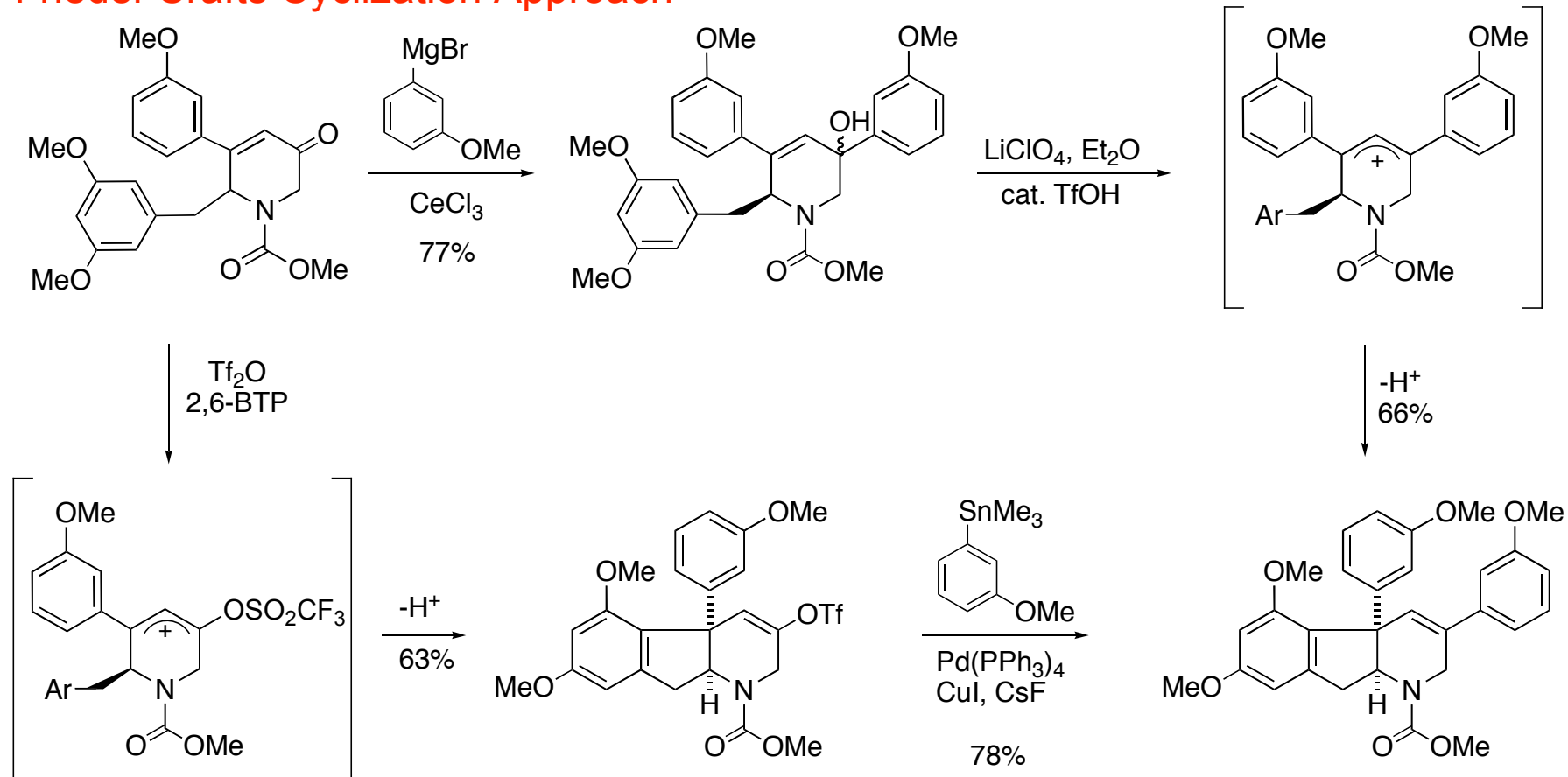
Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309.

Trauner's Approach

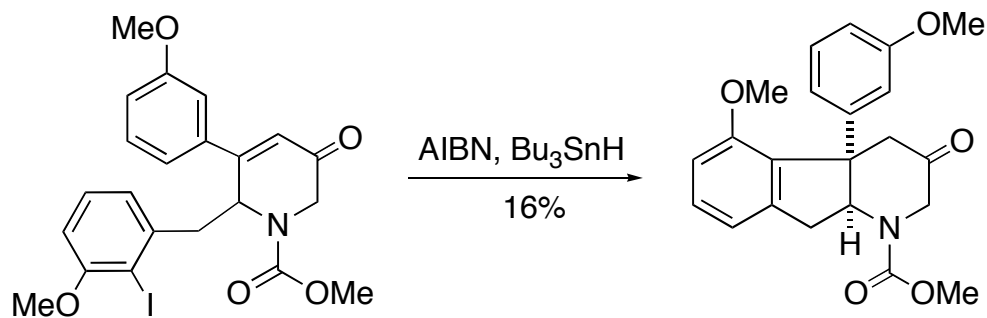
Grundi, M. A.; Trauner, D. *Org. Lett.* **2006**, 8, 23.



Friedel-Crafts Cyclization Approach

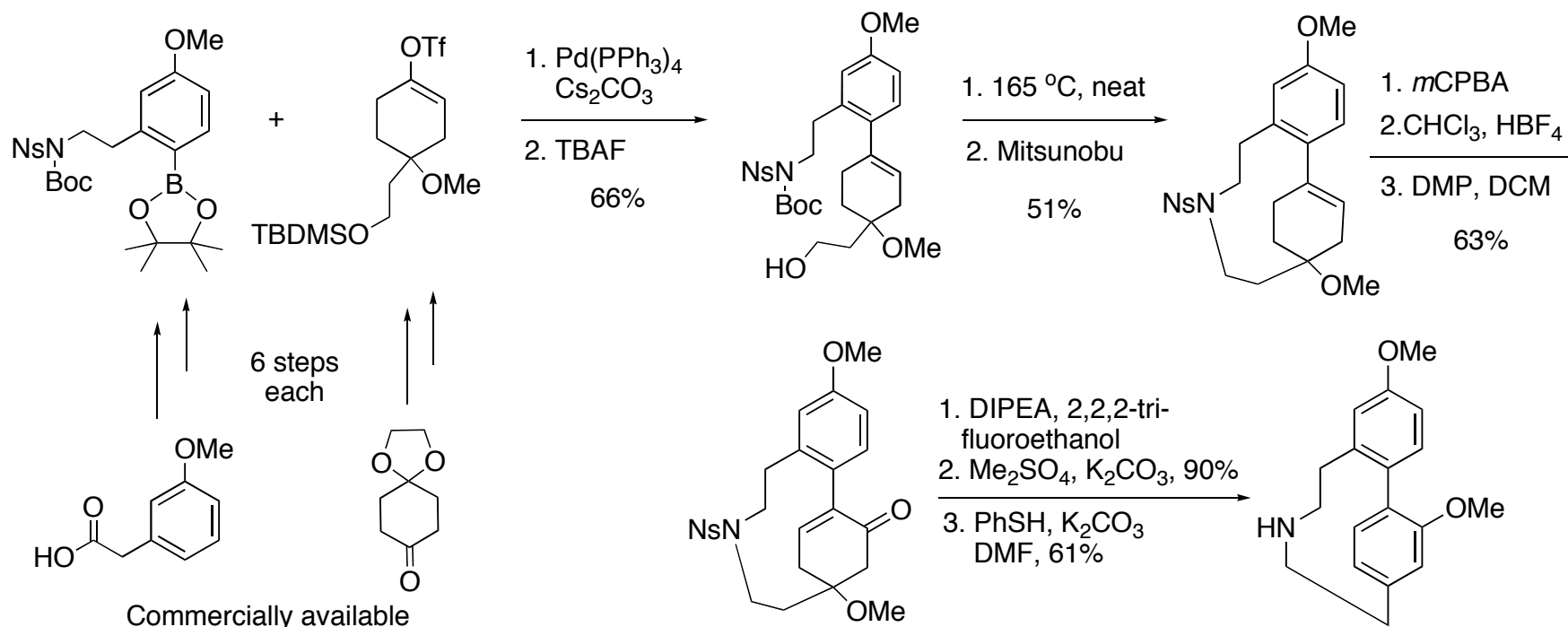
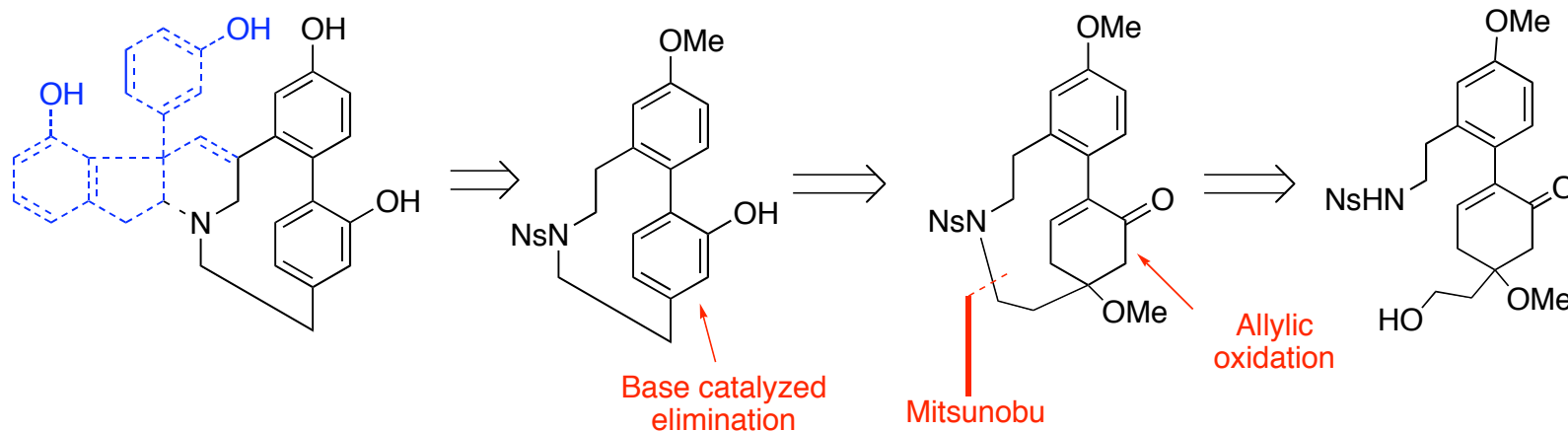


Raical Cyclization Approach



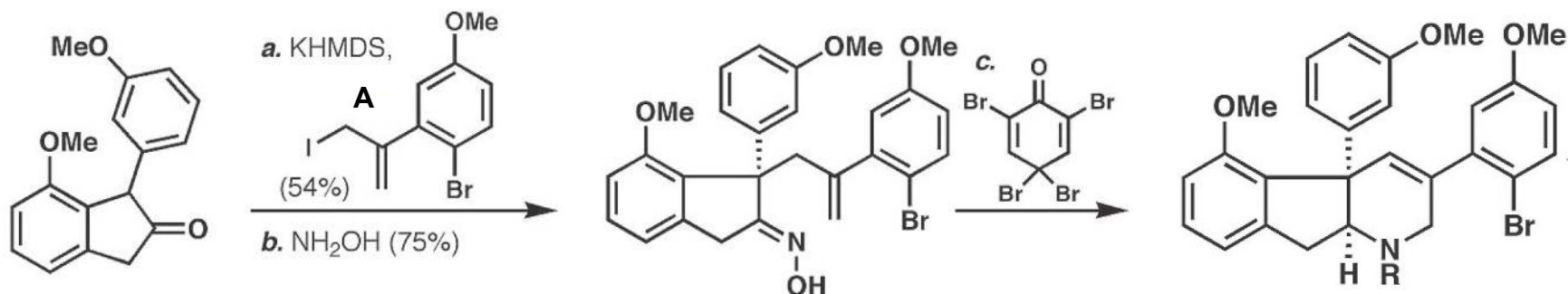
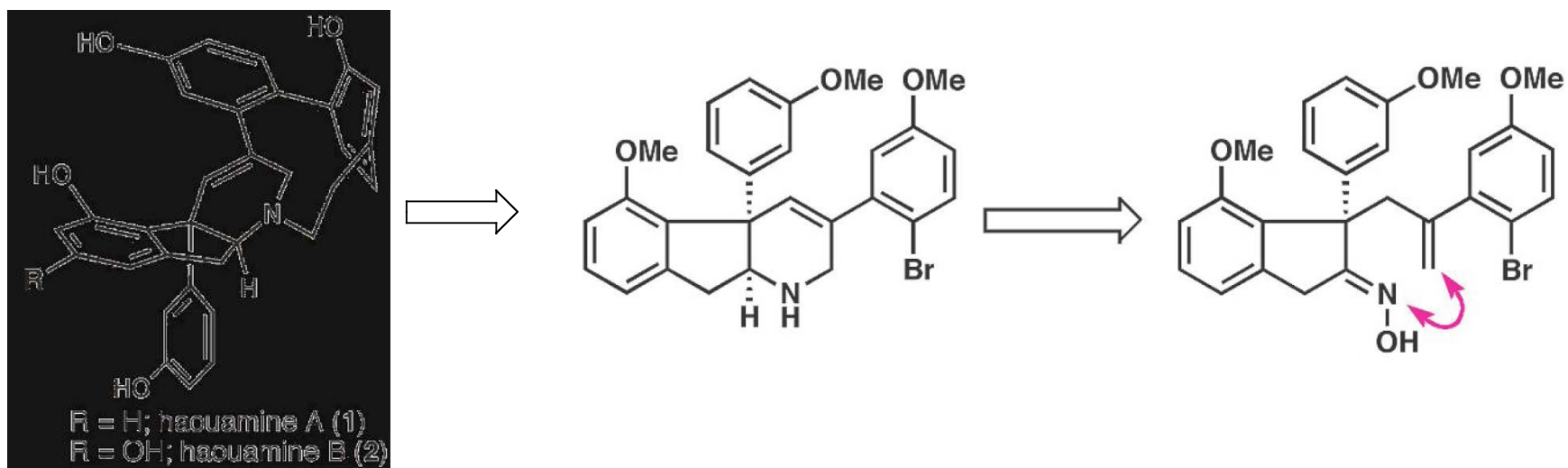
Grundi, M. A.; Trauner, D. *Org. Lett.* **2006**, *8*, 23

Wipf's Approach



Furegati, M.; Wipf, P. *Org. Lett.* (In press).

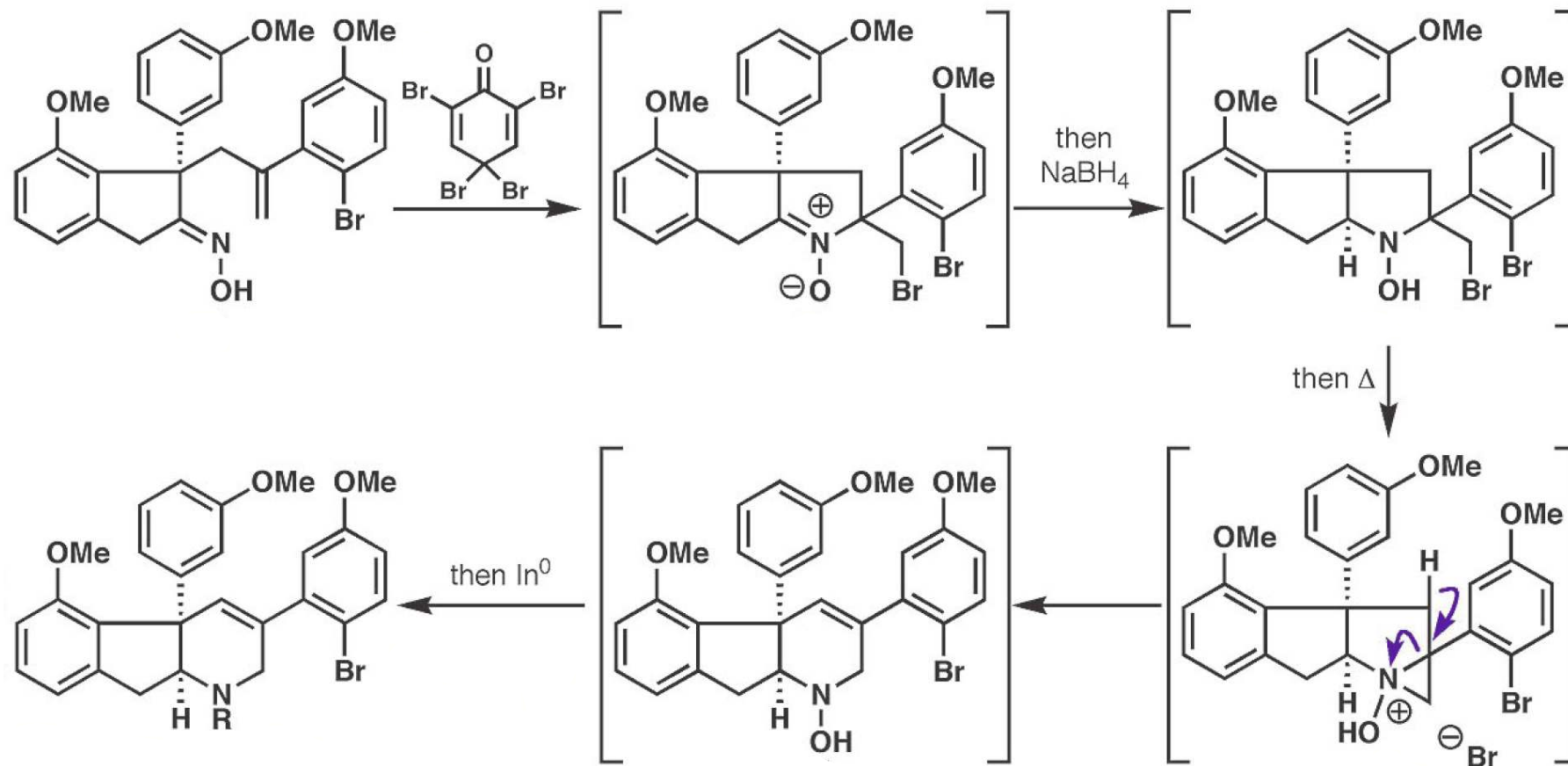
Total Synthesis of (\pm)-Haouamine A



^a Reagents and conditions: (a) KHMDS (1.1 equiv), 5:1 THF/DMPU, 0 °C, 30 min; **A** (1.5 equiv), -78 to 23 °C, 54%; (b) $\text{NH}_2\text{OH}\cdot\text{HCl}$ (20 equiv), NaOAc (15 equiv), EtOH, reflux, 24 h, 75%; (c) 2,4,4,6-tetrabromo-2,5-cyclohexadienone (2.2 equiv), DCE, 0 °C, 30 min, then NaBH_4 (5.0 equiv), EtOH, 50 °C, 1 h; In powder (2.0 equiv), 2:1 EtOH/saturated aqueous NH_4Cl , reflux, 3.5 h, 57% overall; (d) Boc_2O (1.2 equiv), DCM, 30 min

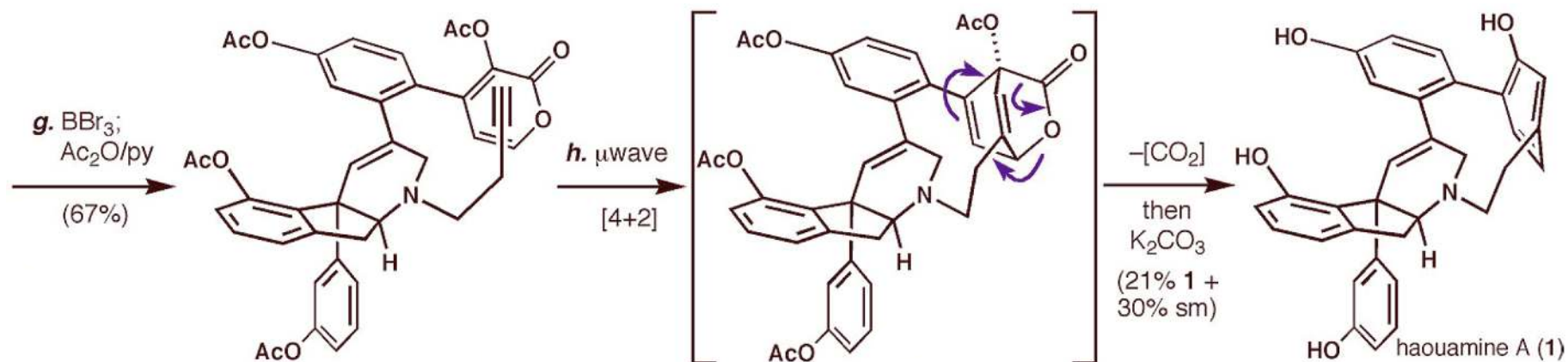
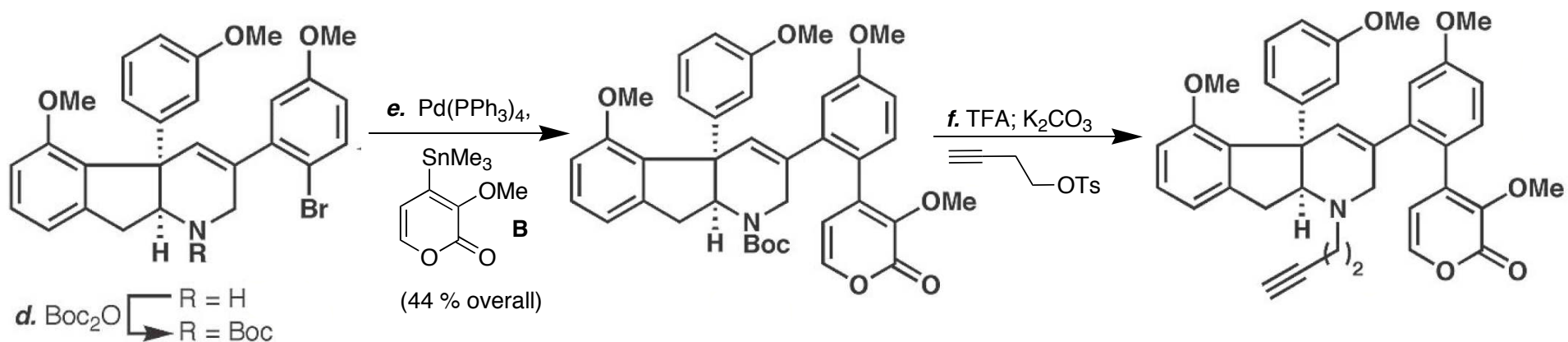
Baran, P. B.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908.

Cascade annulation



Baran, P. B.; Burns, N. Z. *J. Am. Chem. Soc.* **2006**, *128*, 3908.

Pyrone-alkyne Diels-Alder Reaction



(d) Boc_2O (1.2 equiv), DCM, 30 min; (e) **B** (1.6 equiv), $\text{Pd}(\text{PPh}_3)_4$ (0.1 equiv), CuI (0.2 equiv), toluene, reflux, 12 h, 44% overall; (f) 10:1 DCM/TFA, 3 h; 4-tosyloxybutyne (5.0 equiv), K_2CO_3 (2.5 equiv), CH_3CN , reflux, 6 h, 70%; (g) BBr_3 (10.0 equiv), DCM, -78 to 23 °C, 1:1 $\text{Ac}_2\text{O}/\text{pyr}$, 3 h, 67%; (h) DCB (0.001 M), 250 °C, BHT (7.7 equiv), 10 h; PTLC; K_2CO_3 (4.0 equiv), MeOH, 30 min, 21% **1** + 30% **sm** BHT = 2,6-di-*tert*-butylmethyl phenol; DCE = 1,2-dichloroethane; KHMDS = potassium hexamethyldisilazide; DCB = *o*-dichlorobenzene.

Baran, P. B.; Burns, N. Z. *J. Am. Chem.* **2006**, *288*, 3908.

Summary

- ❖ The first total synthesis of (\pm)-haouamine A has been achieved in 10 Steps from commercial materials.
- ❖ Highlights of the synthesis include: an unprecedented halogen-induced cascade cyclization of an unsaturated oxime to give the desired tetrahydropyridine ring system, and an intramolecular pyrone-alkyne Diels-Alder macrocyclization.
- ❖ Asymmetric synthesis of an early intermediate makes an asymmetric synthesis of haouamine A or B possible.
- ❖ “ it features some highly creative and unusual steps. It shows what can be achieved in synthesis if one thinks outside the box.” Dirk Trauner C&E News
- ❖ “is definitely not the final word, because the percent conversion is relatively low. There is room for further innovation here.” Steven M. Weinreb C&E News