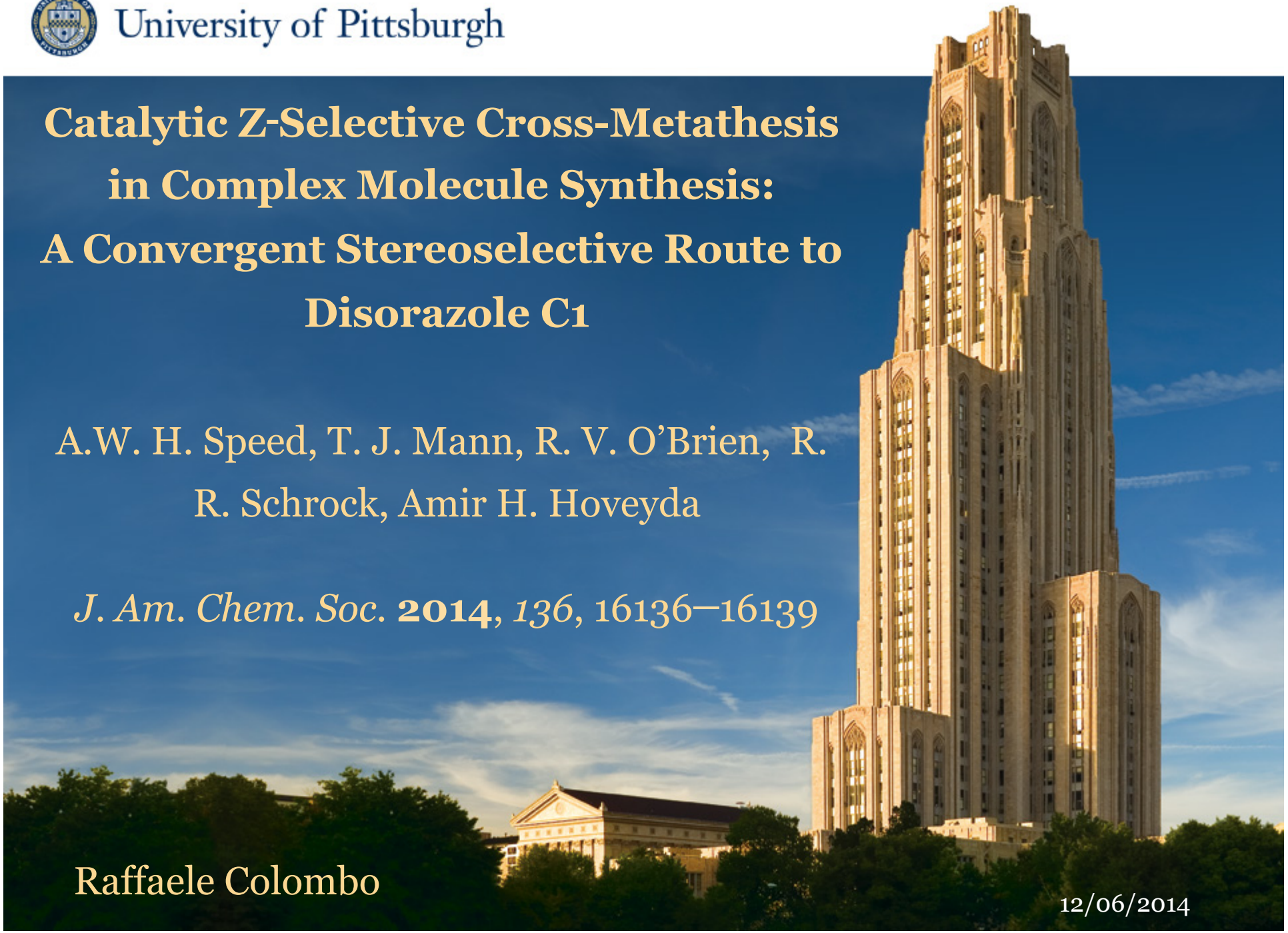
University of Pittsburgh

Catalytic Z-Selective Cross-Metathesis in Complex Molecule Synthesis: A Convergent Stereoselective Route to Disorazole C1

A.W. H. Speed, T. J. Mann, R. V. O'Brien, R. R. Schrock, Amir H. Hoveyda

J. Am. Chem. Soc. **2014**, *136*, 16136–16139

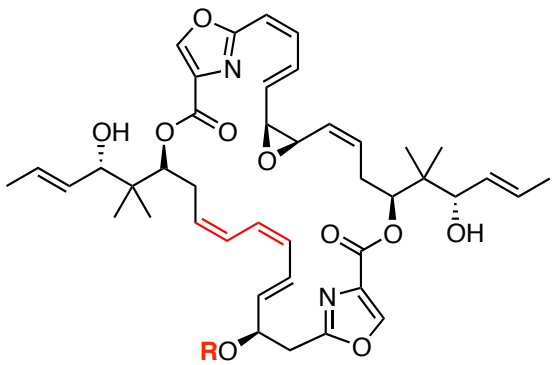


Raffaele Colombo

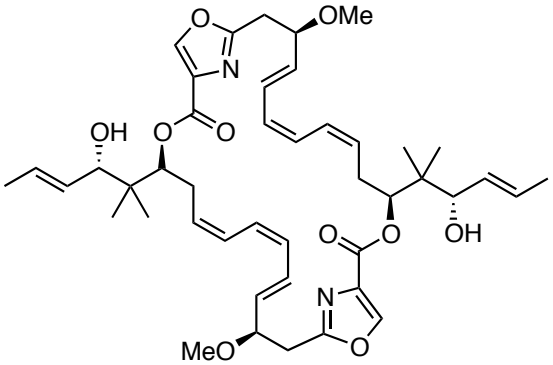
12/06/2014

Disorazoles

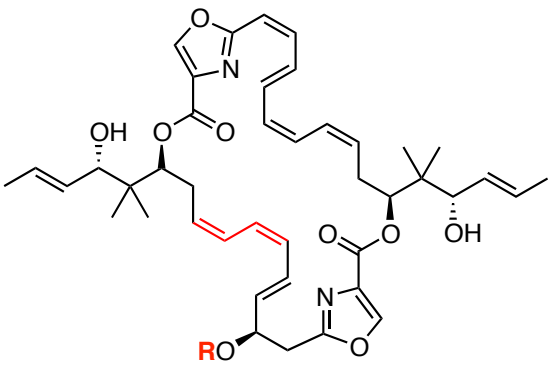
- Disorazoles are a relative **new class** of **microtubule disrupting cytotoxic macrodiolides**
- They are **isolated in 1994** from the fermentation broth of the myxobacterium *Sorangium cellulosum* So ce12
- **Disorazole A1** was identified as the major component between the 28 disorazoles isolated
- Minor members could be **artifacts** derived from side reactions during the isolation processes



Disorazole A_1 (R = Me)



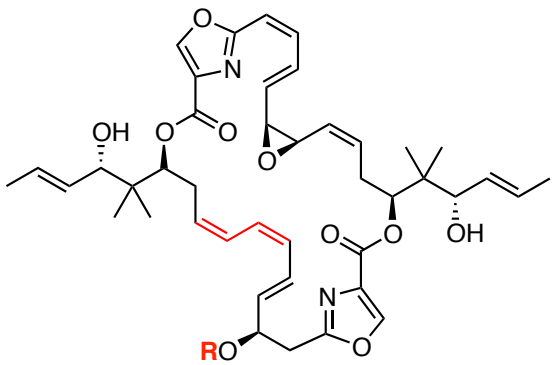
Disorazole C_1



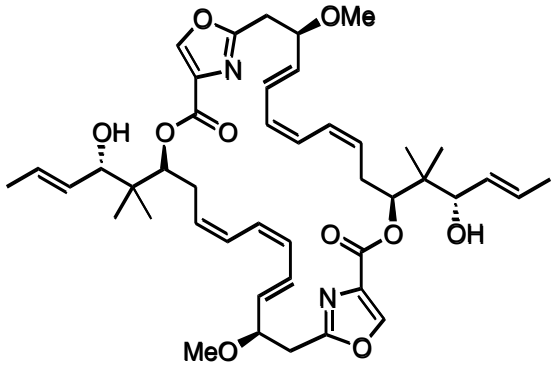
Disorazole F_1 (R = Me)

Disorazole C1

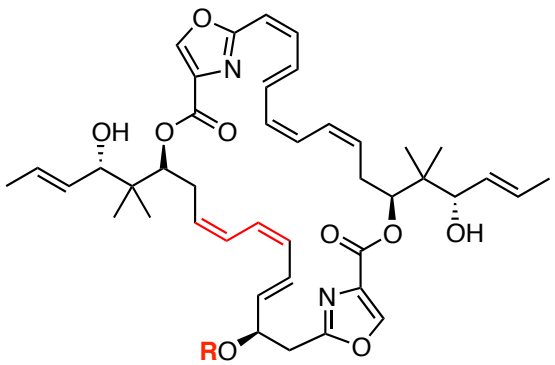
- **Disorazole C1** promotes **depolymerization** of the microtubules binding to or **near the vinca domain**, resulting in cell cycle arrest at the G2/M checkpoint and apoptotic cell death cascade
- Disorazole C1 is an **effective cytotoxic agent** with IC_{50} values < 10 nM in various human cancer cell lines
- The **absence of the epoxide** in the disorazole C1 **reduced** its cytotoxicity by 50–100 fold compare to disorazole A1
- **It has a C2-symmetry**



Disorazole A_1 (R = Me)



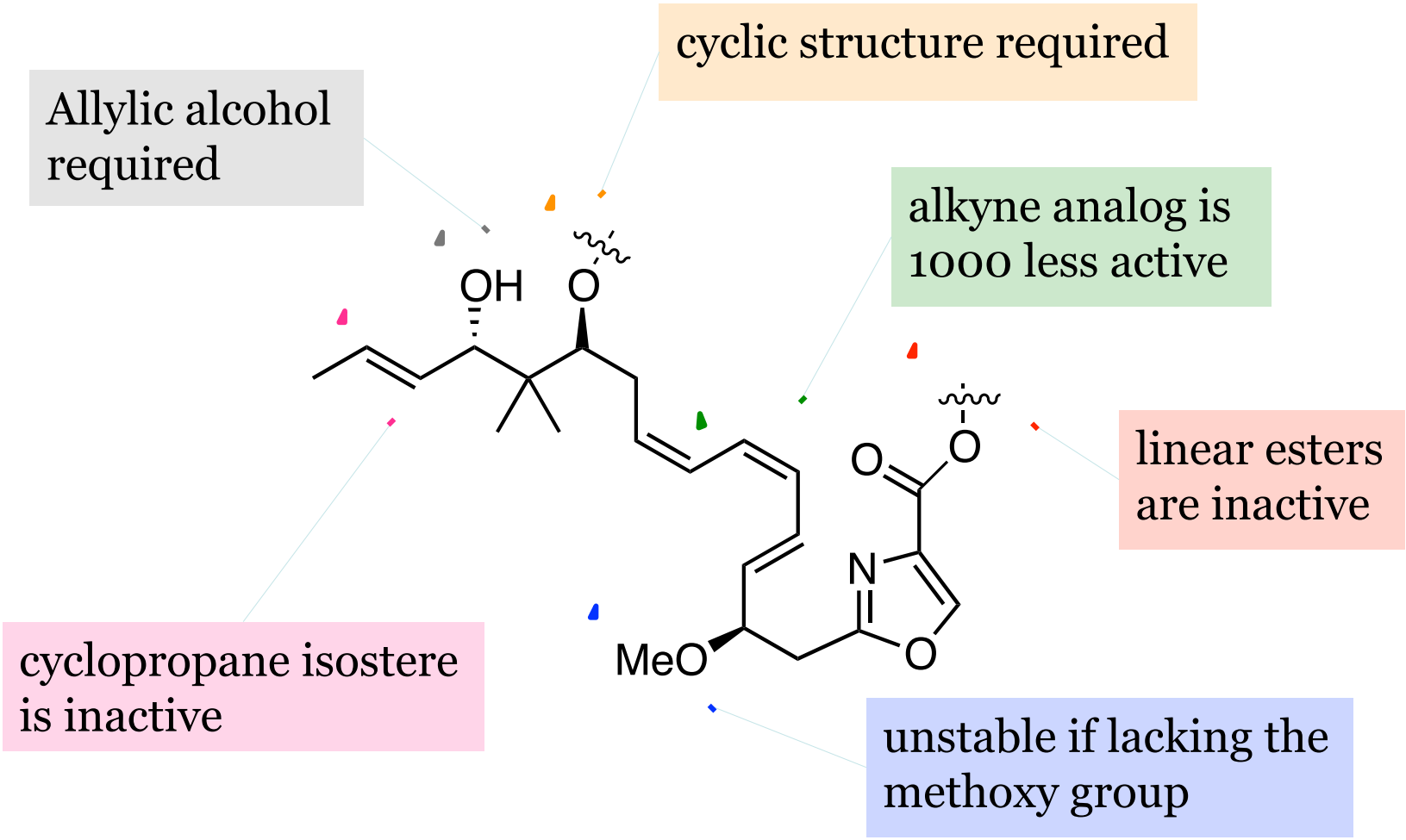
Disorazole C_1



Disorazole F_1 (R = Me)

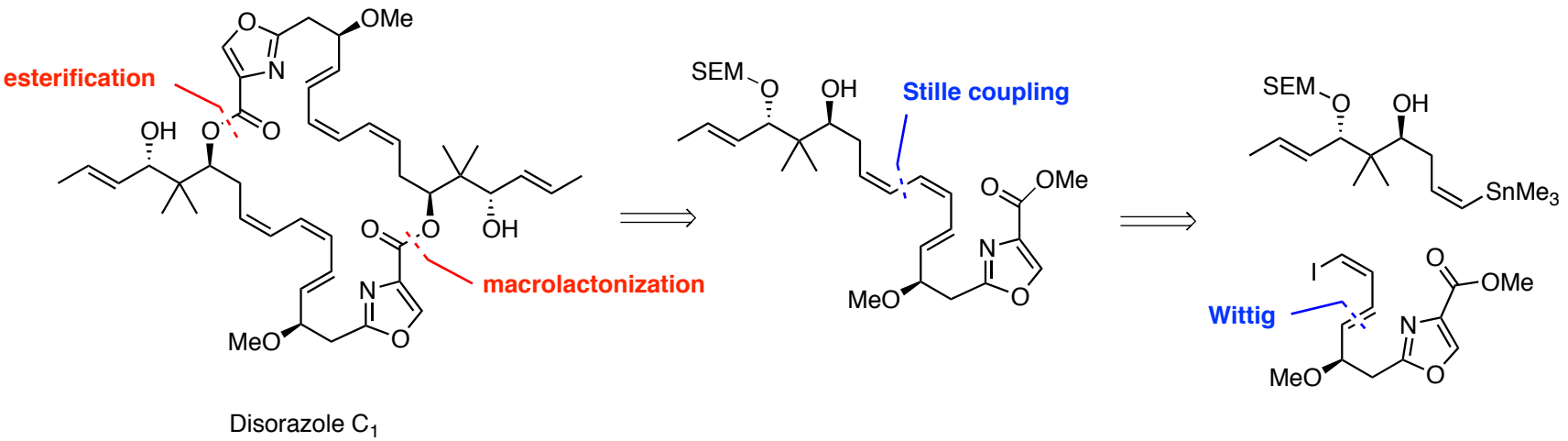
Disorazole C1 SAR

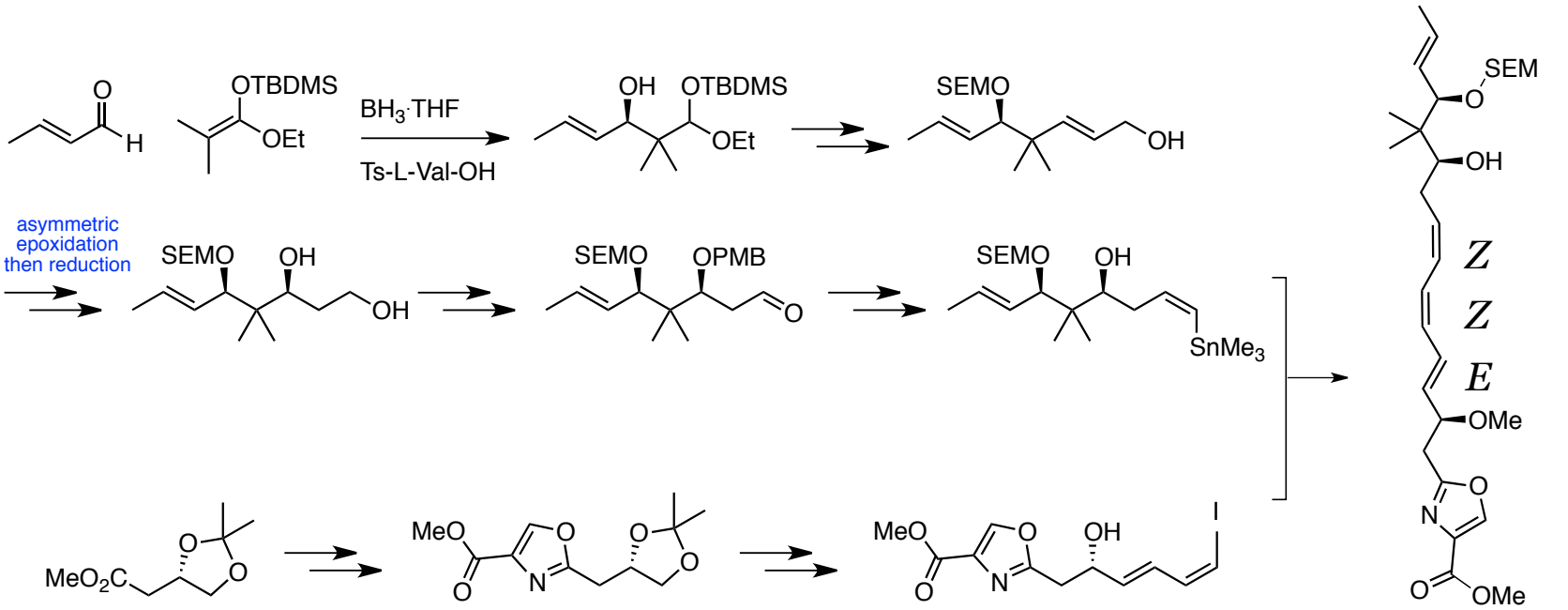
- Truncations or alterations of the backbone reduce the activity



C. D. Hopkins, P. Wipf *Natural Product Reports* **2009**, *26*, 585

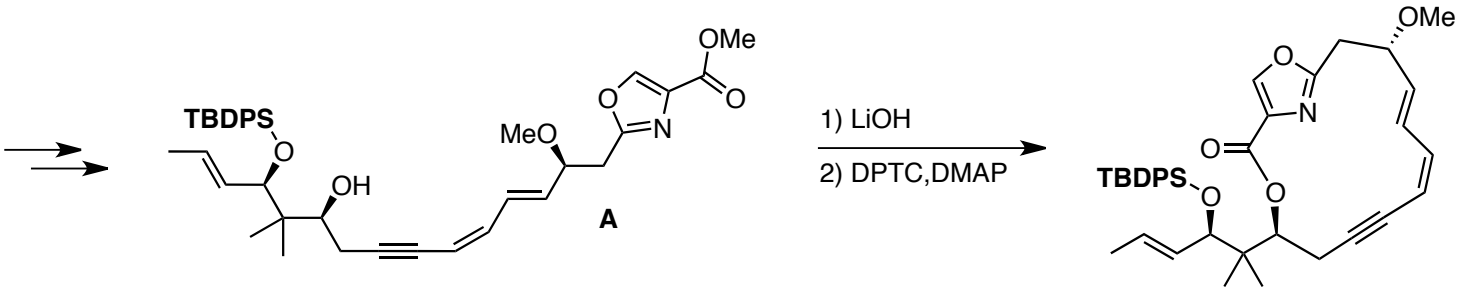
Meyer's 1st approach





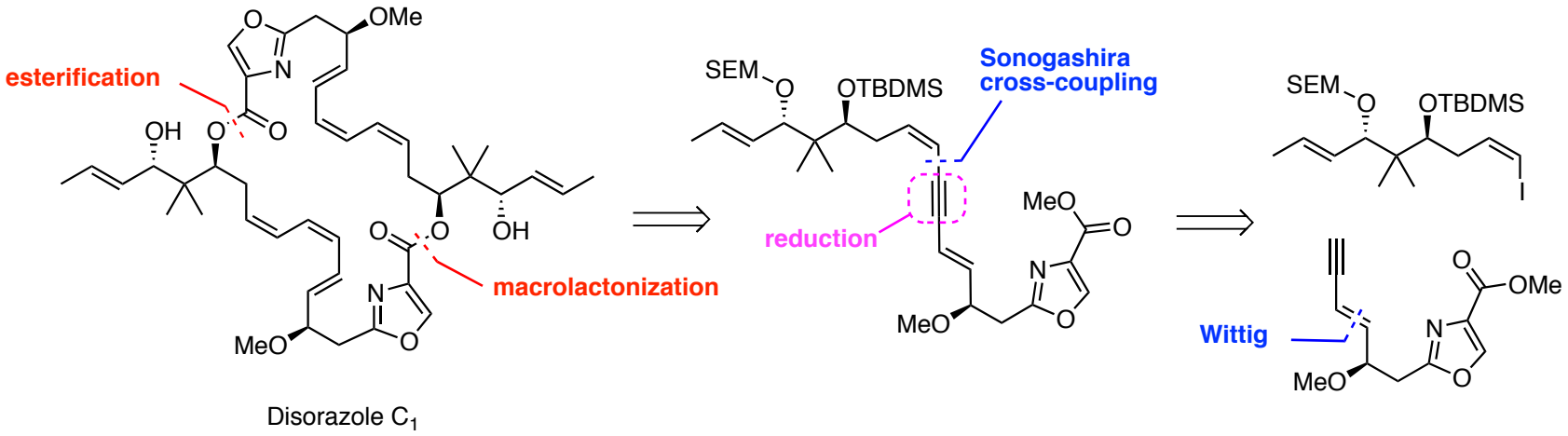
M. C. Hillier, D. H. Park, A. T. Price, R. Ng, A. I. Meyers, *Tetrahedron Lett.*, **2000,** *41*, 2821–2824

Meyer's 2st approach



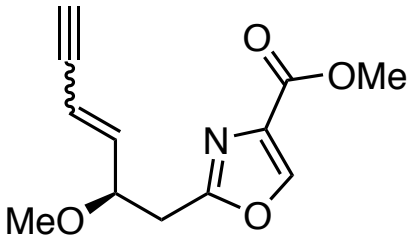
M. C. Hillier, A. T. Price and A. I. Meyers, *J. Org. Chem.*, **2001**, *66*, 6037–6045

Hoffmann's 1st approach



Disorazole C_1

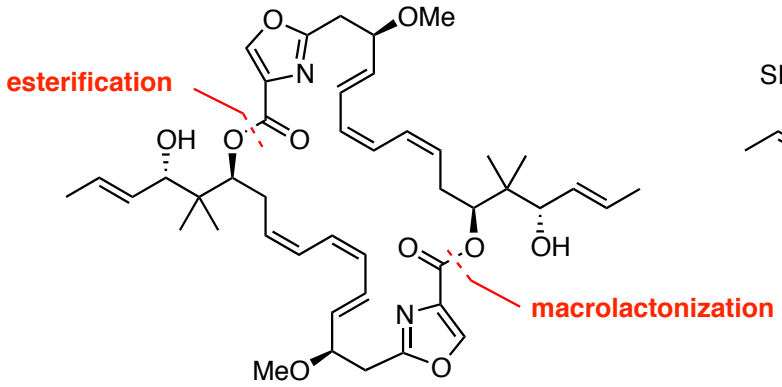
- The position of the alkyne was chosen to increase the strain of the 15-membered cycle in order to suppress the intramacrocyclization



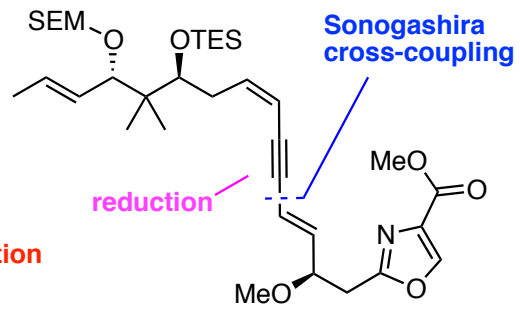
2.5 : 1 E/Z mixture (not separable)

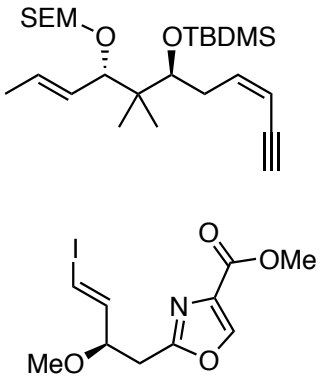
poor overall yield

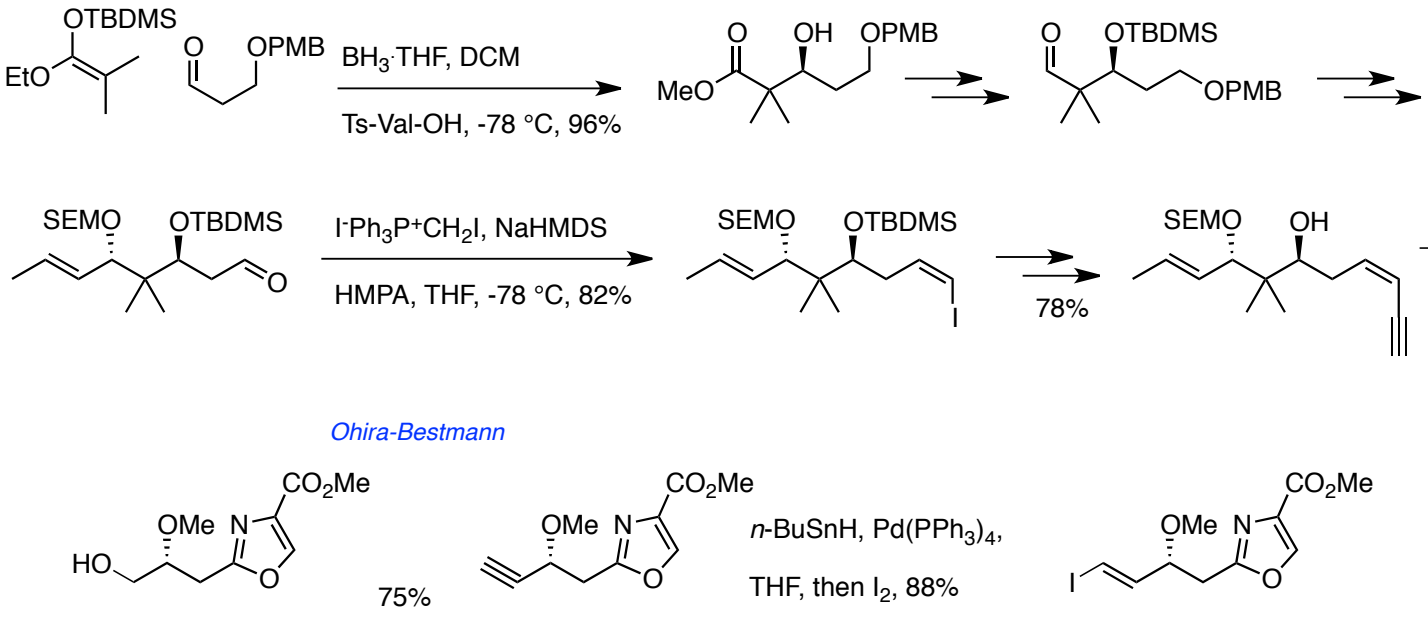
Hoffmann's 2nd approach



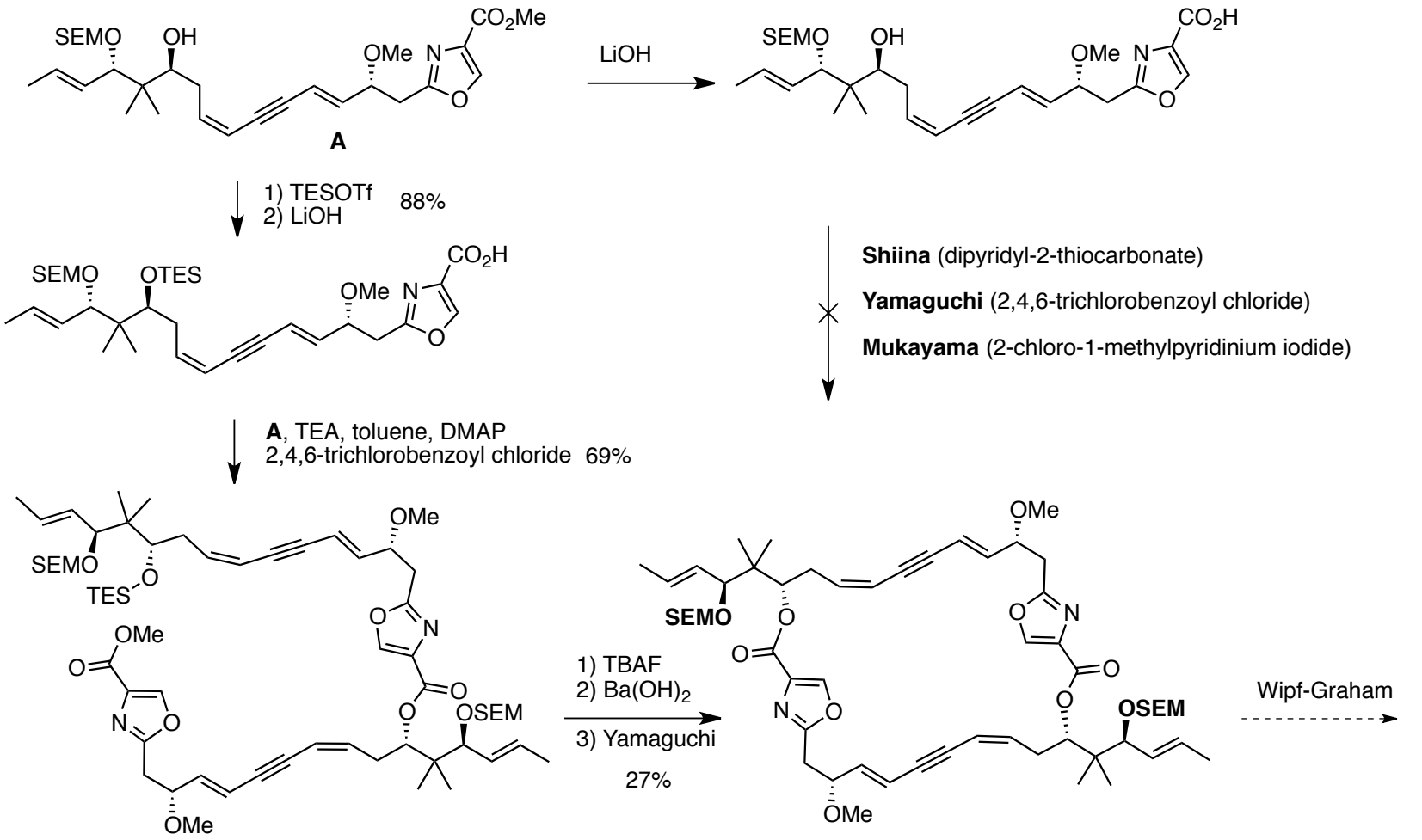
Disorazole C_1







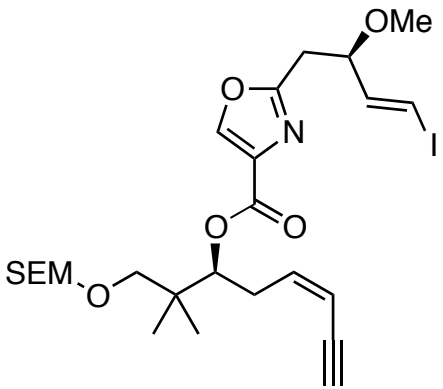
Hoffmann's approach



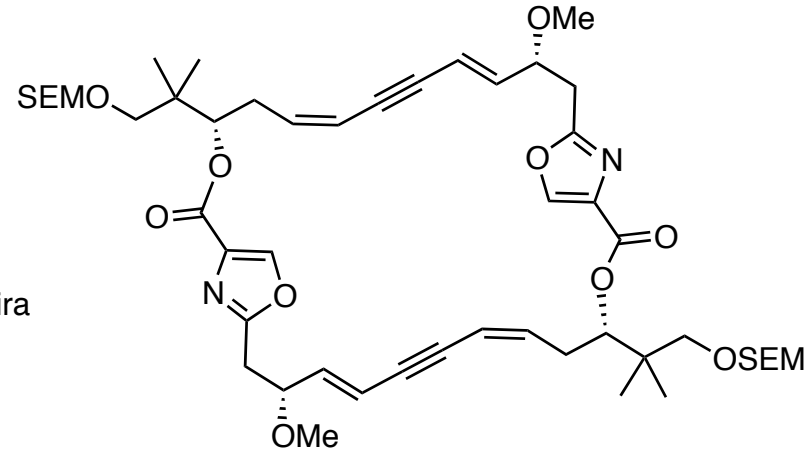
Almost a formal synthesis (different PGs)

Barbara Niess, Ingo V. Hartung, Lars O. HaustedtH. Martin R. Hoffmann *EurJOC,* **2006**, 1132-1143

Hoffmann's (unsuccessful) approach

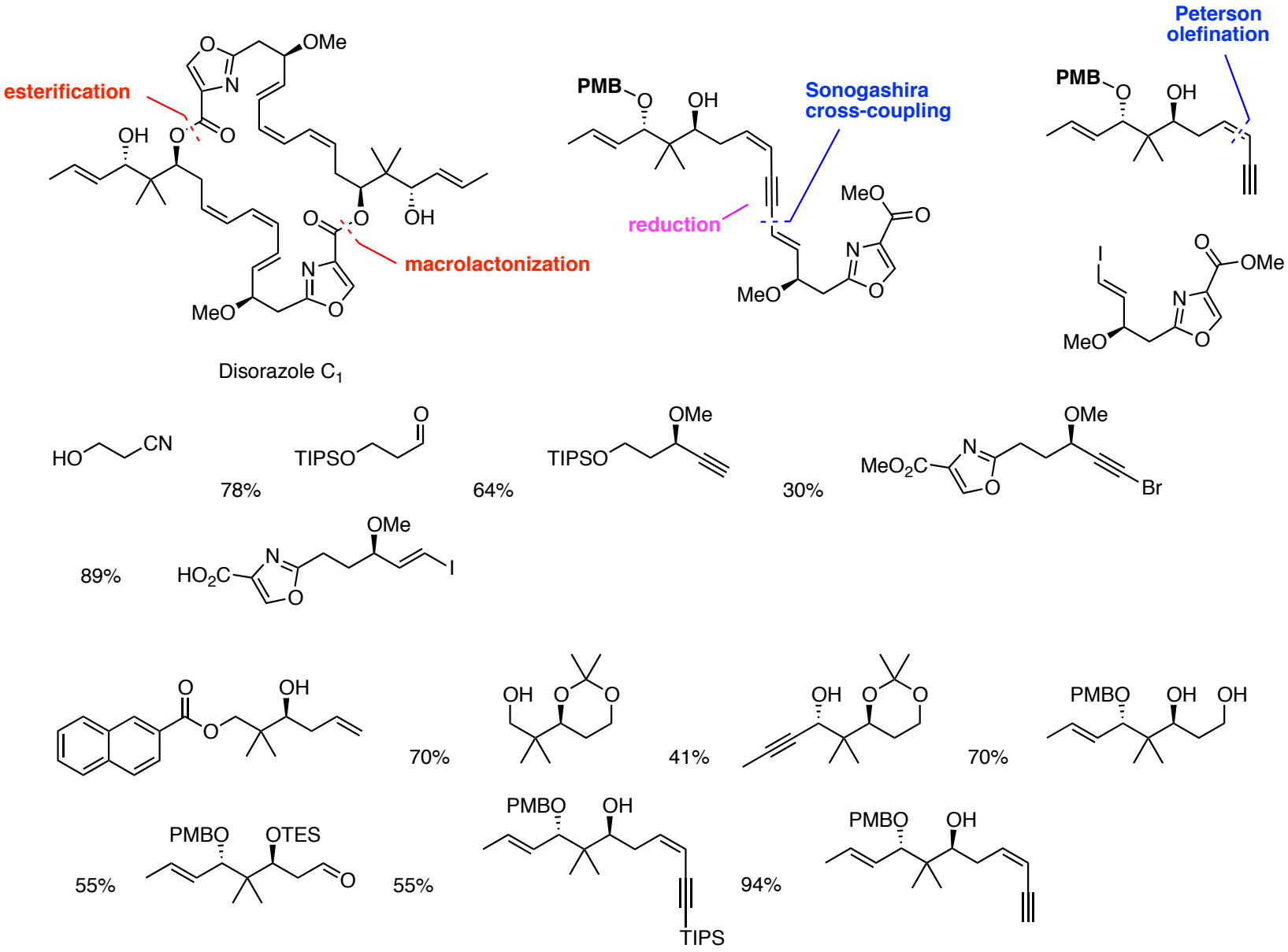


double Sonogashira



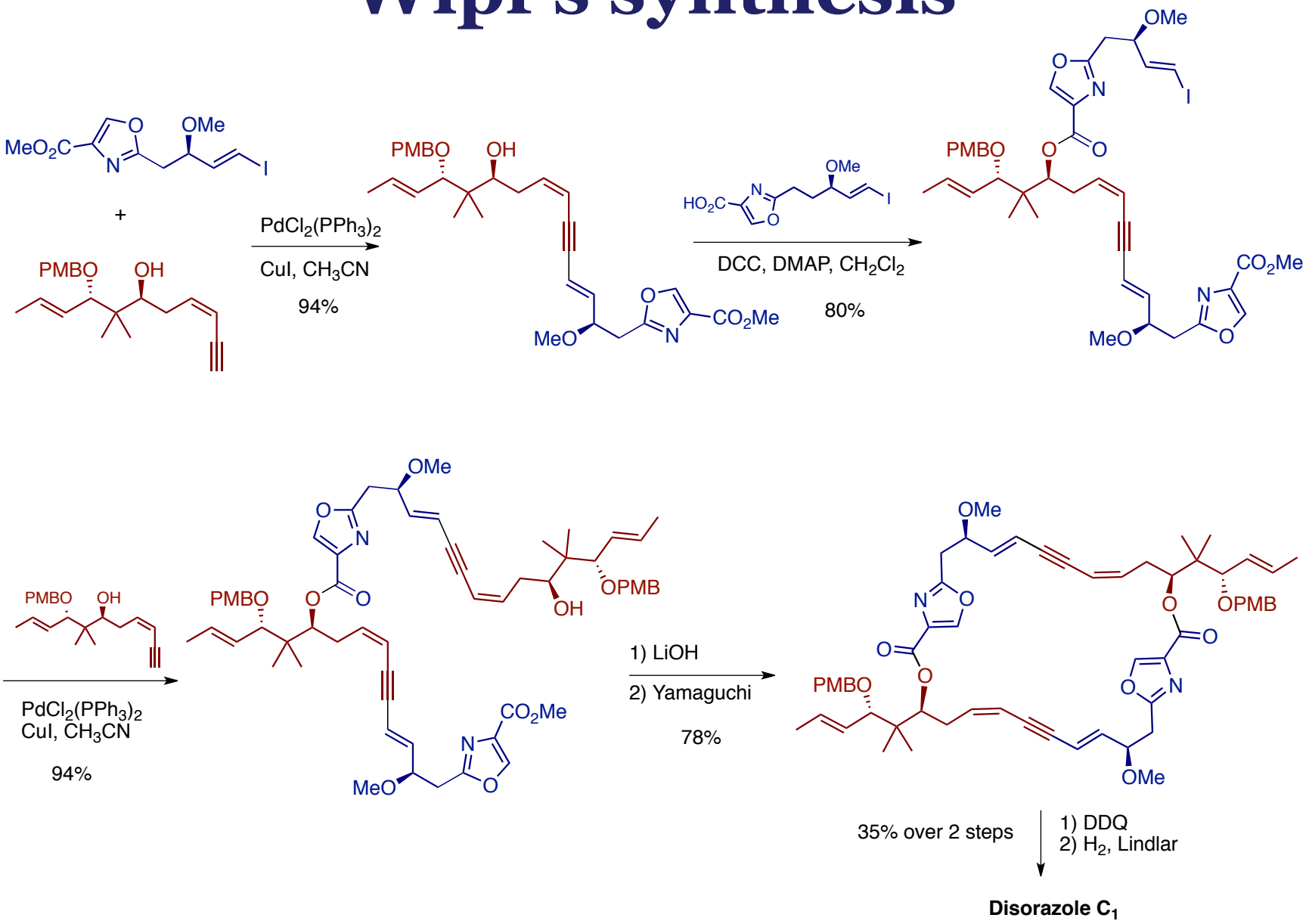
Barbara Niess, Ingo V. Hartung, Lars O. HaustedtH. Martin R. Hoffmann *EurJOC,* **2006**, 1132-1143

Wipf's synthesis



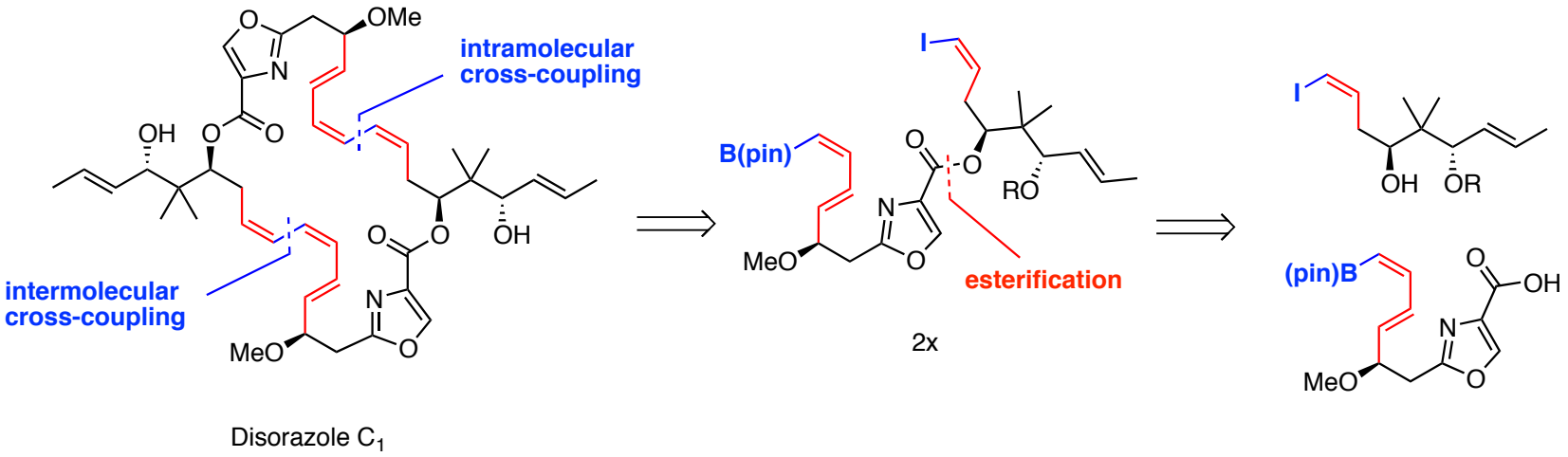
P. Wipf, T. H. Graham, *J. Am. Chem. Soc.* **2004**, *126*, 15346-15347

Wipf's synthesis



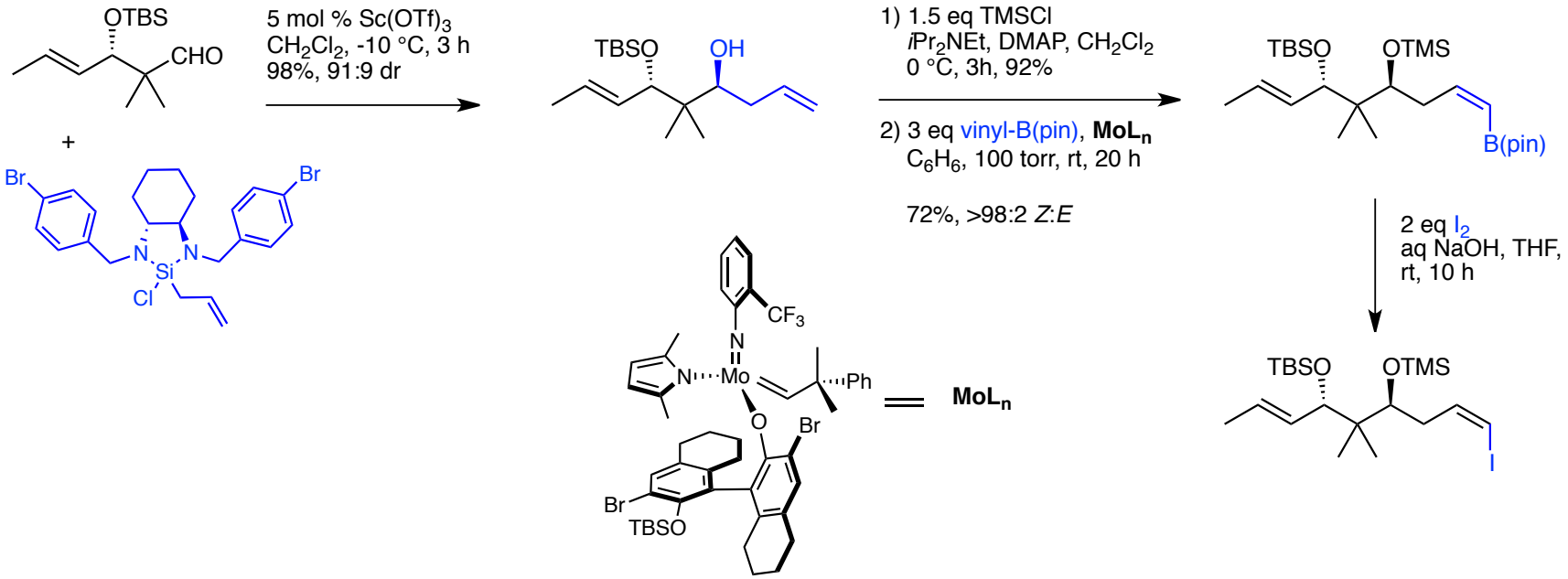
20 steps, 1.5% for the longest sequence

Current work

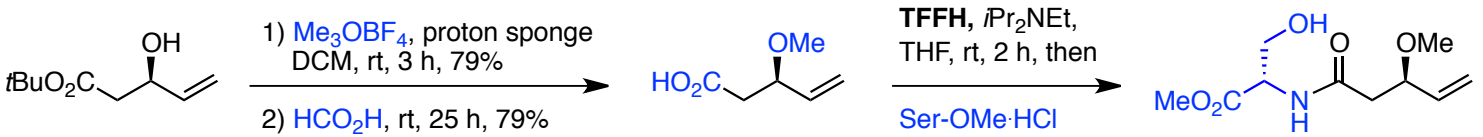


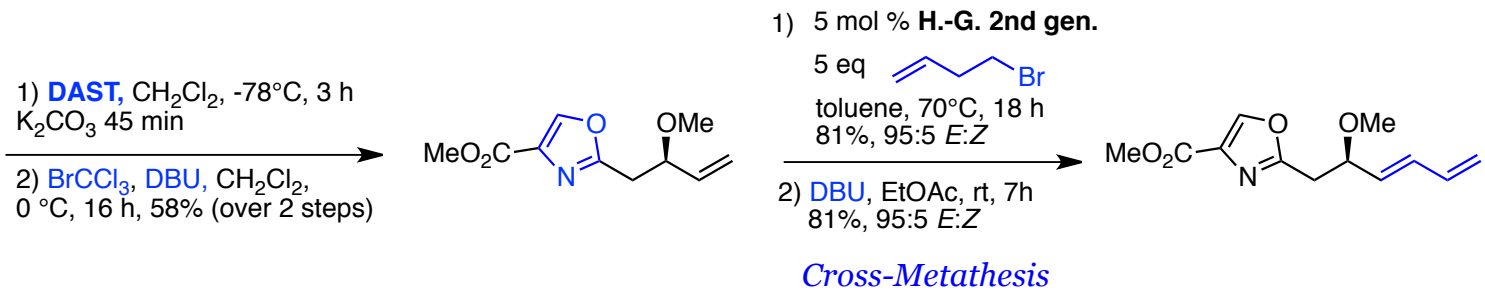
Disorazole C_1

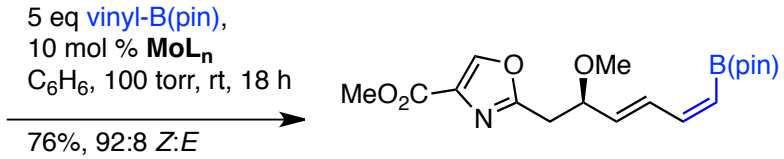
Cross-Metathesis

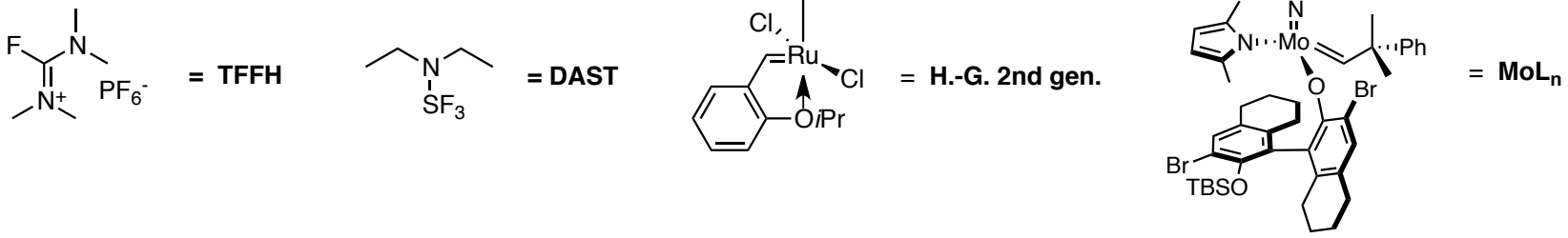


Current work









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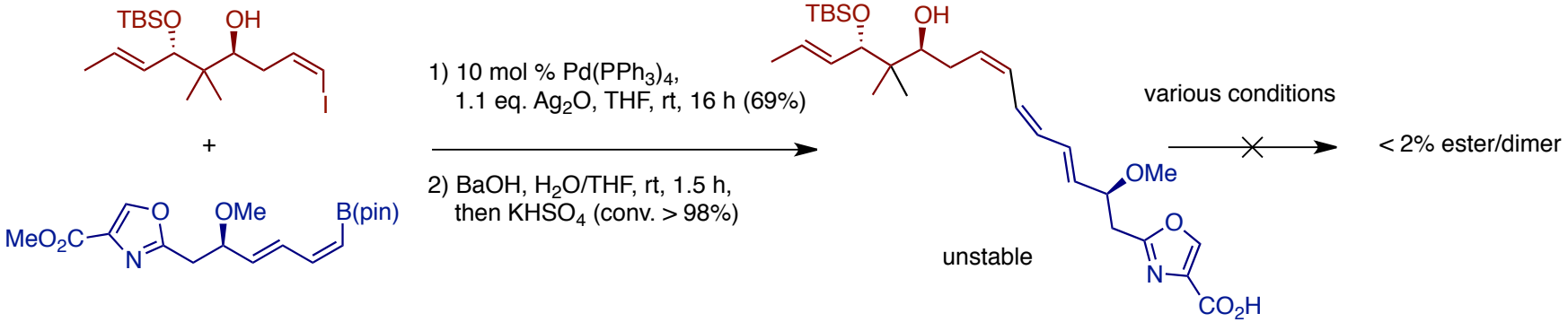

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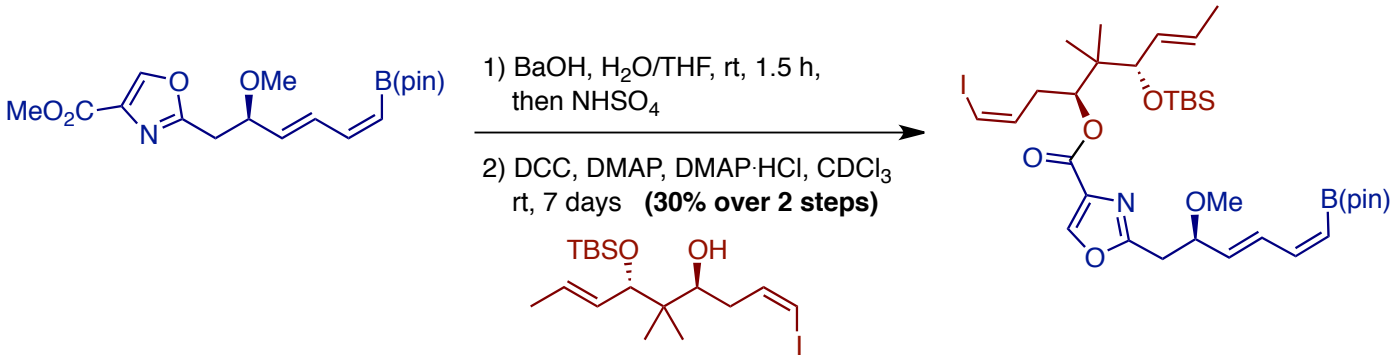
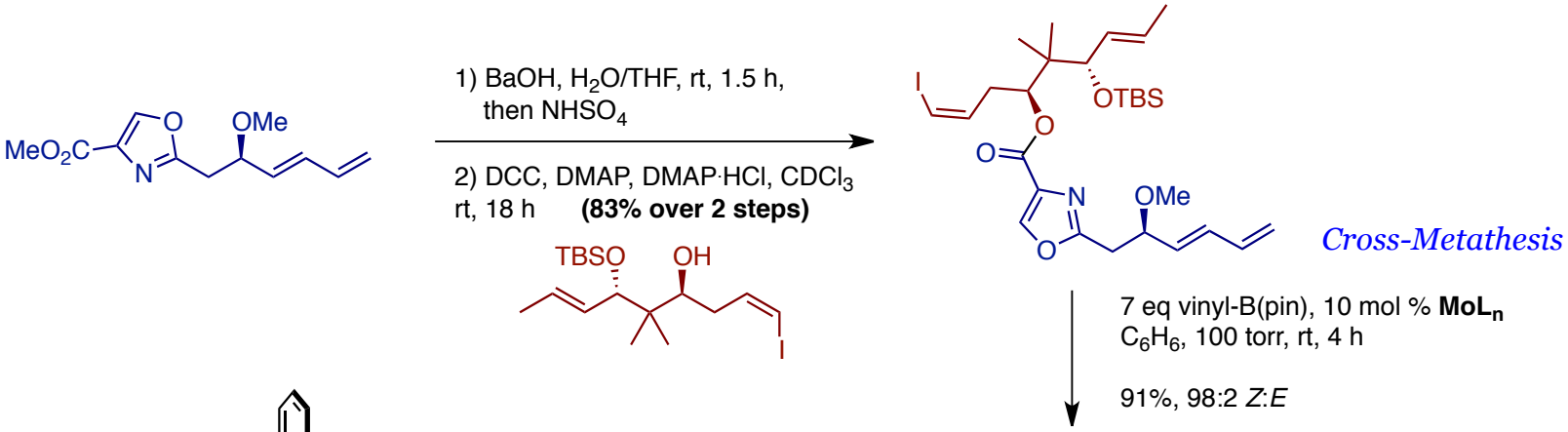
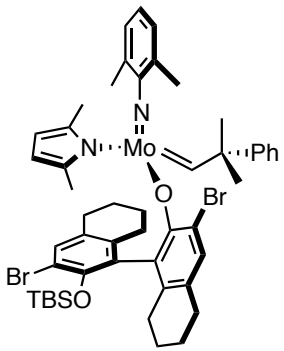
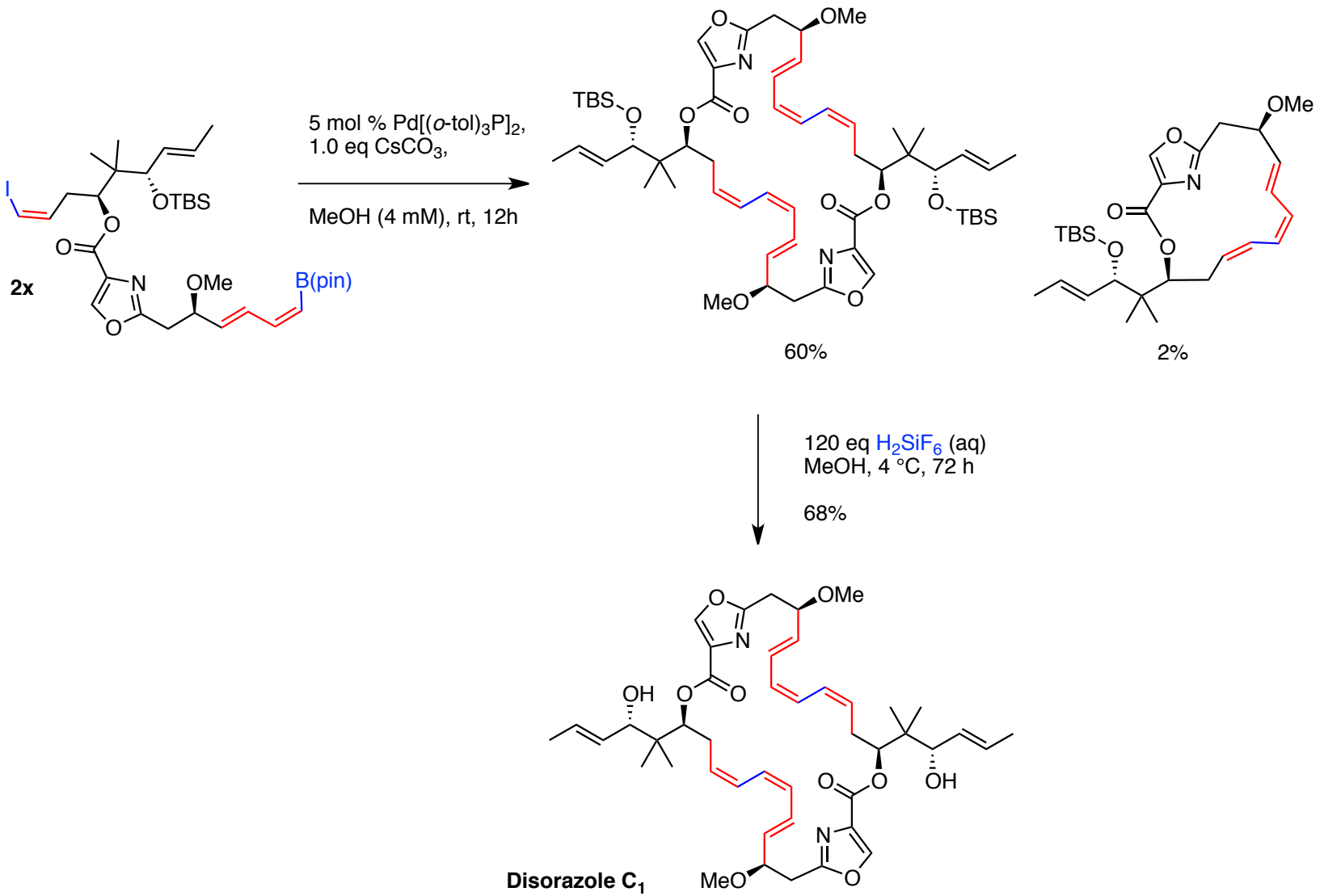






= **MoL$_n$**

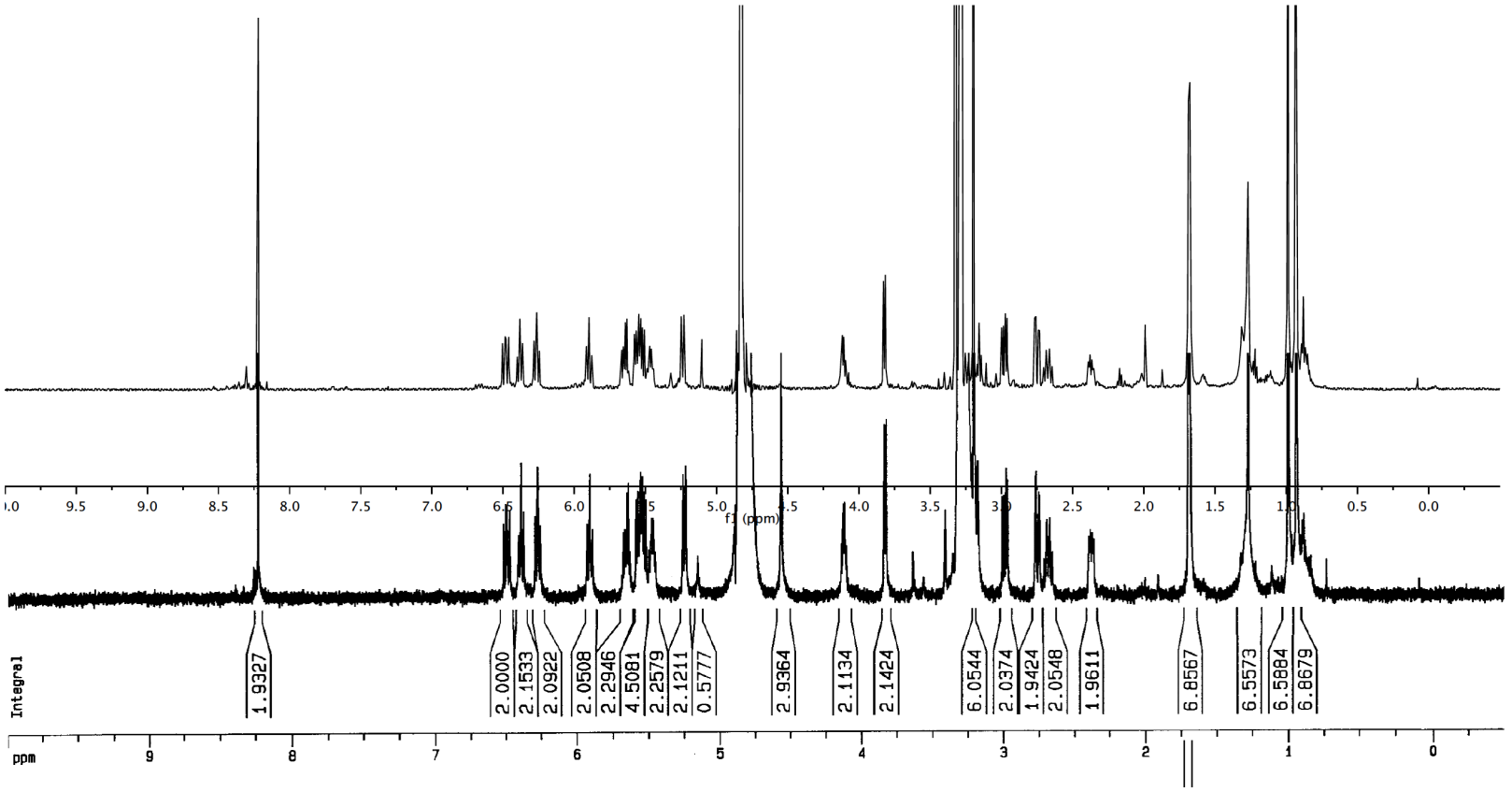
Current work



12 steps, 8% for the longest sequence

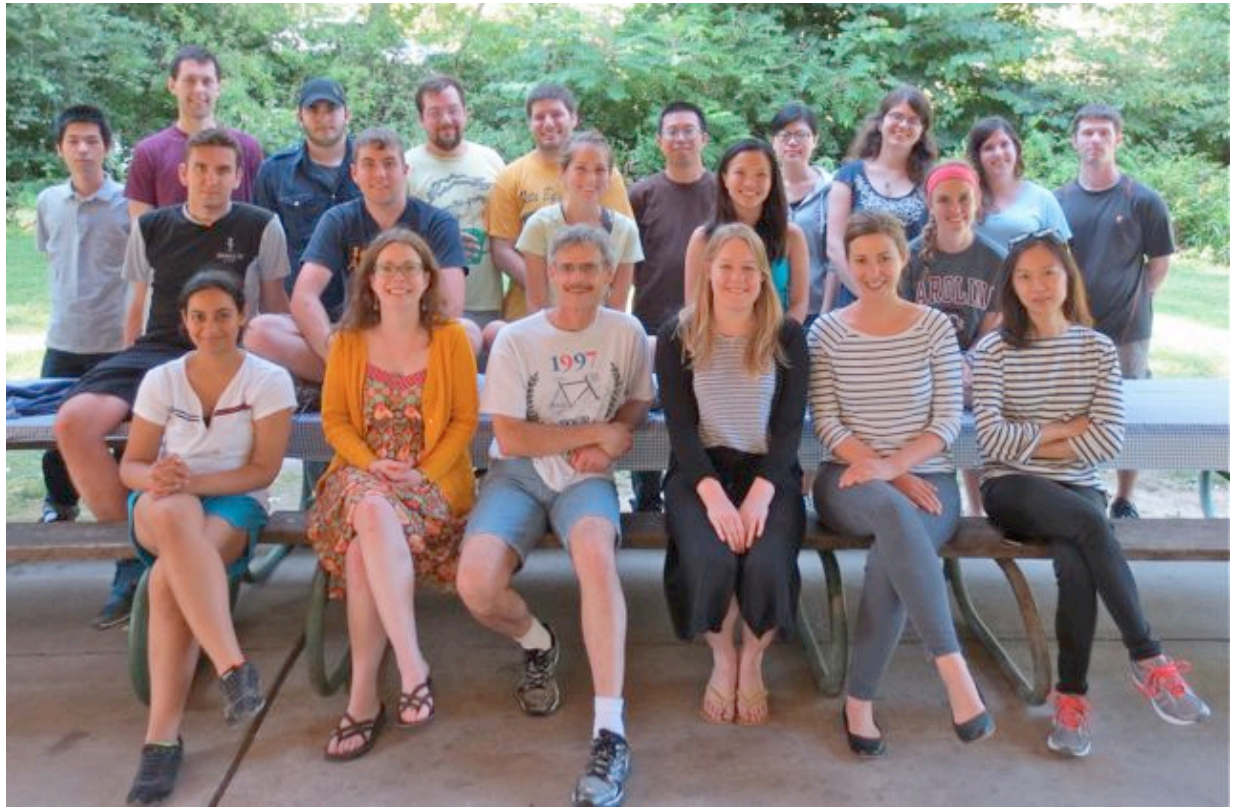
NMR comparison

Top: Hoveyda ^{1}H, 600 MHz
Bottom: Wipf ^{1}H, 600 MHz[13]



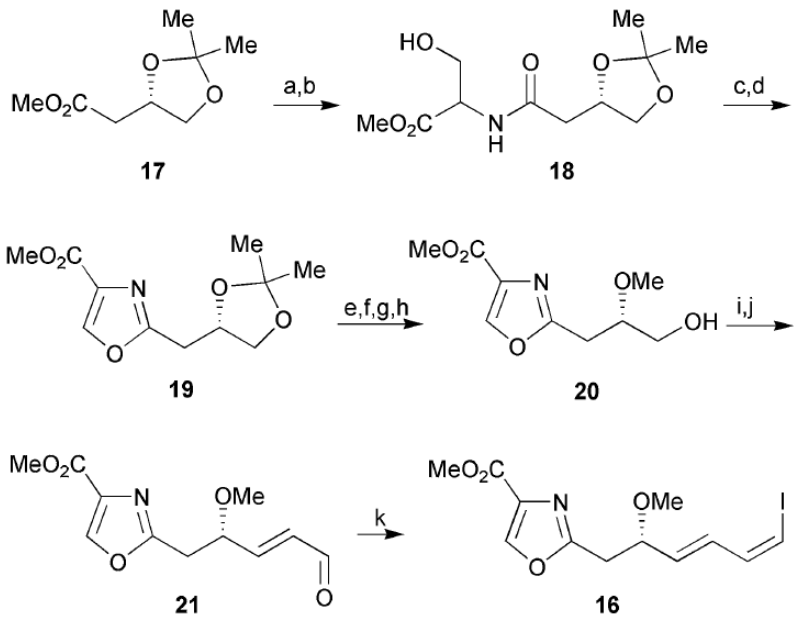
Thanks!

Prof. Wipf
Wipf group past & present



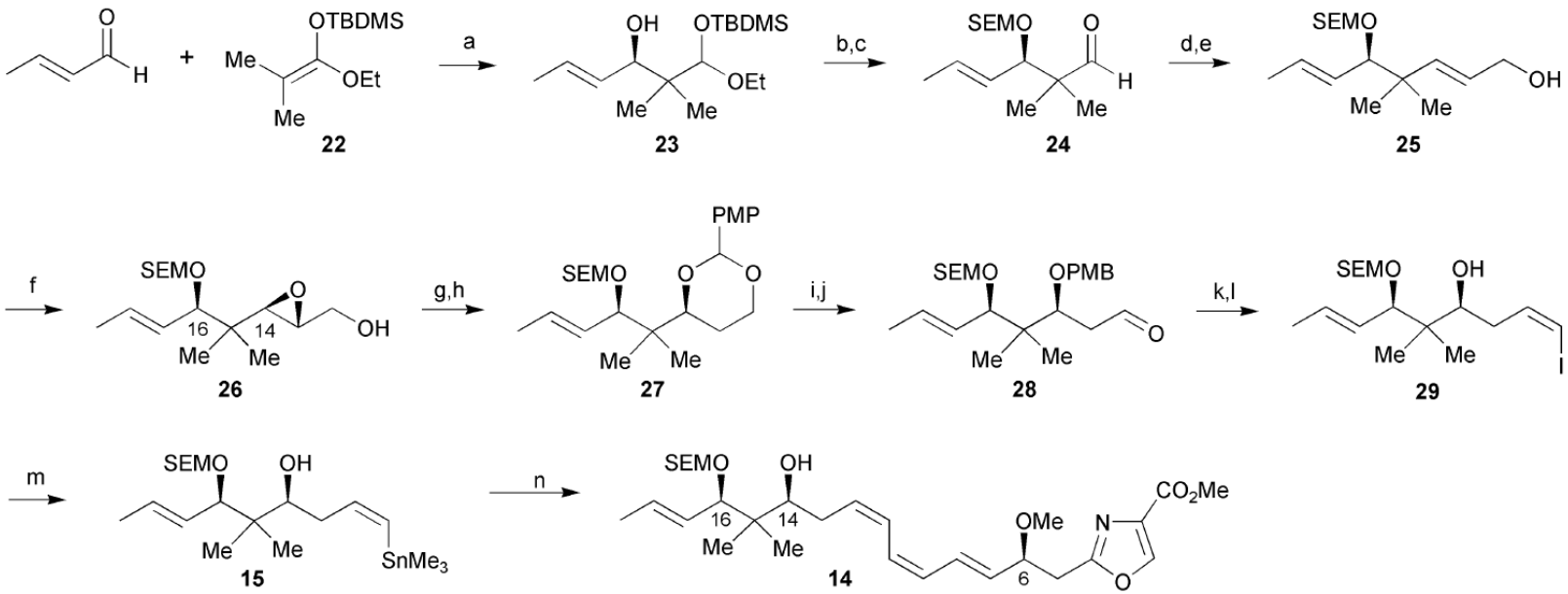
Eli Lilly – LIFA (Lilly innovation fellowship award)

Meyer's 1st approach



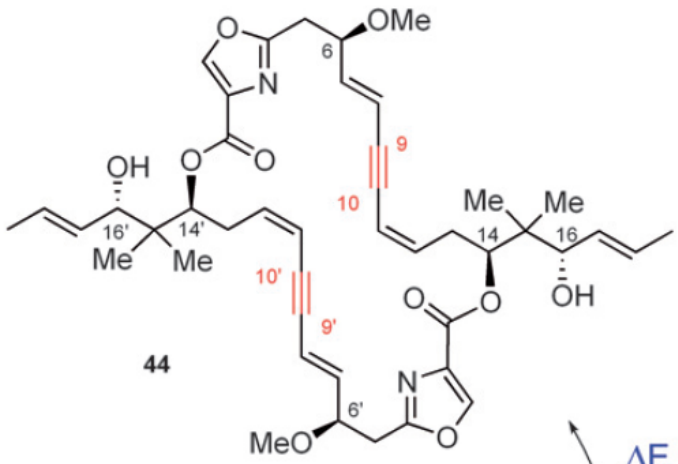
Scheme 1 Meyers' oxazole segment synthesis. *Reagents and conditions*: (a) 2N LiOH, THF; (b) D,L-Ser·OMe, 1,1′-CDI, THF, 67% (over 2 steps); (c) DAST, CH_2Cl_2, −78 °C; (d) DBU, $BrCCl_3$, 0 °C to rt, 79% (over 2 steps); (e) Dowex-H^+, MeOH; (f) TIPSOTf, 2,6-lutidine, CH_2Cl_2 (0.05M), −78 °C, 74% (over 2 steps); (g) MeI, Ag_2O, CH_3CN, Δ; (h) TBAF, THF, 75% (over 2 steps); (i) SO_3·Pyr, DMSO, Et_3N, CH_2Cl_2; (j) $Ph_3P{=}CH_2CHO$, benzene, Δ, 62% (over 2 steps); (k) $I^-Ph_3P^+CH_2I$, NaHMDS, HMPA, THF, −78 °C, 71%.

Meyer's 1st approach



Scheme 2 Meyers' 1st generation synthesis of the southern fragment of disorazole C_1. *Reagents and conditions*: (a) $BH_3 \cdot THF$, *N*-Ts-L-Val, CH_2Cl_2, −78 °C, 73%; (b) SEMCl, Hünig's base, CH_2Cl_2, −78 °C; (c) 80% AcOH, 79% (over 2 steps); (d) $(EtO)_2P(O)CH_2CO_2Et$, NaH, toluene/THF, 95%; (e) DIBAL-H, CH_2Cl_2, −78 °C, 76%; (f) D-(−)-DIPT, *t*-BuOOH, $Ti(Oi\text{-}Pr)_4$, CH_2Cl_2, −30 °C, 95%; (g) Red-Al, THF, −20 °C; (h) *p*-methoxybenzylidene dimethyl acetal, PPTS, CH_2Cl_2, 83% (over 2 steps); (i) DIBAL-H, CH_2Cl_2, −78 °C, 92%; (j) Dess–Martin periodinane, pyridine, *t*-BuOH, CH_2Cl_2, 83%; (k) $I^-Ph_3P^+CH_2I$, NaHMDS, HMPA, THF, −78 °C, 67%; (l) DDQ, CH_2Cl_2, H_2O, 79%; (m) $PdCl_2(PPh_3)_2$, $(Me_3Sn)_2$, Li_2CO_3, THF, 74%; (n) $PdCl_2(CH_3CN)_2$, **16**, DMF, 76%.

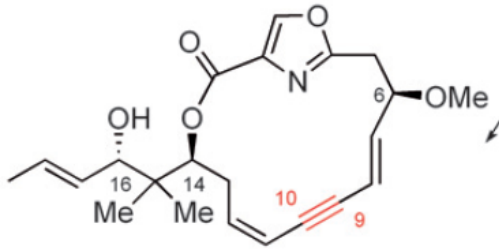
Hoffmann' s 1st approach



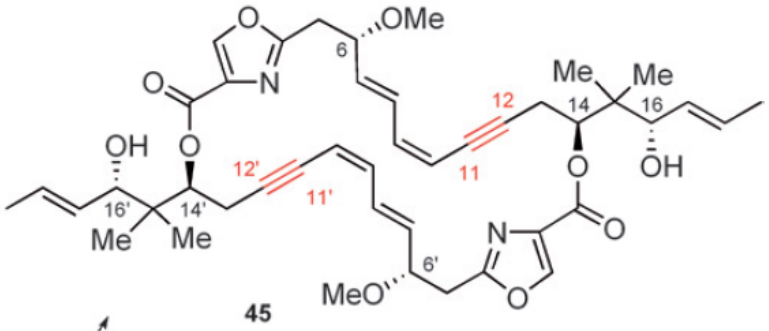
44

465.8 kJ/mol

ΔE 135.6 kJ/mol



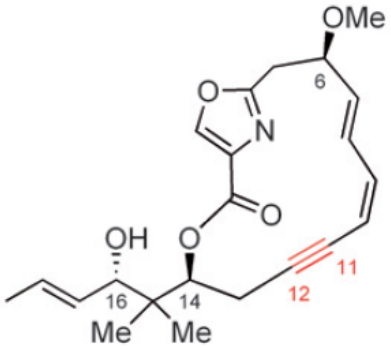
46 330.2 kJ/mol



45

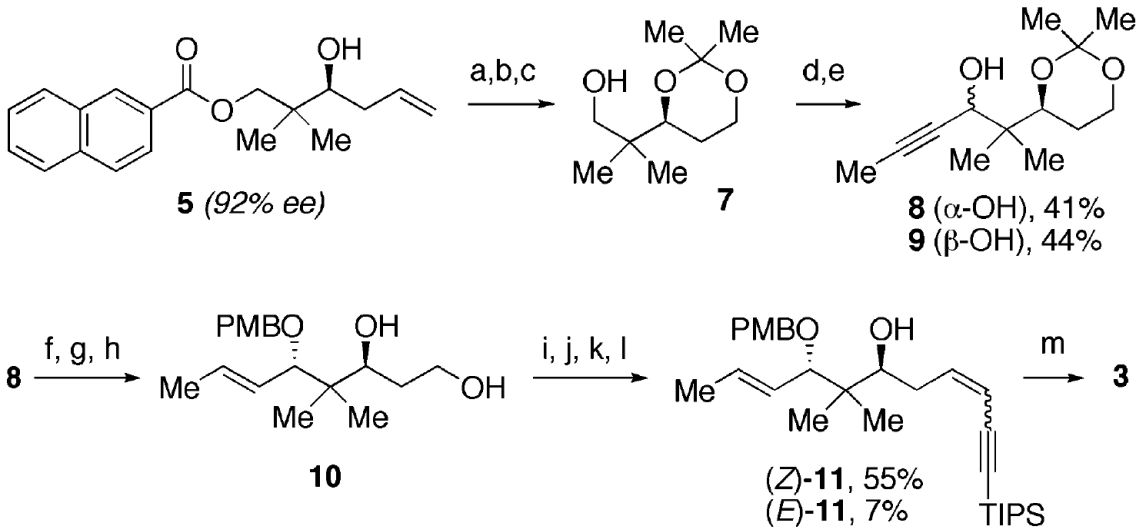
499.3 kJ/mol

ΔE 254.3 kJ/mol



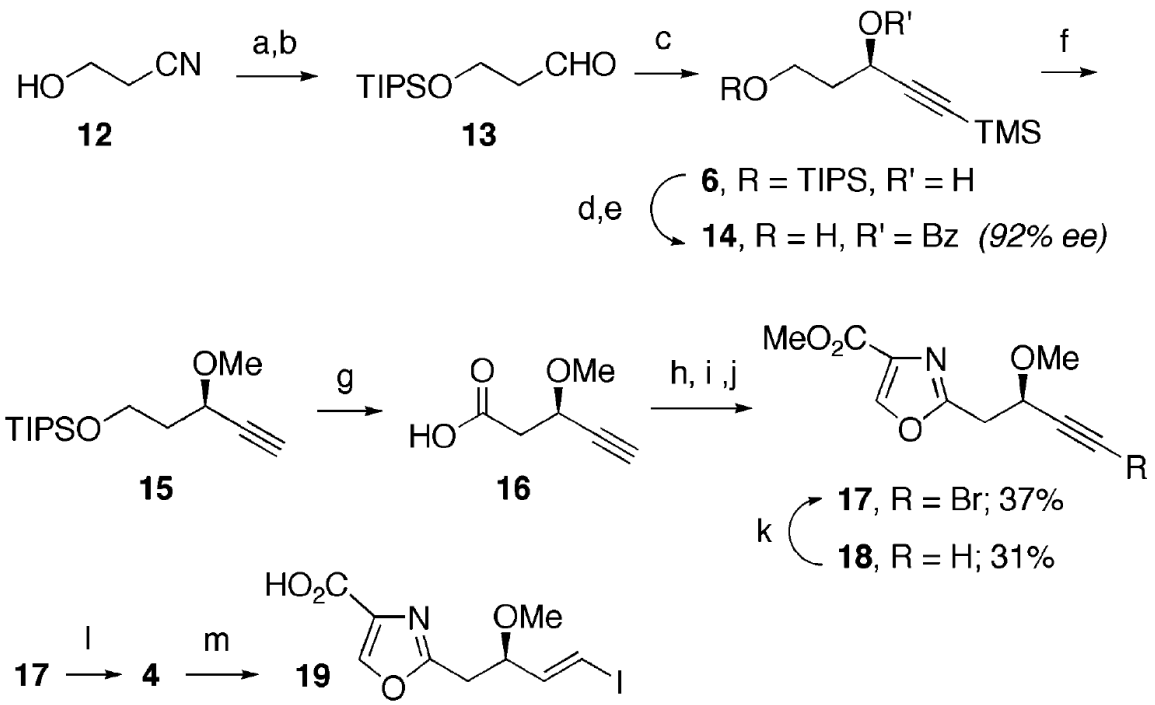
47 245.0 kJ/mol

Wipf's synthesis

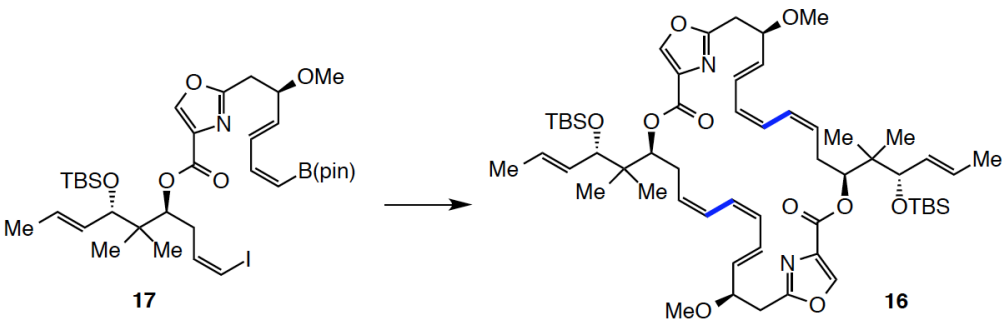


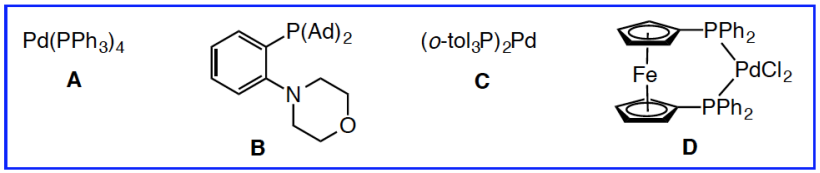
[a] (a) O_3/O_2, Sudan III, MeOH, CH_2Cl_2, −78 °C then $NaBH_4$, −78 °C to rt, 88%; (b) 2,2-dimethoxypropane, PPTS, THF, 0 °C to rt, 36 h, 97%; (c) 1 M LiOH, THF, MeOH, 0 °C to rt, 20 h, 82%; (d) oxalyl chloride, DMSO, Et_3N, −78 °C; (e) propyne, *n*-BuLi, THF, −78 °C to 0 °C, 1.5 h; (f) Red-Al, THF (degassed), 70−75 °C, 25 h, 83%; (g) PMB-Br, Et_3N, KHMDS, THF, −78 °C, 1 h then rt, 2 h; (h) AcOH, THF, H_2O (4:1:1), 60 °C, 12 h, 84% (2 steps); (i) TES-OTf, 2,6-Lutidine, CH_2Cl_2, 0 °C, 30 min; (j) oxalyl choride, DMSO, Et_3N, CH_2Cl_2, 75% (2 steps); (k) 1,3-bis(TIPS)propyne, *n*-BuLi, THF, −78 °C, 30 min; (l) chloroacetic acid, MeOH/CH_2Cl_2, rt, 14 h; (m) TBAF, THF, 0 °C to rt, 14 h, 94%.

Wipf's synthesis

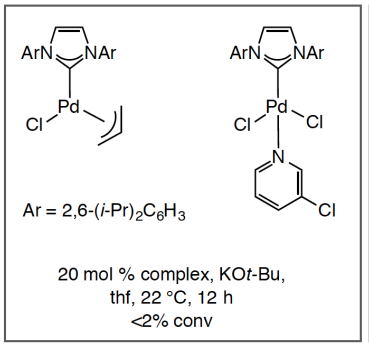


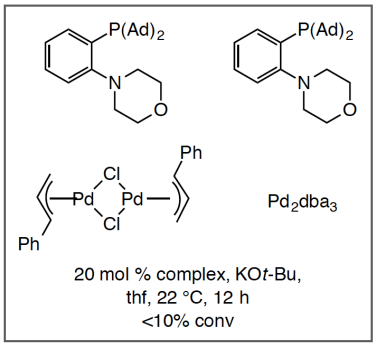
[a] (a) TIPS-Cl, imid, DMF, rt, 16 h; (b) DiBAl-H, CH_2Cl_2, −10 °C, 50 min, 78% (2 steps); (c) TMS-acetylene, Et_2Zn, toluene, reflux, 1 h, then (*S*)-Binol, Ti(O*i*-Pr)$_4$, then **13**, rt, 20 h, 66%; (d) benzoyl chloride, DMAP, pyridine, rt, 4 h, 100%; (e) HF/H_2O, CH_3CN, rt, 12 h, 93%; (f) Dimethyl sulfate, *n*-Bu_4NHSO_4, NaOH, toluene/H_2O, 0 °C to rt, 3.5 h, 95%; (g) HF, CH_3CN, rt, 24 h then NaOCl, $NaClO_2$, TEMPO, CH_3CN, phosphate buffer (pH 6.7), 45 °C, 18 h, 99%; (h) SerOMe·HCl, EDC, HOBT, NMM, CH_2Cl_2, 0 °C to rt, 16 h, 55%; (i) DAST, CH_2Cl_2, −78 °C, 1 h then K_2CO_3, −78 °C to rt, 40 min; (j) DBU, $BrCCl_3$, CH_2Cl_2, 0 °C to 4 °C, 20 h; (k) NBS, $AgNO_3$, acetone, rt, 1 h, 54%; (l) *n*-Bu_3SnH, $PdCl_2(PPh_3)_2$, THF, −78 °C to rt, 3 h, then I_2, 0 °C, 45 min, 92%; (m) LiOH, H_2O, THF, rt, 12 h, 97%.

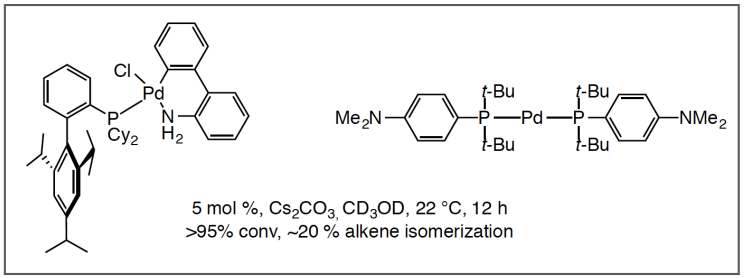


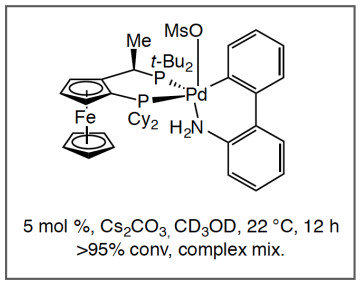


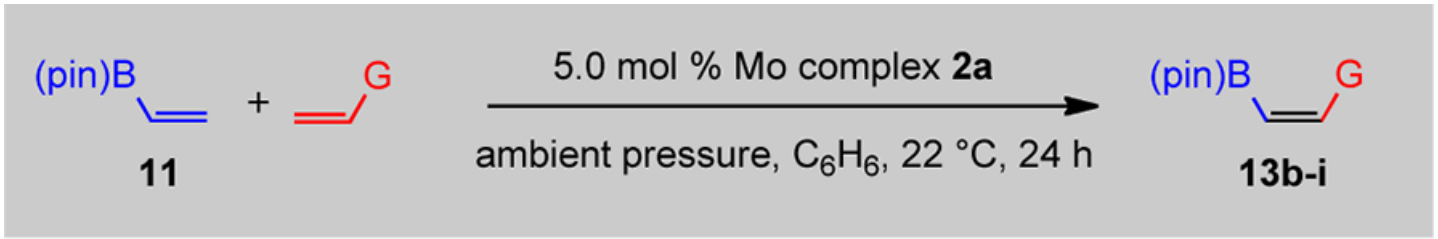
entry	solvent; base	complex (mol %);[b] concentration	conv (%)[b]	**16**:**19**:oligomers[b]	yield (%)[c]
1	thf; Ag_2O	**A** (20); 0.014	>95	complex mix.	na
2	thf; Ag_2O	**A**+**B** (20); 0.014	>95	14.5:9.5:76	9
3	thf; KO*t*-Bu	**A**+**B** (20); 0.014	>95	complex mix.	na
4	thf; Ag_2O	**C** (20); 0.009	10	na	nd
5	thf; KO*t*-Bu	**C** (20); 0.009	>95	13:7:80	nd
6	thf; KO*t*-Bu	**C** (100); 0.001	>95	11:42:47	nd
7	CD_3OD; KO*t*-Bu	**C** (20); 0.007	>95	27:0:73	nd
8	CD_3OD; Cs_2CO_3	**C** (5); 0.007	>95	31:0:69	nd
9	CD_3OD; KO*t*-Bu	**D** (5); 0.007	>95	50:0:50	31
10	CD_3OD; Cs_2CO_3	**D** (5); 0.007	>95	complex mix.	na
11	CD_3OD; KO*t*-Bu	**D** (5); 0.002	30	nd	nd
12	CD_3OD; KO*t*-Bu	**C** (5); 0.002	>95	75:0:25	43
13	CD_3OH; Cs_2CO_3	**C** (5); 0.002	>95	80:0:20	54
14	CD_3OH; Cs_2CO_3	**C** (5); 0.004	>95	66:0:34	60



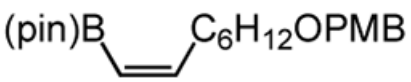




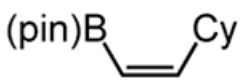




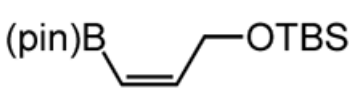
13b
91% conv, 68% yield,
90:10 *Z*:*E*



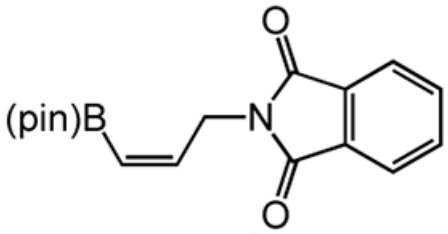
13c
95% conv, 92% yield,
97:3 *Z*:*E*



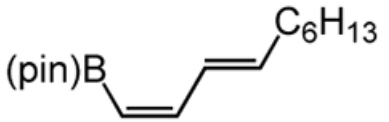
13d
78% conv, 51% yield,
93:7 *Z*:*E*



13e
94% conv, 70% yield,
96:4 *Z*:*E*

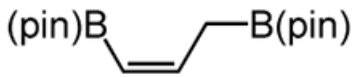


13f
87% conv, 71% yield,
93:7 *Z*:*E*



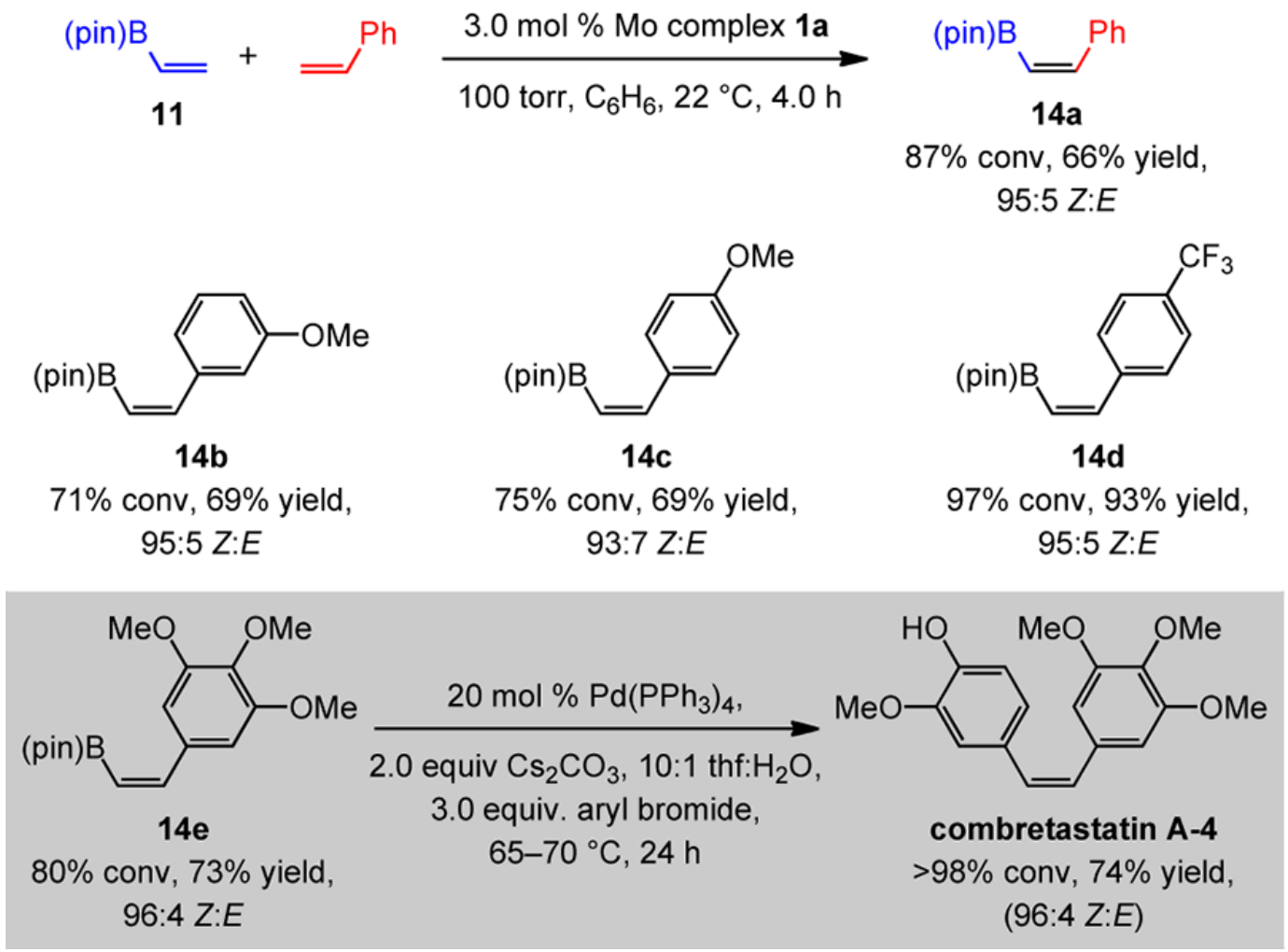
13g
91% conv, 72% yield,
93:7 *Z*:*E*

13h
98% conv, 80% yield,
93:7 *Z*:*E*



13i
91% conv, 60% yield,
97:3 *Z*:*E*

Hoveyda et al., *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029



Hoveyda et al., *J. Am. Chem. Soc.* **2013**, *135*, 6026–6029