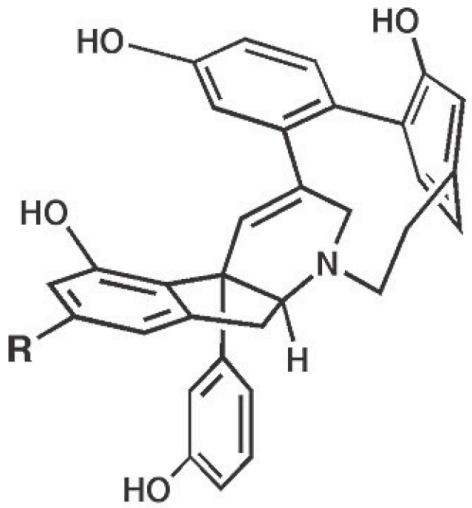
# Total Synthesis of (±)-Haouamine A




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

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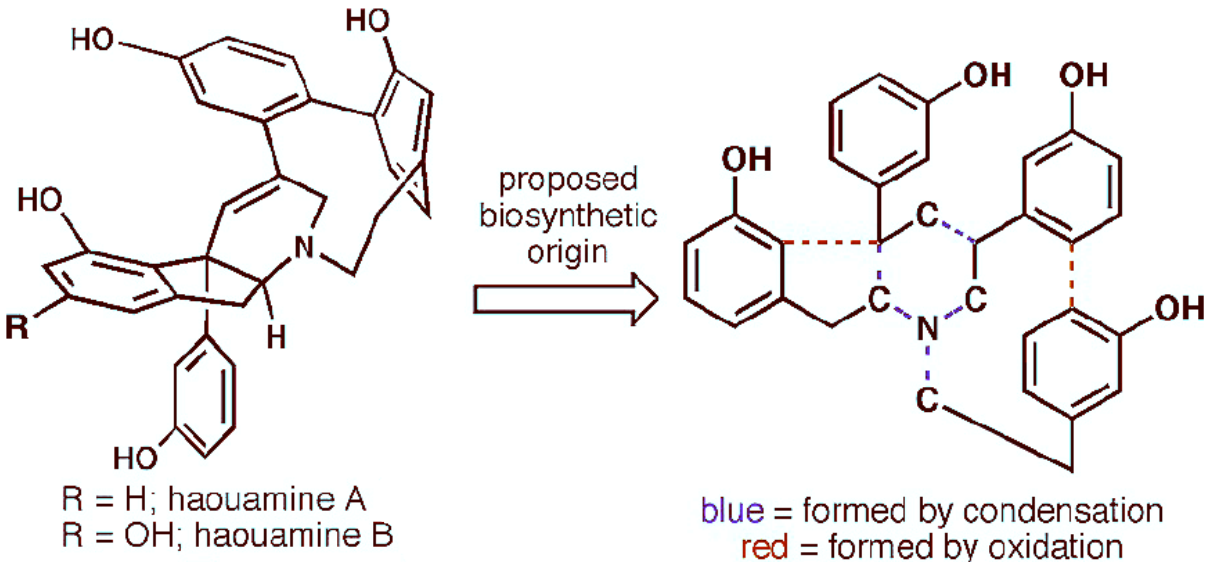
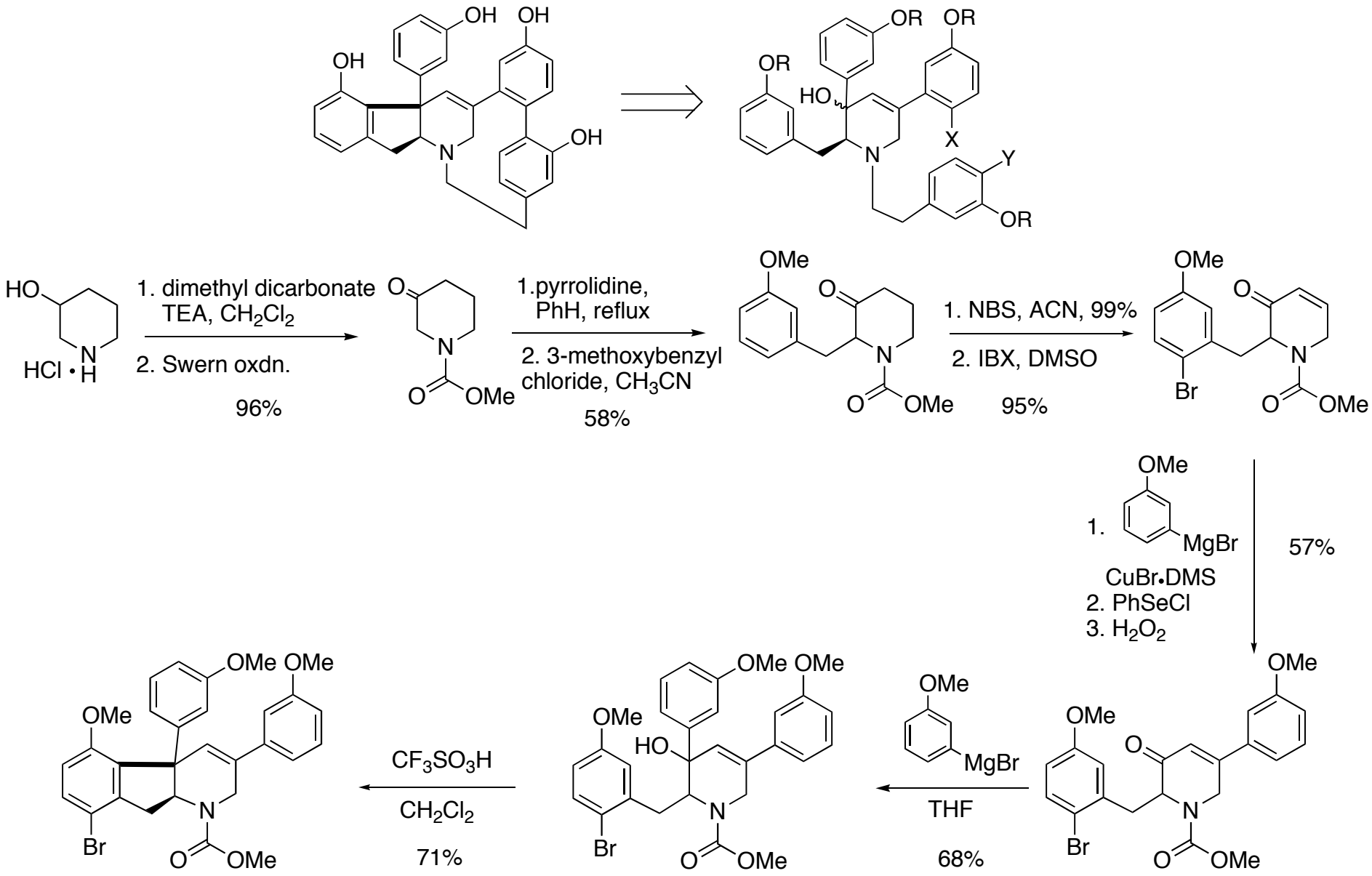
*April 1, 2006*




- 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 μg/mL. Haouamine B is less cytotixic, $IC_{50}$= 5 μg/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.

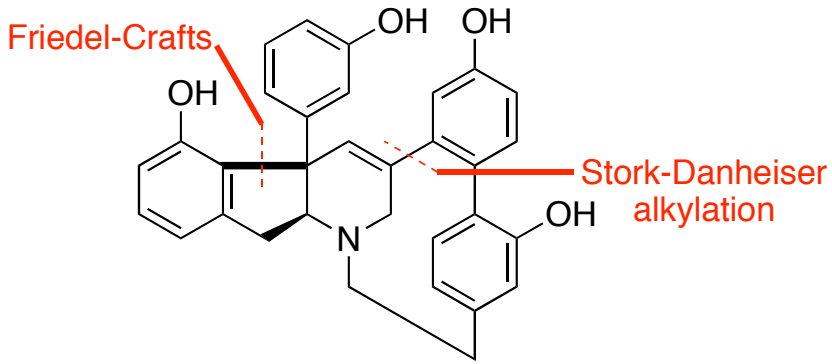
# Rawal's Approach

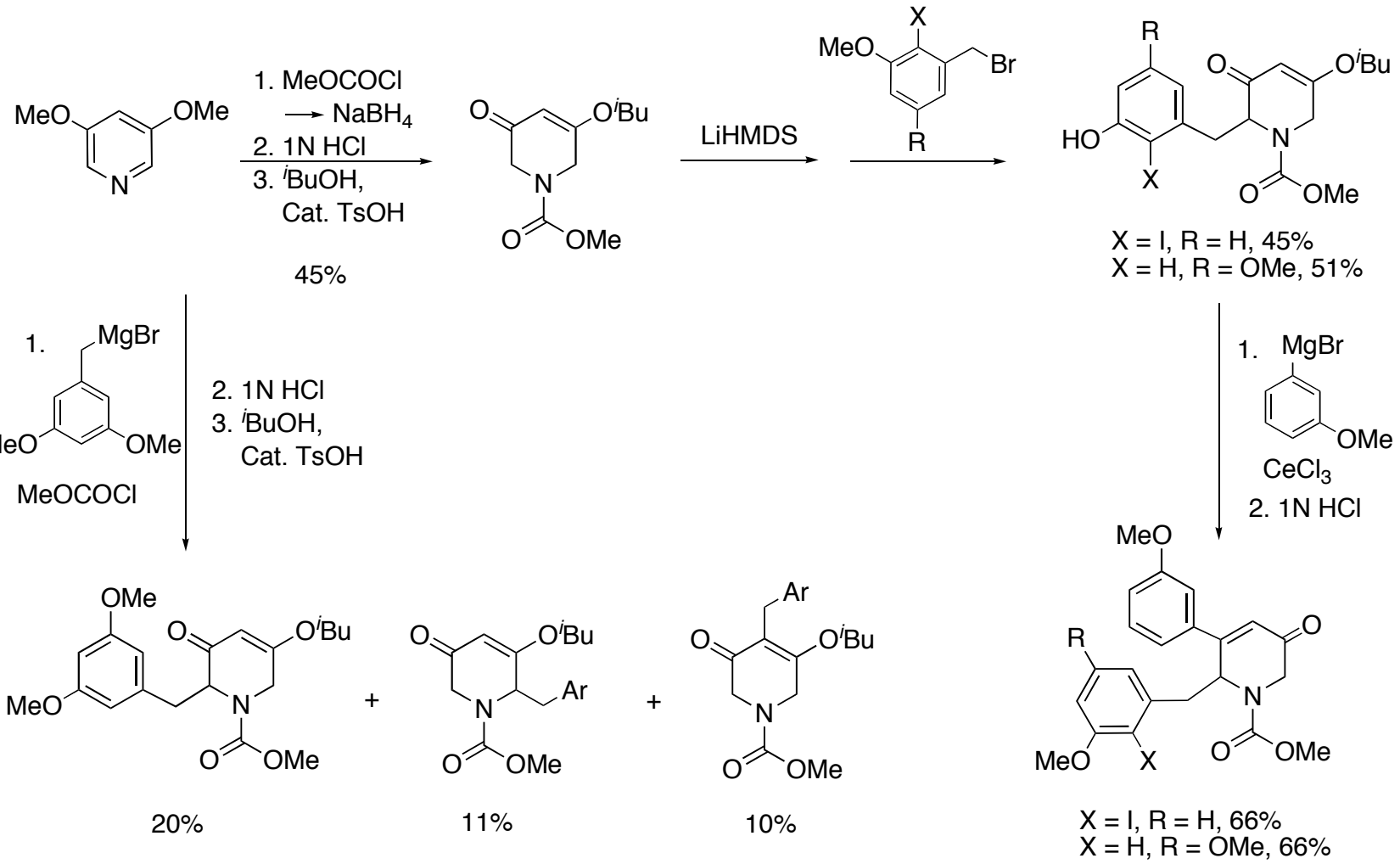



Smith, N. D.; Hayashida, J.; Rawal, V. H. *Org. Lett.* **2005**, *7*, 4309.

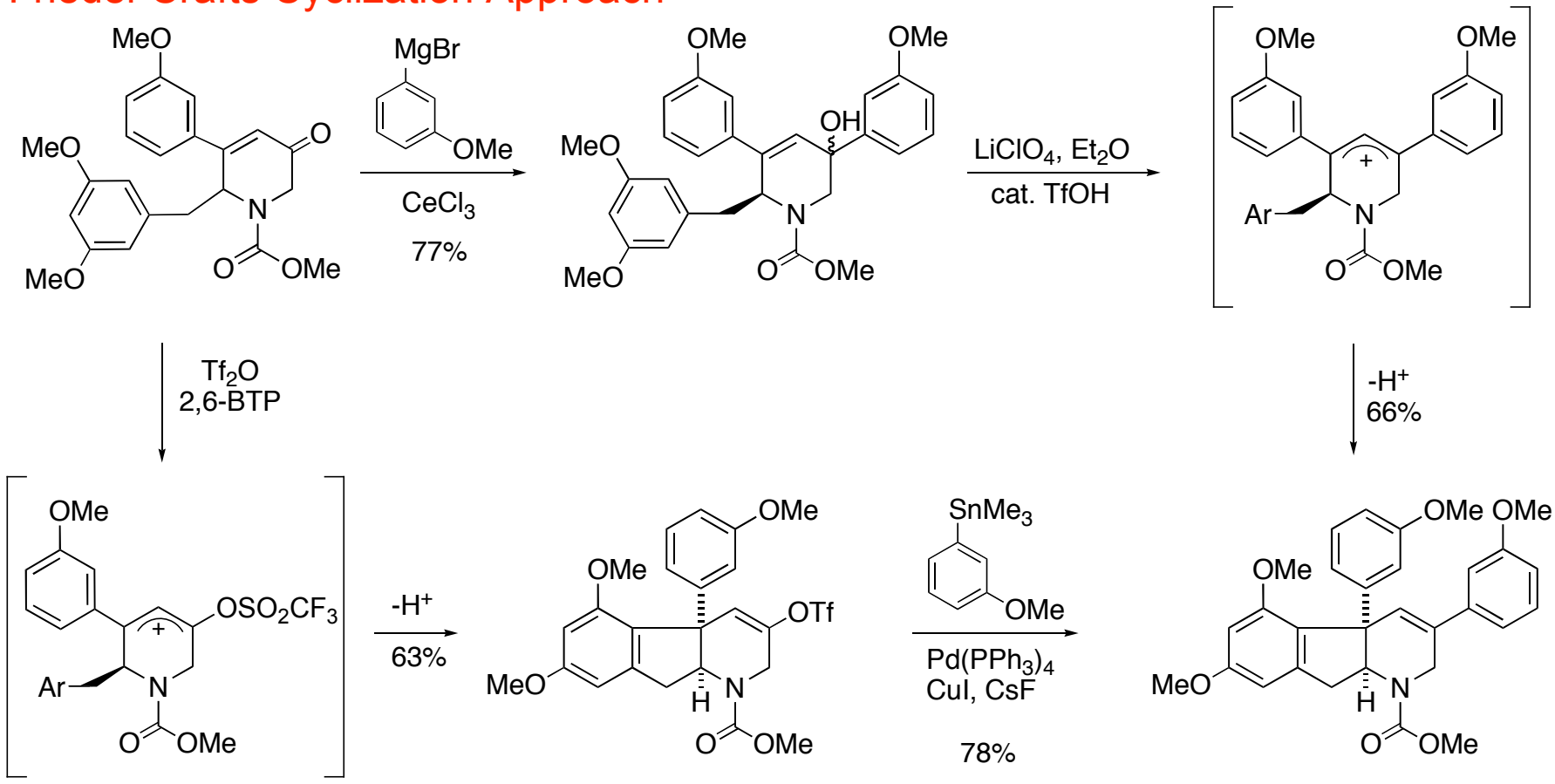
# Trauner's Approach

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

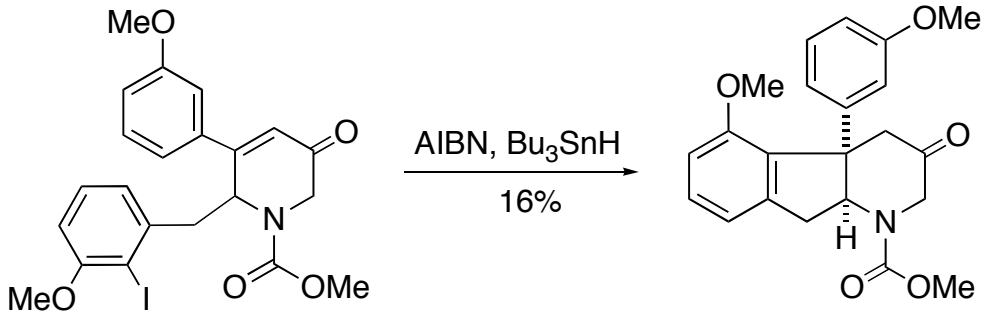


## Friedel-Crafts Cyclization Approach

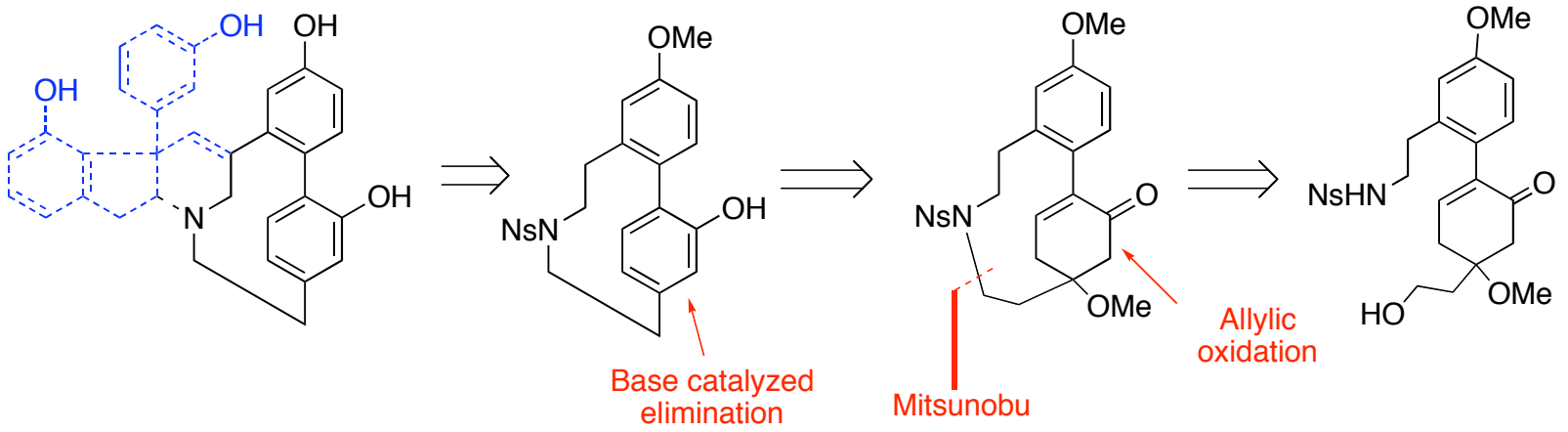


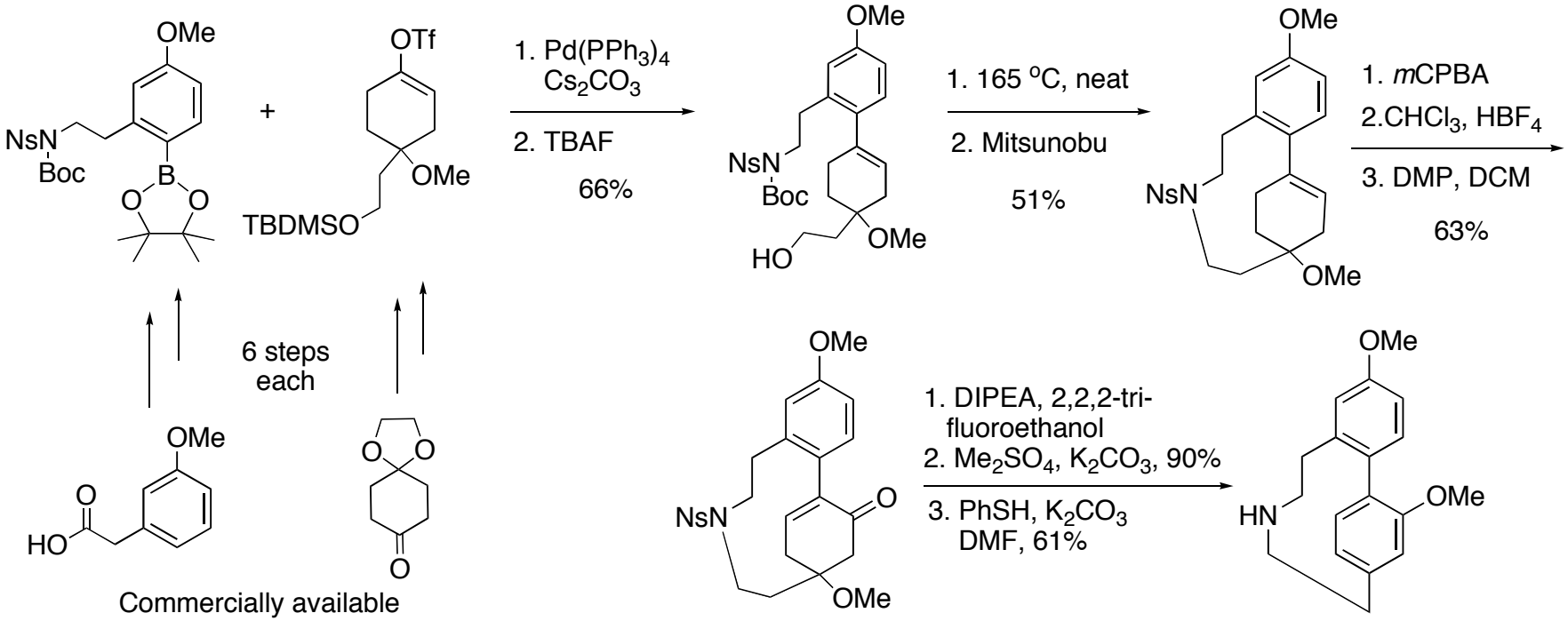

## Raical Cyclization Approach




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

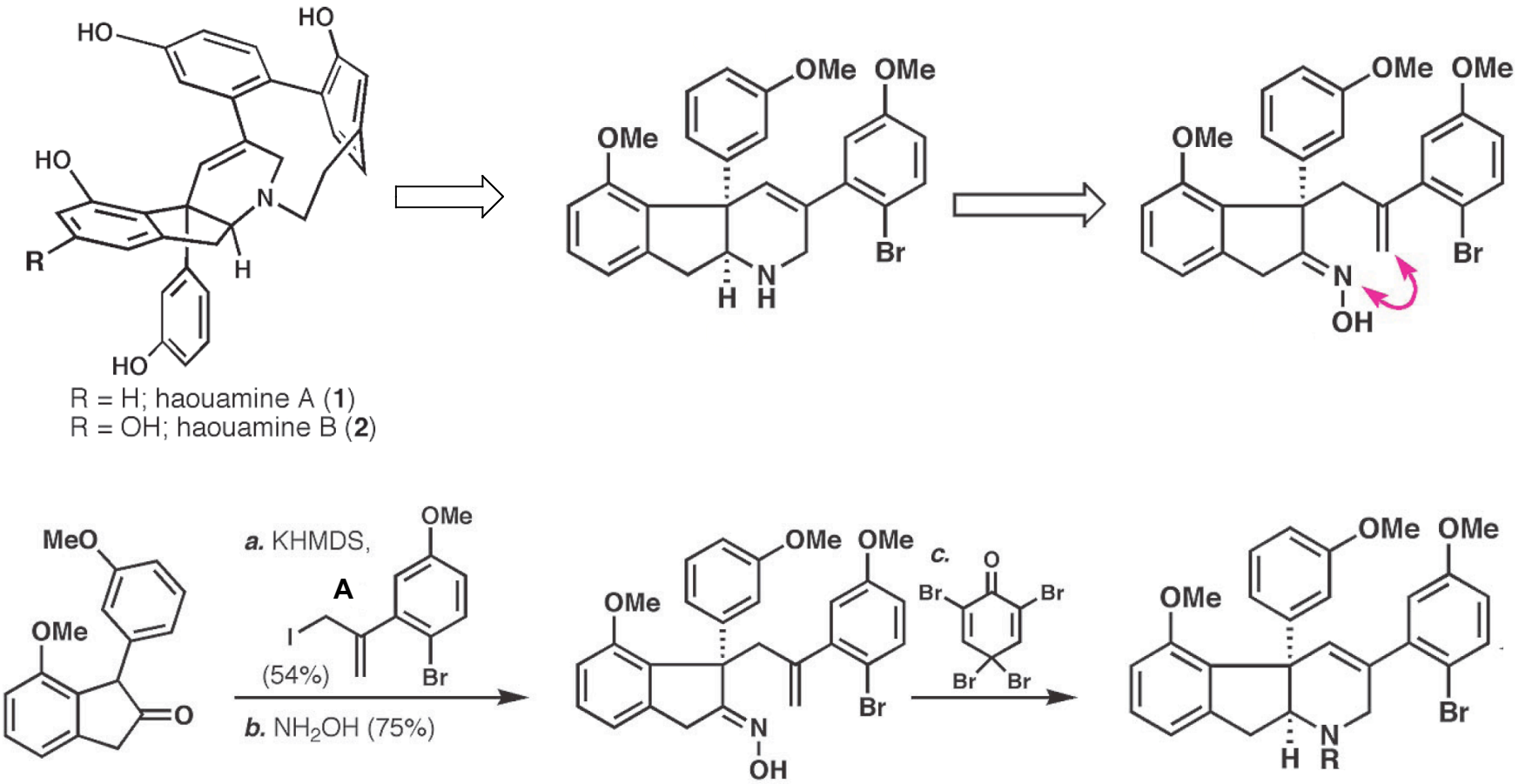
# Wipf's Approach




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

# Total Synthesis of (±)-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) $NH_2OH{\cdot}HCl$ (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

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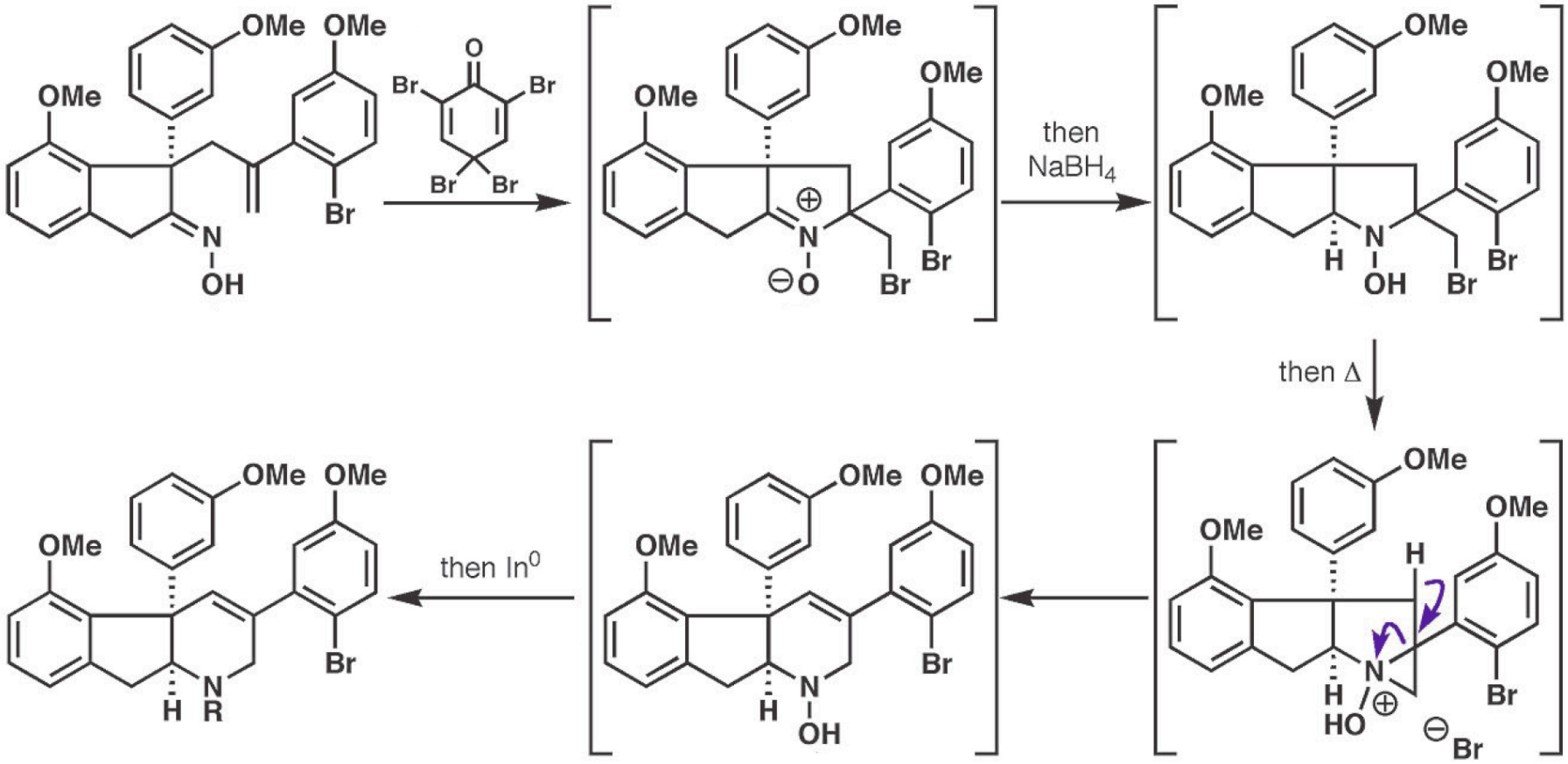
# Cascade annulation

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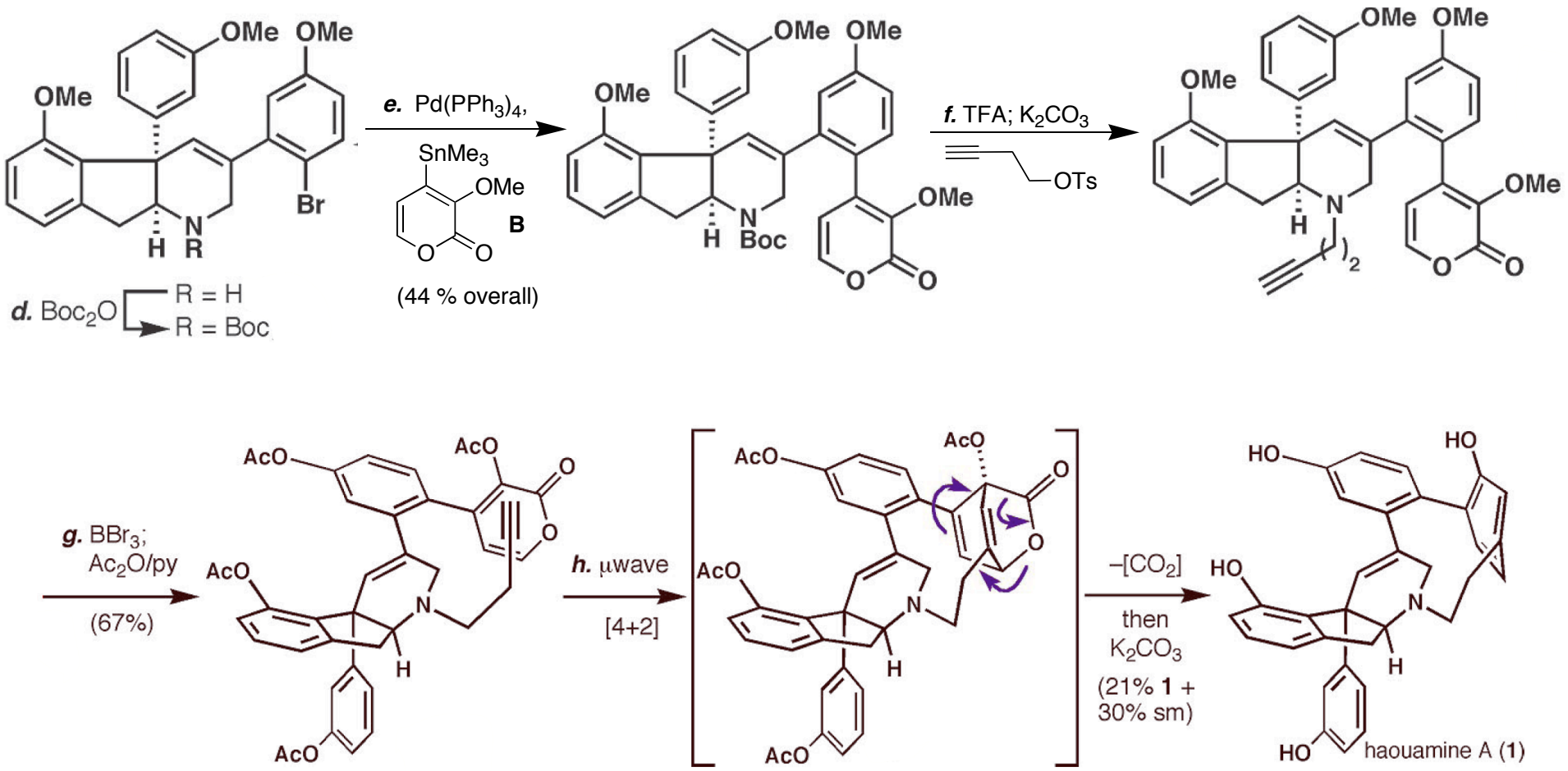
# Pyrone-alkyne Diels-Alder Reaction




(d) $Boc_2O$ (1.2 equiv), DCM, 30 min; (e) **B** (1.6 equiv), $Pd(PPh_3)_4$ (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 $Ac_2O$/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 (±)-haouamione 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 desire 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 an 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