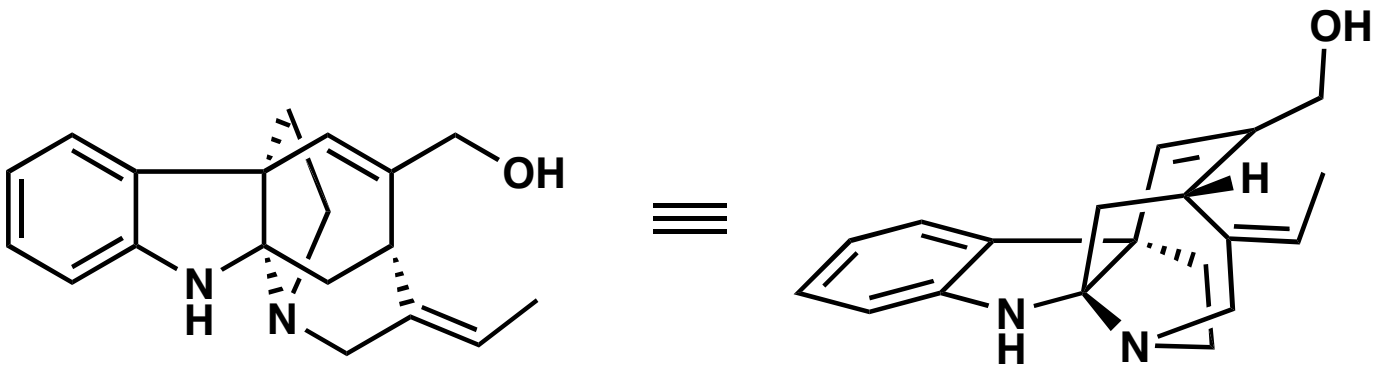
Total Syntheses of Minfiensine

Douany, A. B.; Humphreys, P. G.; Overman, L. E.*; Wrobelski, A. D., *J. Am. Chem. Soc.* **2008**, ASAP. DOI: 10.1021/ja800163v

Shen, L.; Zhang, M.; Wu, Y.; Qin, Y.*, *Angew. Chem. Int. Ed.* **2008**, Early View. DOI: 10.1002/anie.200800566



Overman Qin

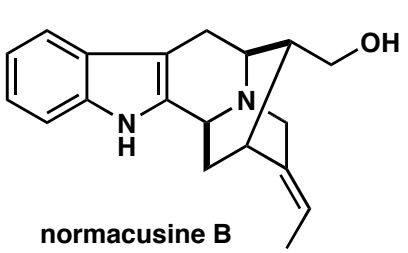
Adam Hoye

Current Literature

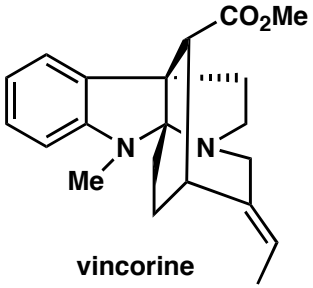
April 26th, 2008

Wipf Group

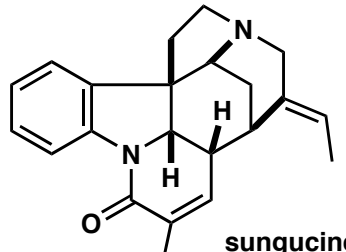
Strychnos alkaloids



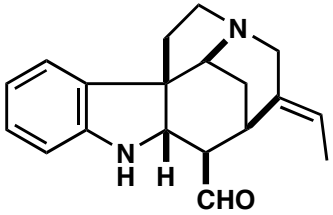
normacusine B



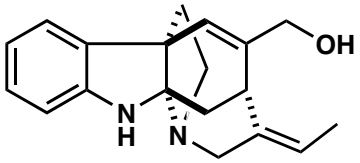
vincorine



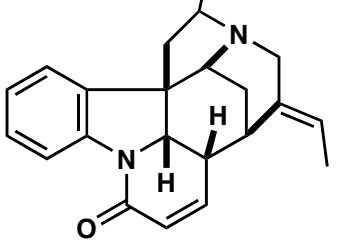
sungucine

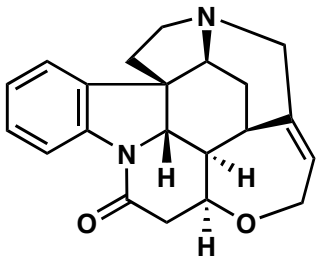


18-desoxy-Weiland-Gumlich aldehyde

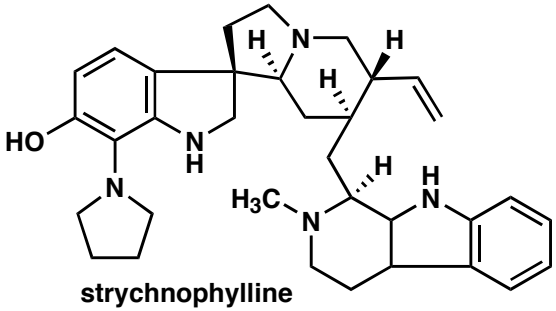


minfiensine





strychnine



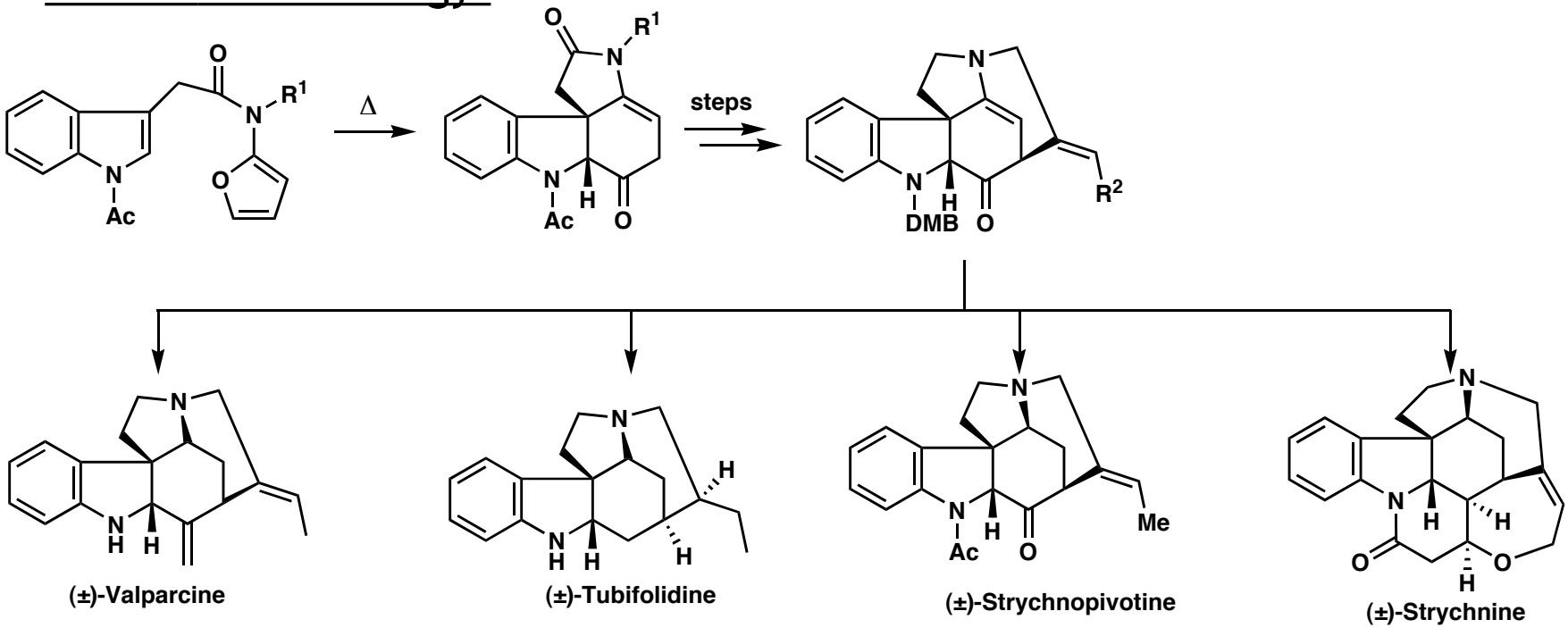
strychnophylline

Biological activities: folk medicine, cytotoxic, antimalarial, anticancer
Synthetic intrigue- compact complexity

On strychnine: "For its molecular size it is the most complex substance known."
-Sir Robert Robinson, 1952
Robinson, R. *Prog. Org. Chem.* **1952**, *1*, 2.

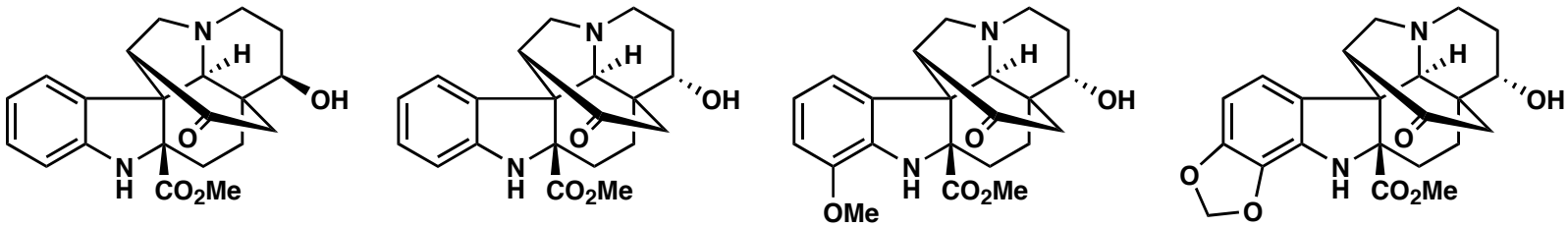
Strychnos alkaloids in current literature

Padwa methodology:



Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A. *J. Org. Chem.*, **2008**, ASAP

Flavisiamine A-D



Sekiguchi et al. Heterocycles, **2008**, Prepress

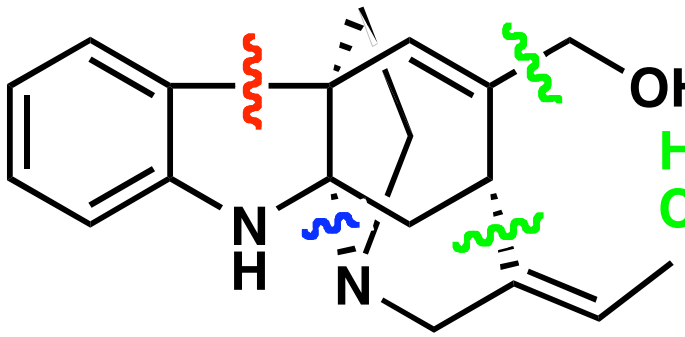
Overman disconnections

In this full article publication:

-Summary of 2005 synthesis with full account of what didn't work

-2nd generation synthesis featuring a more concise end game strategy

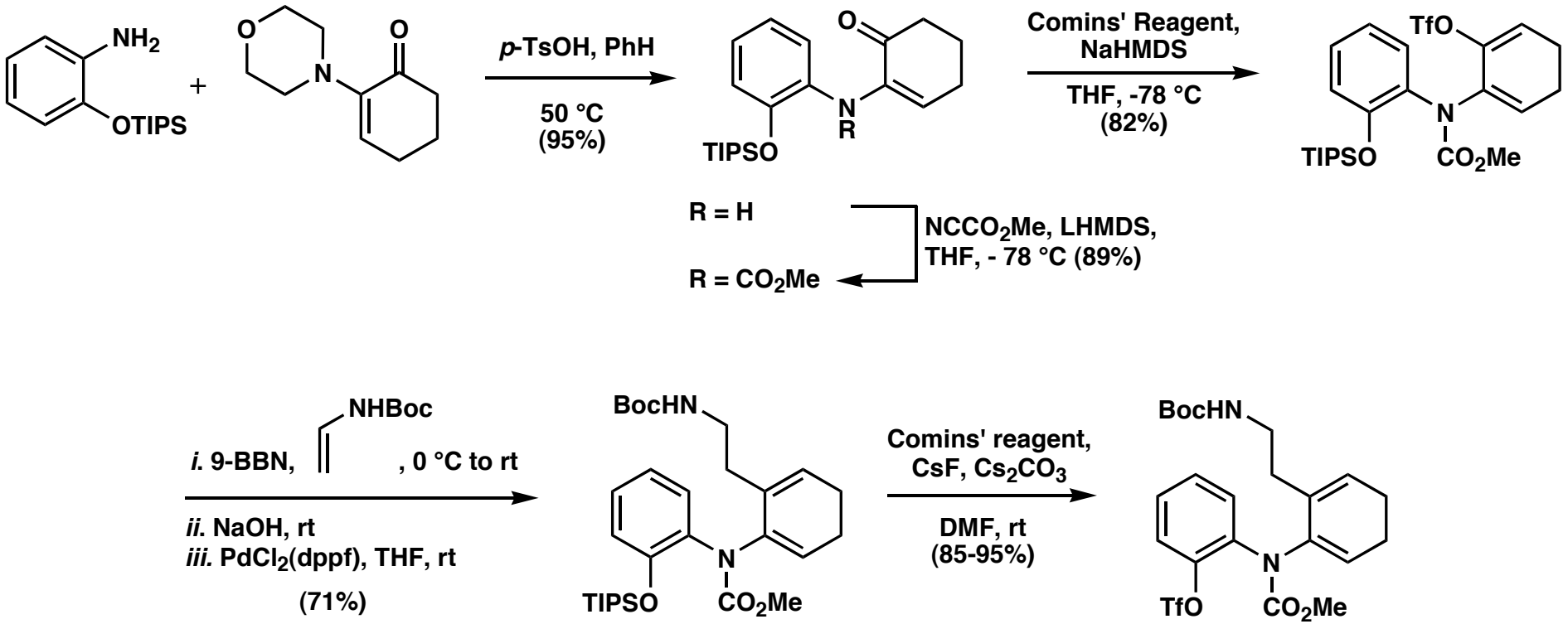
Catalytic asymmetric Heck



Heck cyclization/ Carbonylation

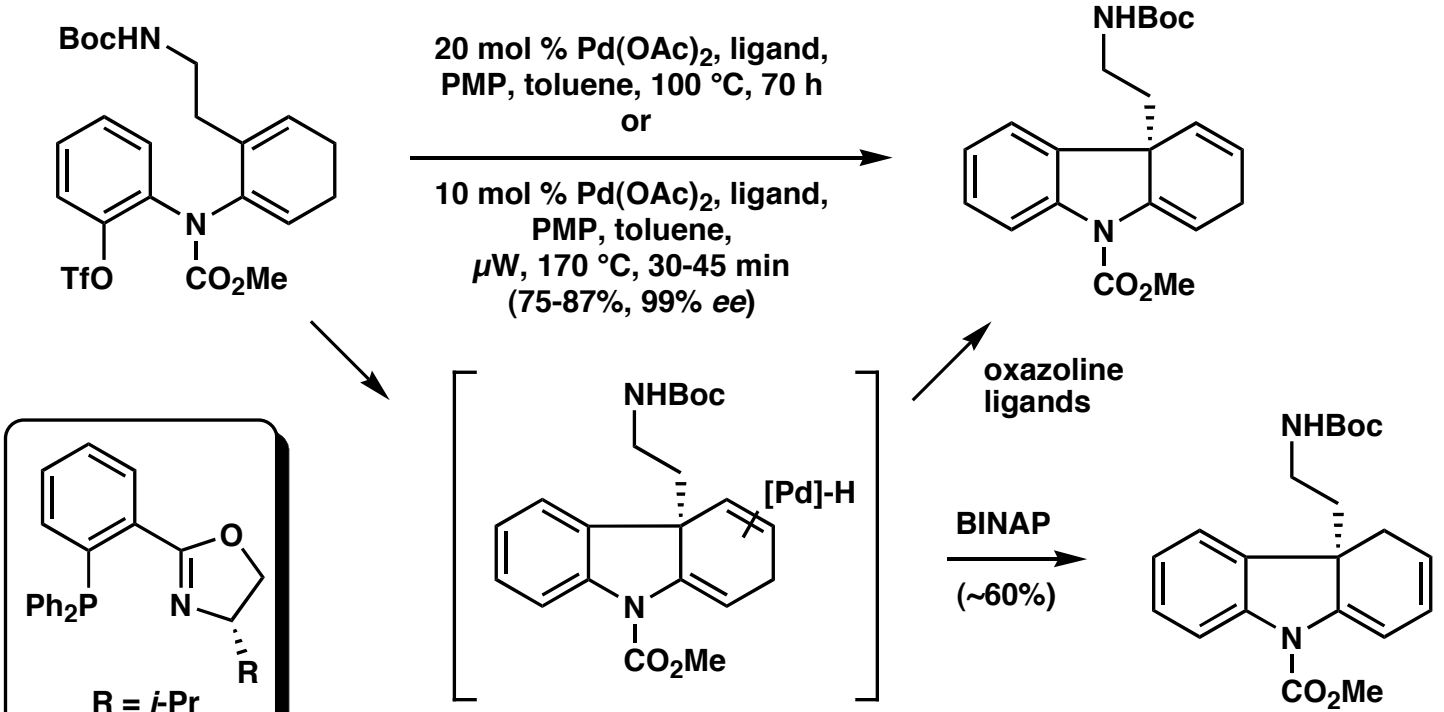
Iminium ion addition

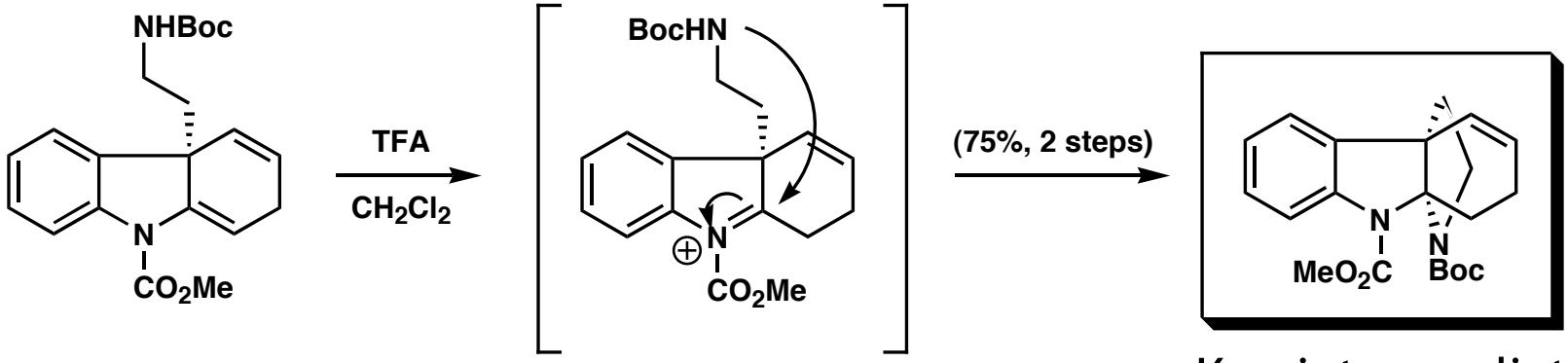
2005 synthesis



Douany, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186-10187

Catalytic asymmetric Heck reaction

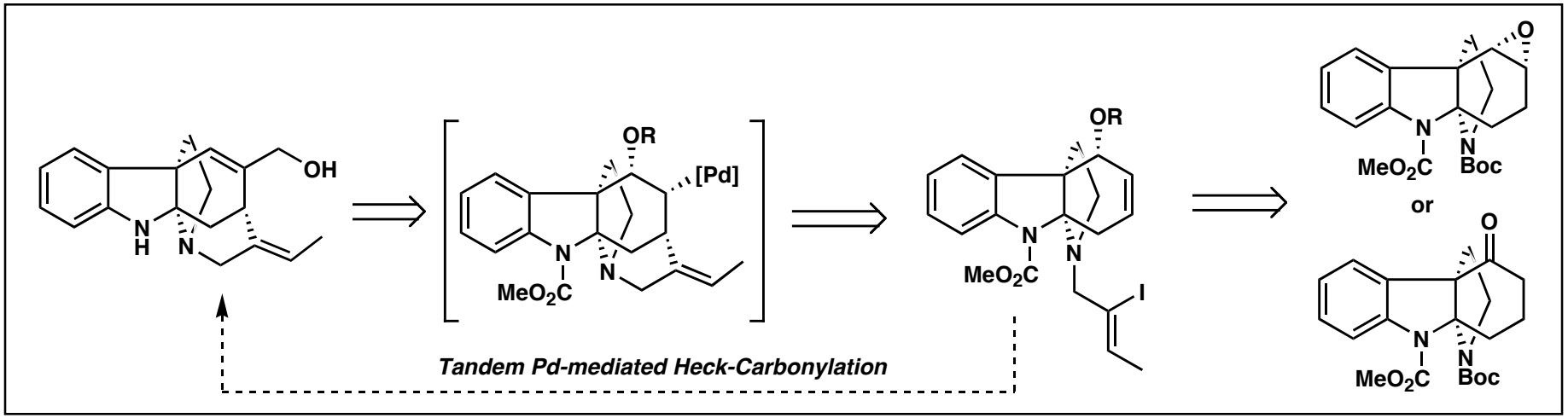




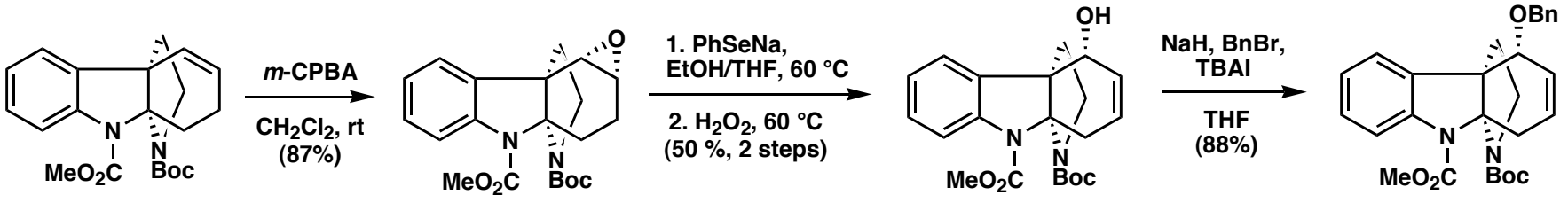
Key intermediate

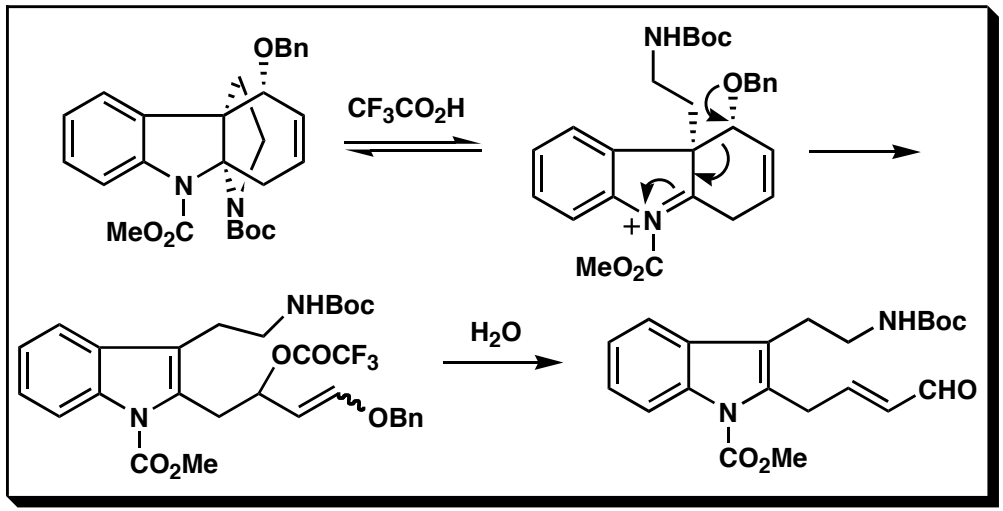
Douany, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186-10187

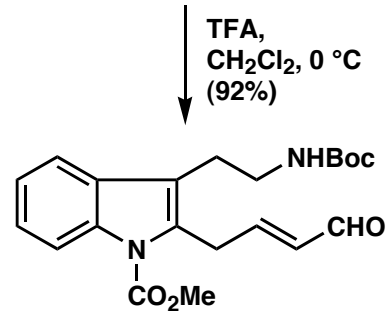
2005 synthesis



Epoxide route:

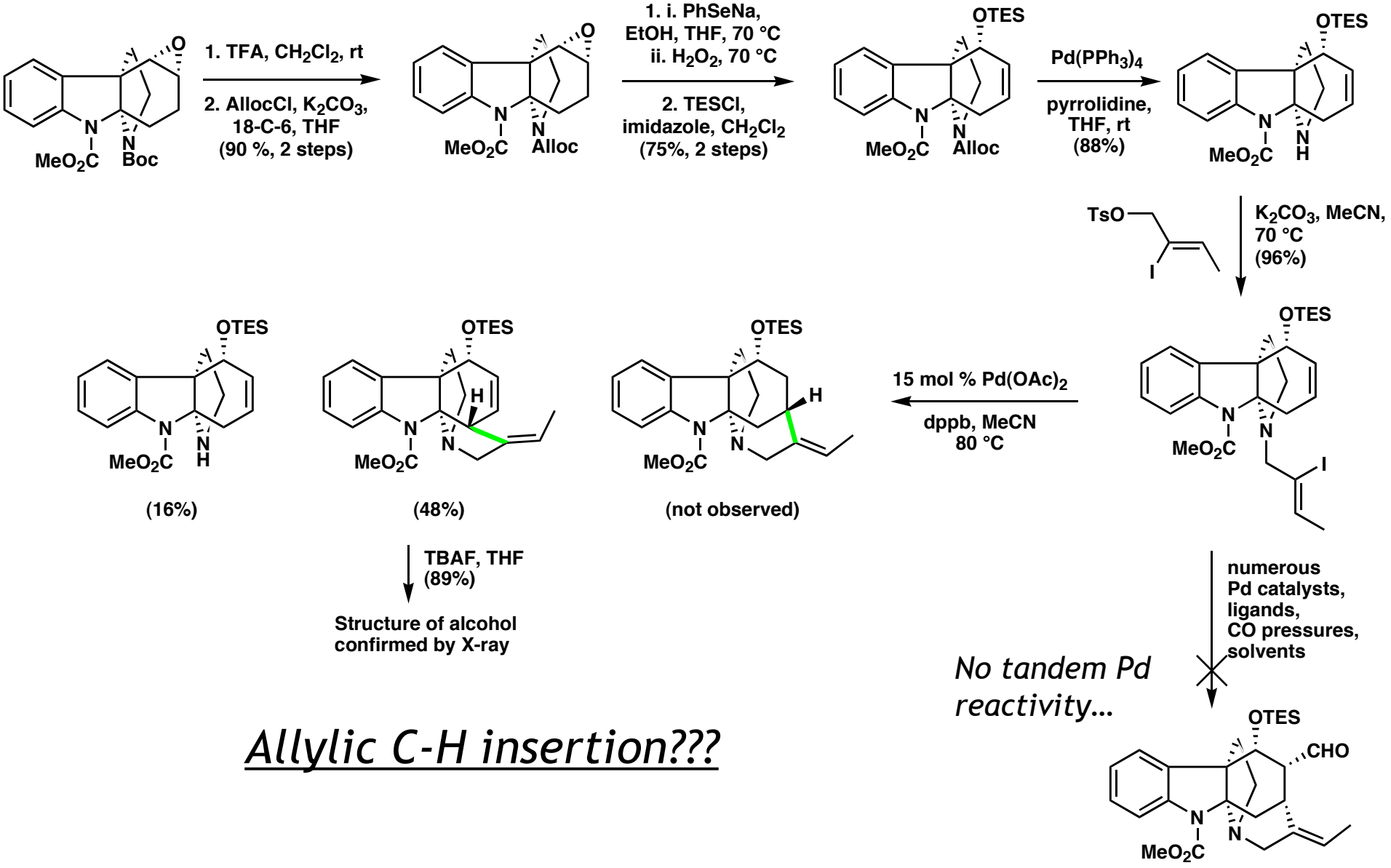






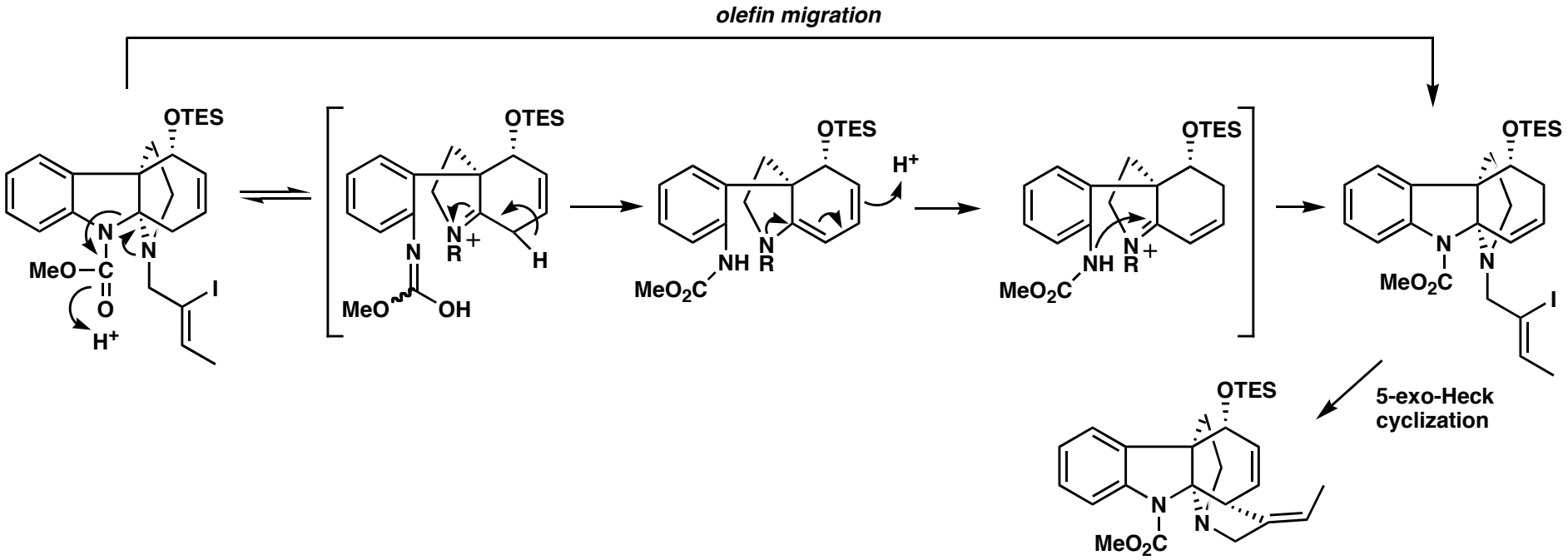
troublesome N-Boc deprotection…

Protecting group switch…



Pd-mediated C-H insertion vs. Rearrangement/Heck

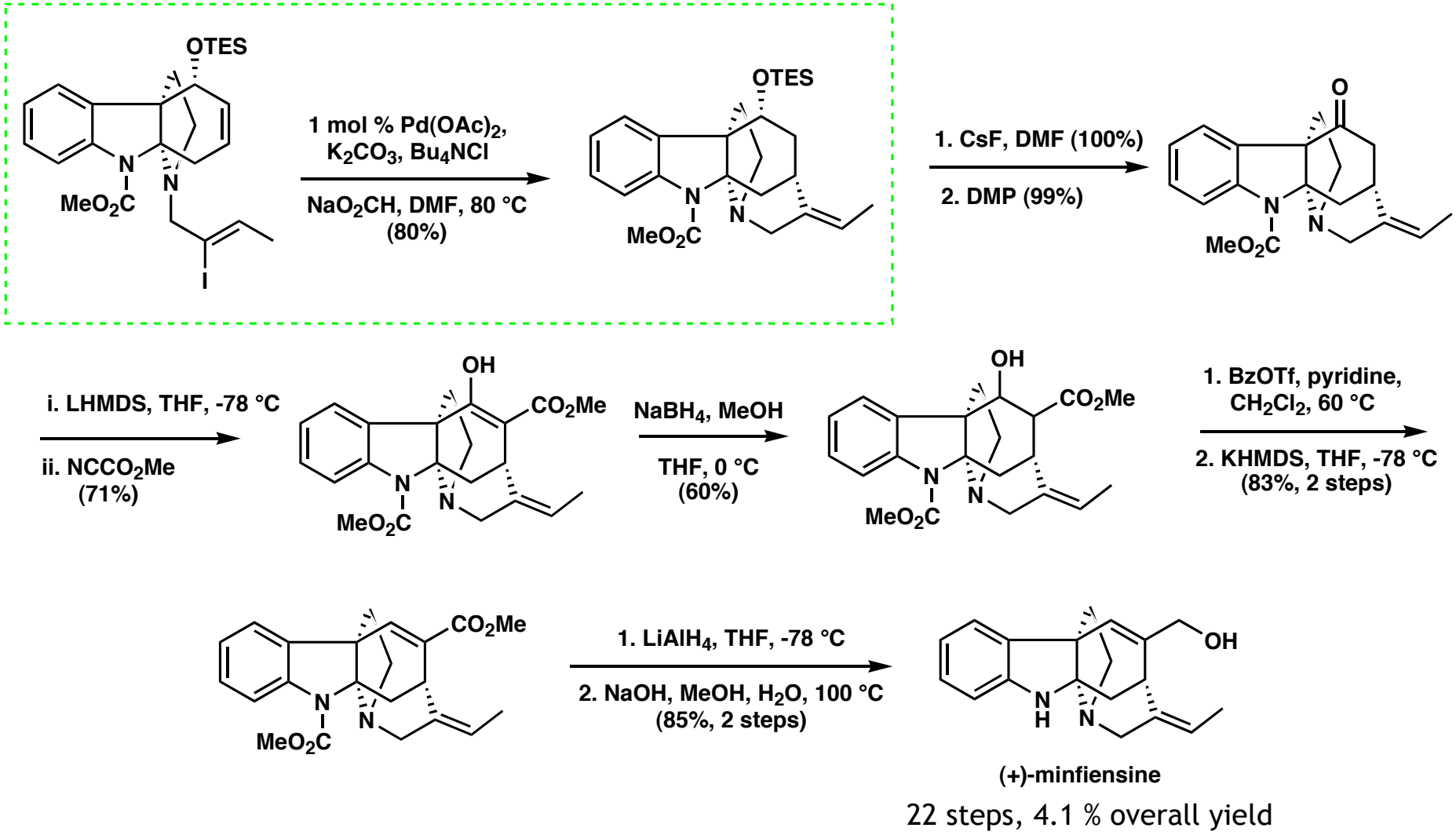
Instead a more conservative (rational) proposal…



…but is $r_{catalyst} > r_{rearrangment}$?

Phosphine-free reductive Heck conditions; completion of the molecule

$r_{catalyst} > r_{rearrangment}$? *High catalyst rates under phosphine-free Heck conditions*



(+)-minfiensine

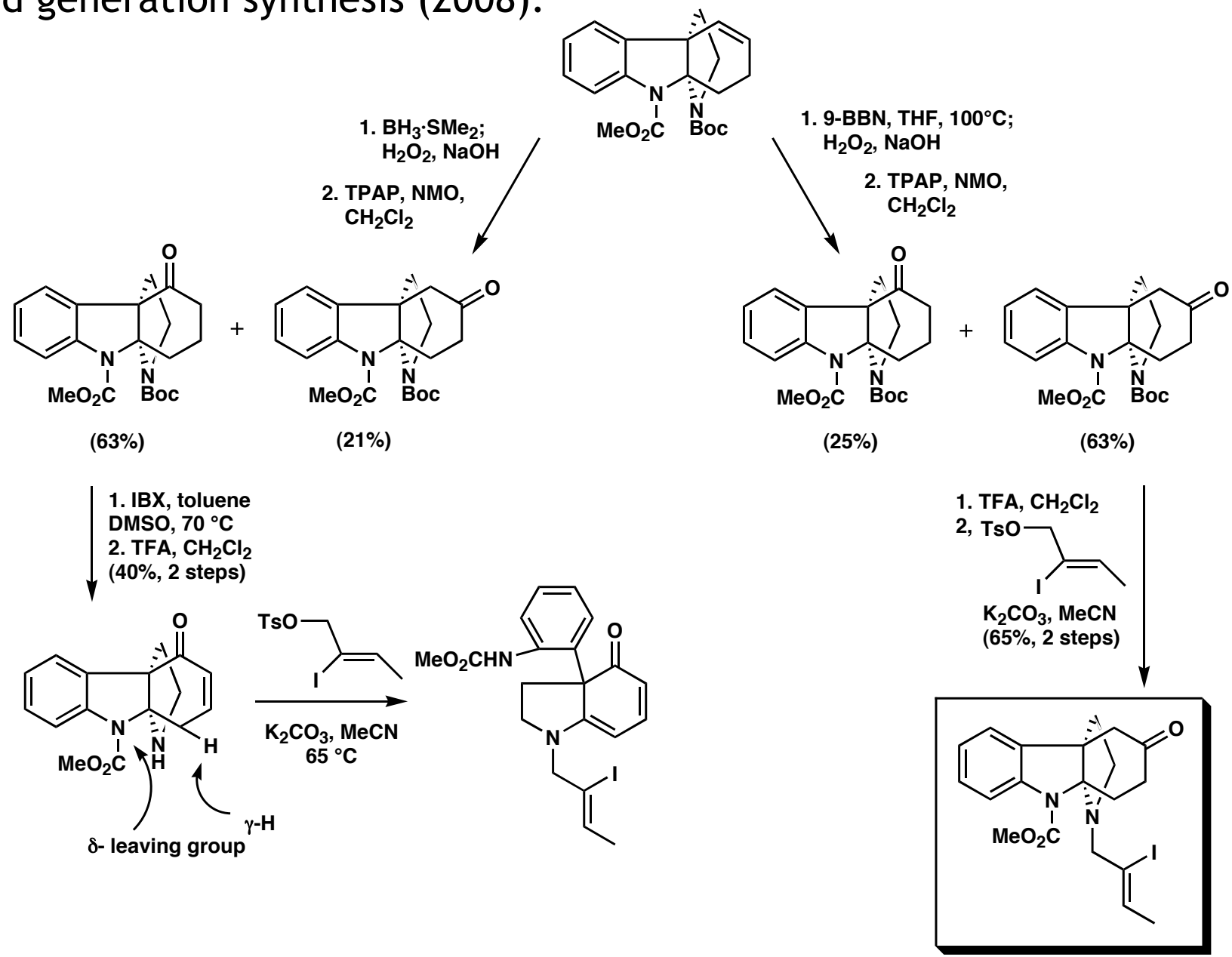
22 steps, 4.1 % overall yield

(a) Jeffery, T. *Tetrahedron Lett.* **1985**, 26, 2667–2670. (b) Jeffery, T. *Tetrahedron* **1996**, 52, 10113–10130.

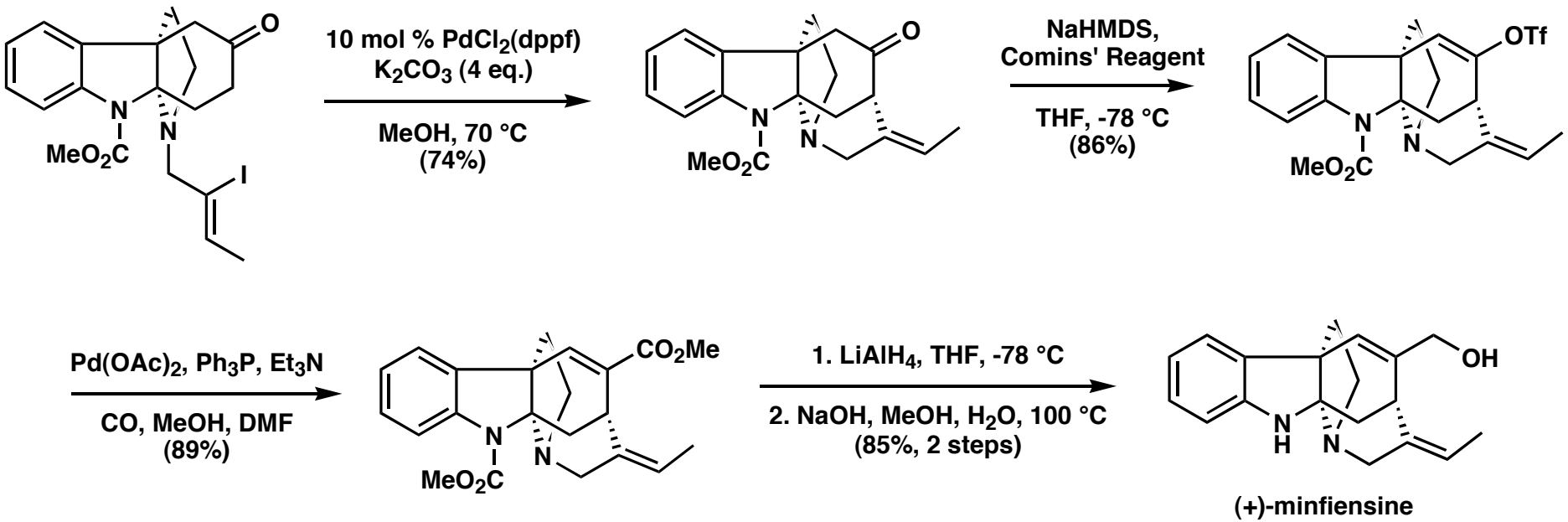
Douany, A. B.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 10186-10187

Hydroboration/oxidation regioselectivity

2nd generation synthesis (2008):



2nd-generation end game



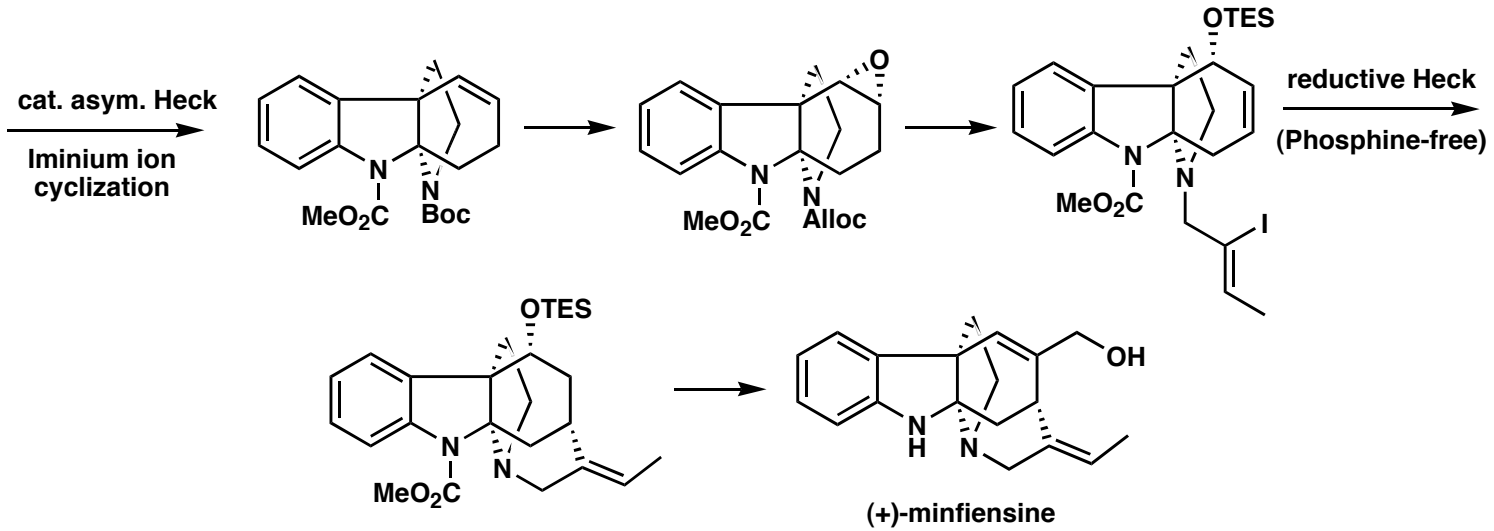
formally 15 steps

1st end game- 16 steps from catalytic asymmetric Heck, 11.8% yield

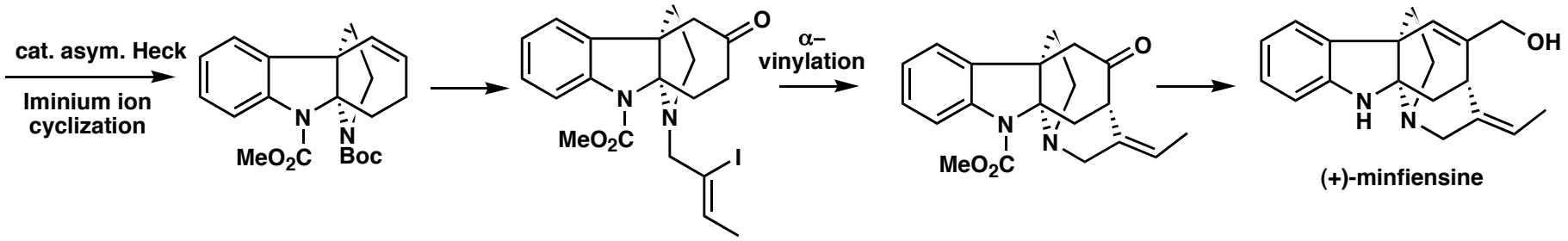
2nd end game- 9 steps from cat. asym. Heck, 19% yield

Summary of Overman routes

1st generation:

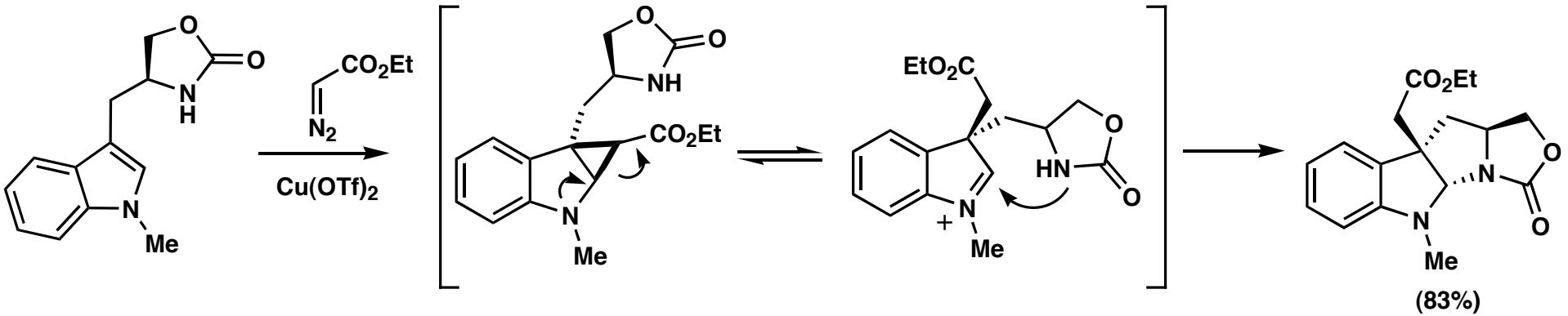


2nd generation:

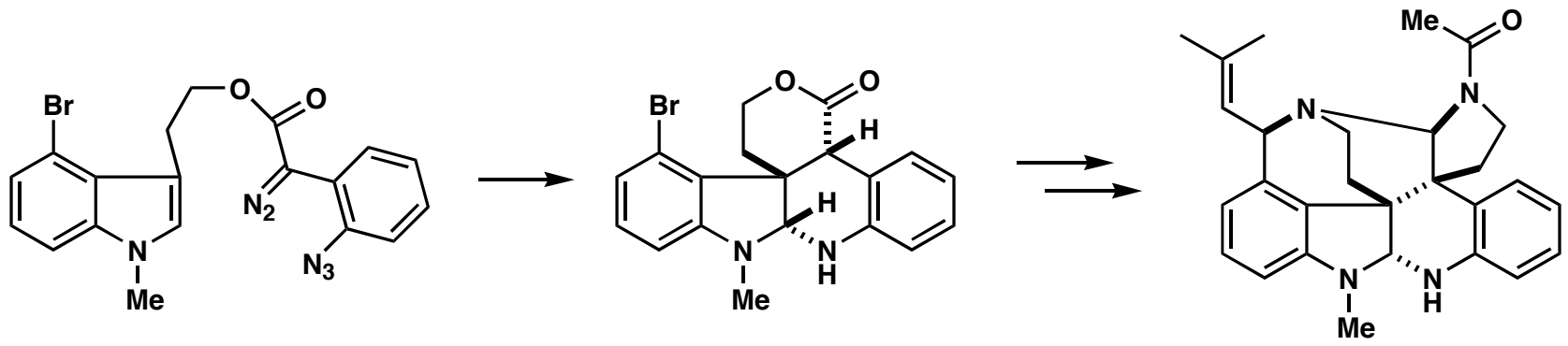


Qin indole alkaloids

"Methodology-driven" synthesis: Three-step, one-pot cascade cyclization



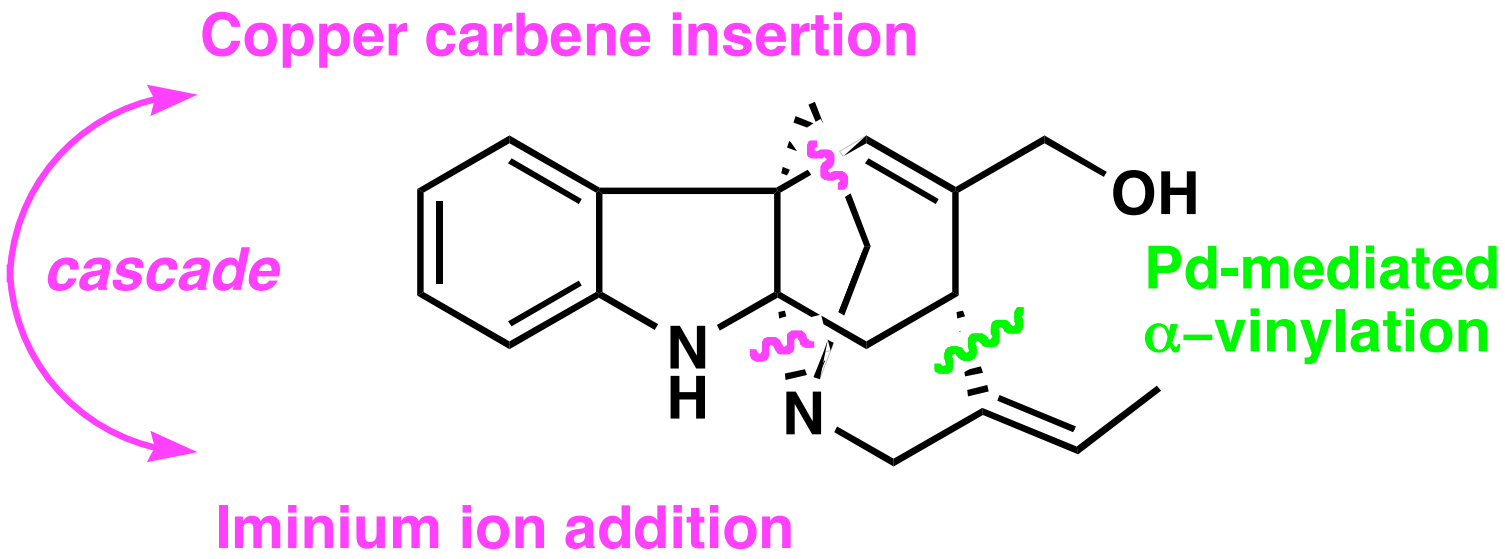
Qin et al. *Org. Lett.*, **2006**, *8*, 6011-6014



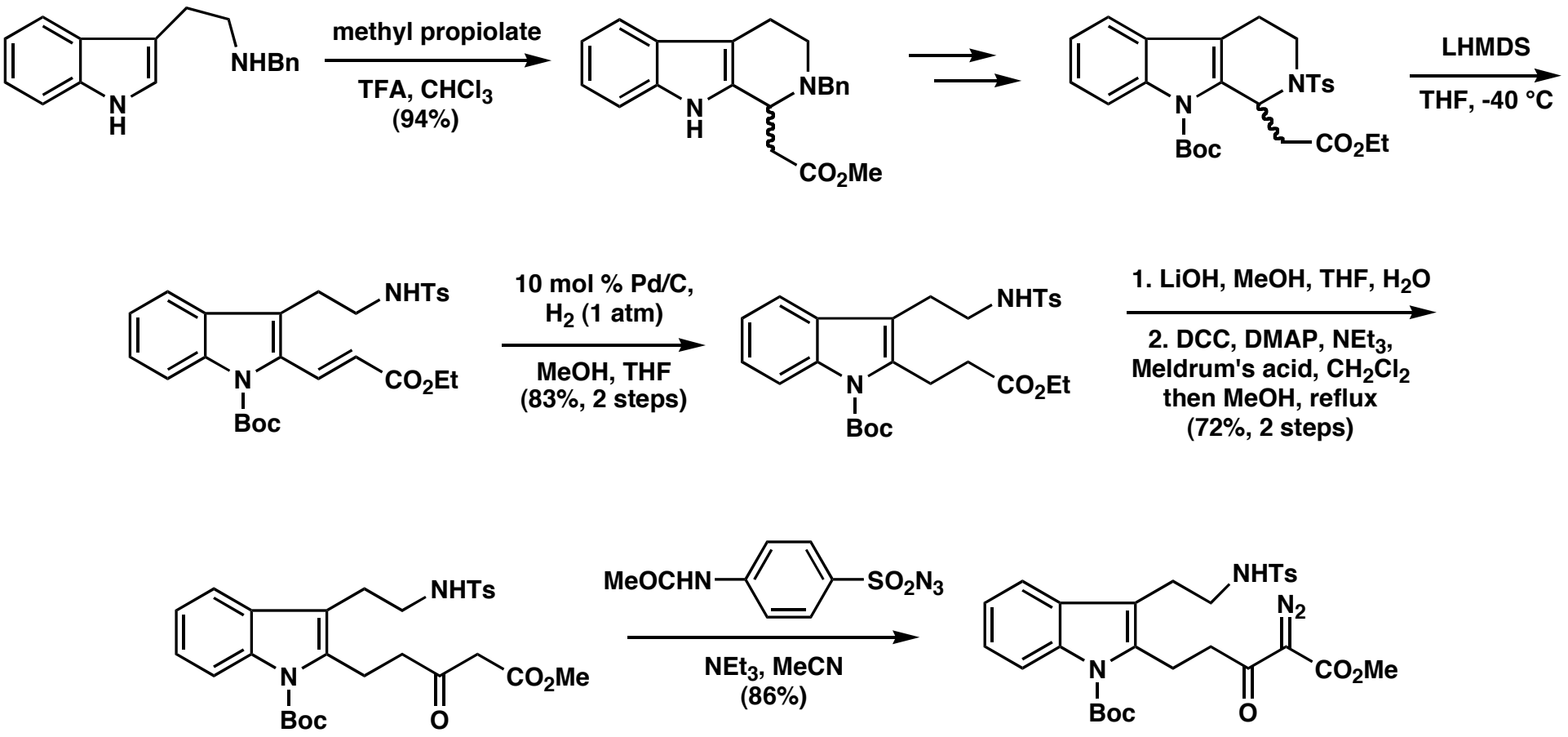
Qin et al. *J. Am. Chem. Soc.*, **2007**, *129*, 13794-13795

Qin disconnections

"Concise total synthesis" of (±)-minfiensine:



Starting material synthesis



Bailey, P.; Hollinshead, S. P.; Dauter, Z. *Chem. Commun.* **1985**, 1507-1509

Shen, L.; Zhang, M.; Wu, Y.; Qin, Y.*, *Angew. Chem. Int. Ed.* **2008**, *Early View*

Cyclopropanation rearrangement

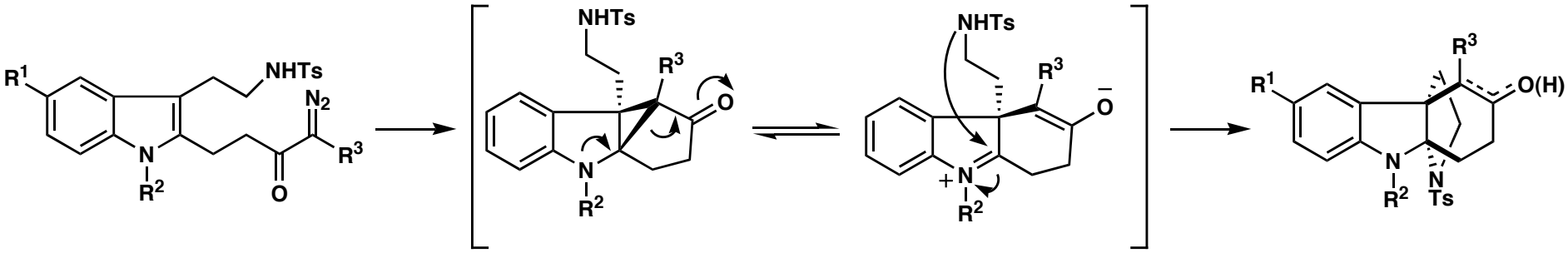
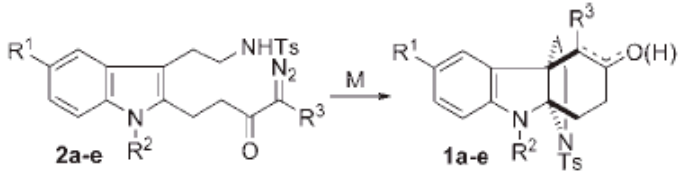
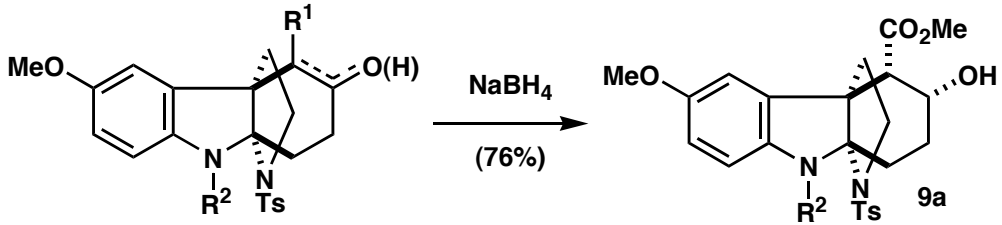


Table 1: Yields of the cascade reaction of diazo ketone **2**.[a]



	R^1	R^2	R^3	Salts	Yield of **1** [%] [b]	Ratio[c] of ketone:enol
2a	H	Boc	COOMe	CuI	0	
2a	H	Boc	COOMe	$[Cu(acac)_2]$	0	
2a	H	Boc	COOMe	$Rh(OAc)_2$	8 (**1a**)	0:1
2a	H	Boc	COOMe	$[Cu(MeCN)_4]PF_6$	15 (**1a**)	0:1
2a	H	Boc	COOMe	$Cu(OTf)_2$	25 (**1a**)	0:1
2a	H	Boc	COOMe	CuOTf	50 (**1a**)	0:1
2b	MeO	Boc	COOMe	CuOTf	52 (**1b**)	0:1
2c	H	Me	COOMe	CuOTf	81 (**1c**)	1:30
2d	MeO	Me	COOMe	CuOTf	82 (**1d**)	1:5
2e	H	Boc	H	CuOTf	42 (**1e**)	1:0

[a] Reaction conditions: metal salt (0.05 equiv), and CH_2Cl_2 as the solvent. [b] Yield of isolated product. [c] Determined from ^1H NMR analysis.



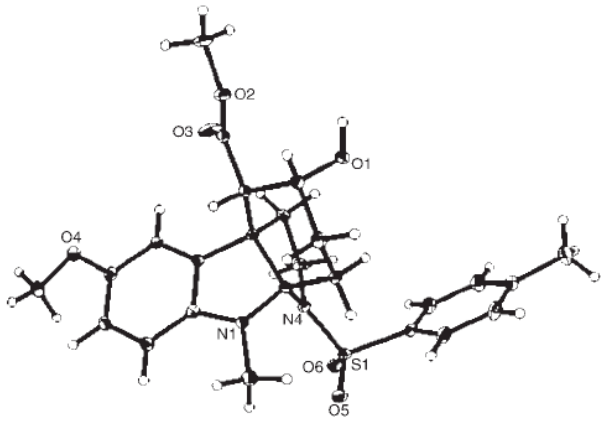
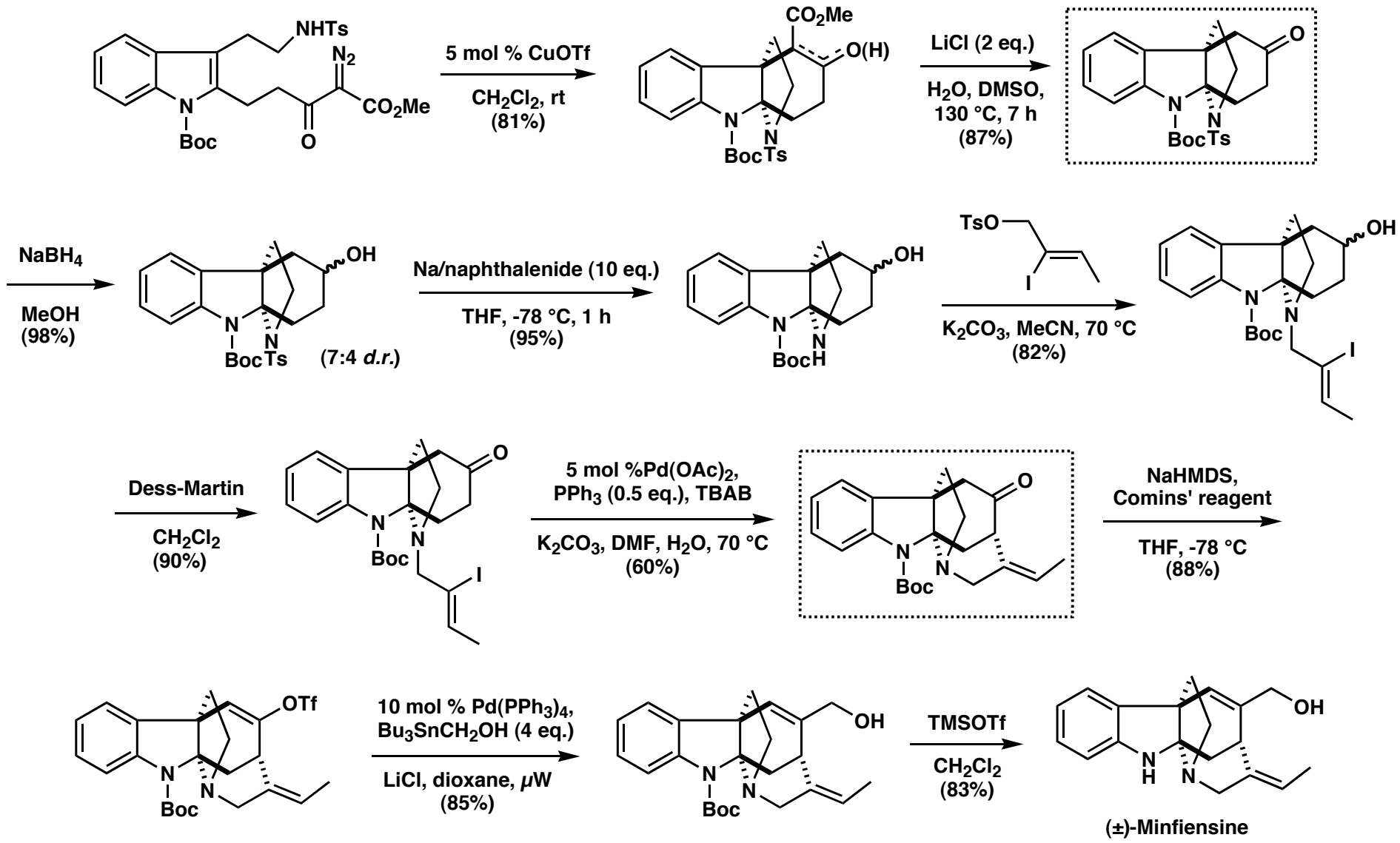


Figure 2. ORTEP diagram of **9a**.

End game… Déjà vu?

Overman-like intermediate



(±)-Minfiensine

14 steps, 9.2% overall yield

Conclusion

Arguably, a case of:
"Target-driven" synthesis (Overman) vs. "Methodology-driven" synthesis (Qin)

Regardless, each group accessed very similar advanced intermediates completely independent of one another-- the chemistry guides them!

Combine end game strategies of each group to maximize efficiency of synthesis:
(Overman protecting groups and Pd-vinylation conditions with Qin stille coupling)