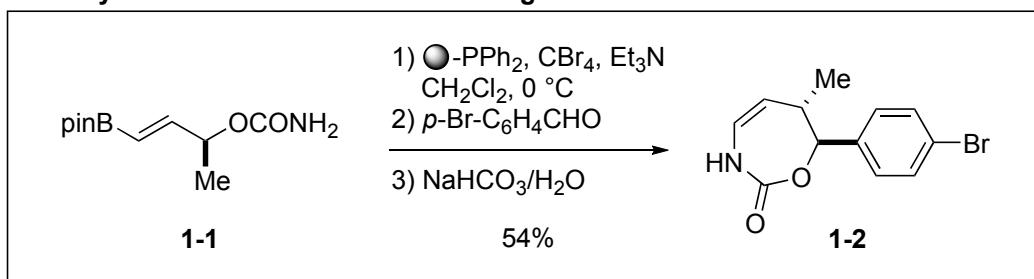


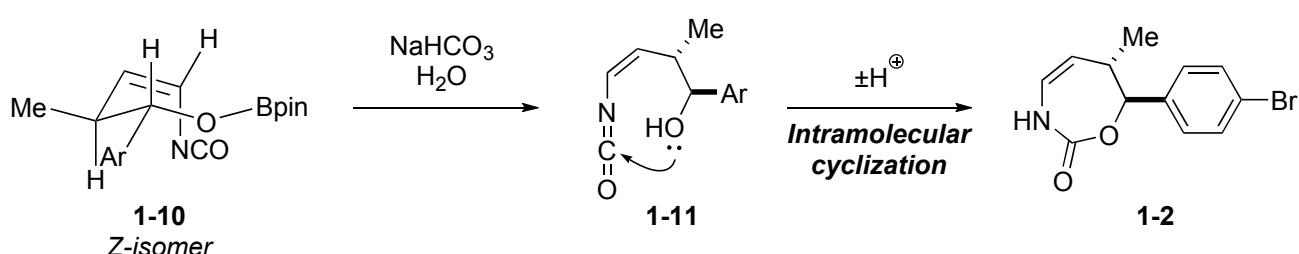
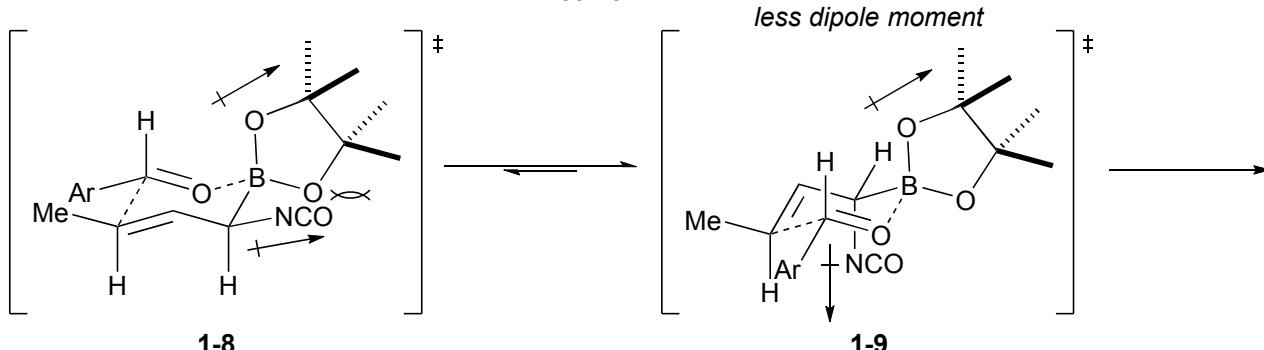
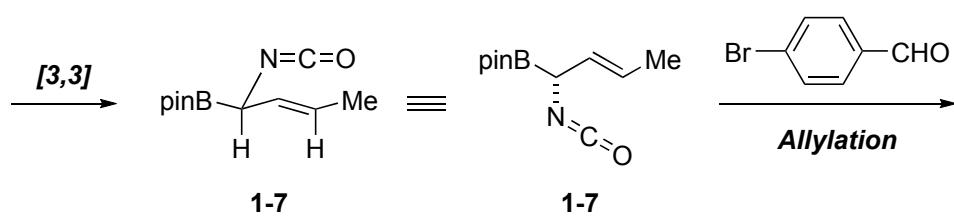
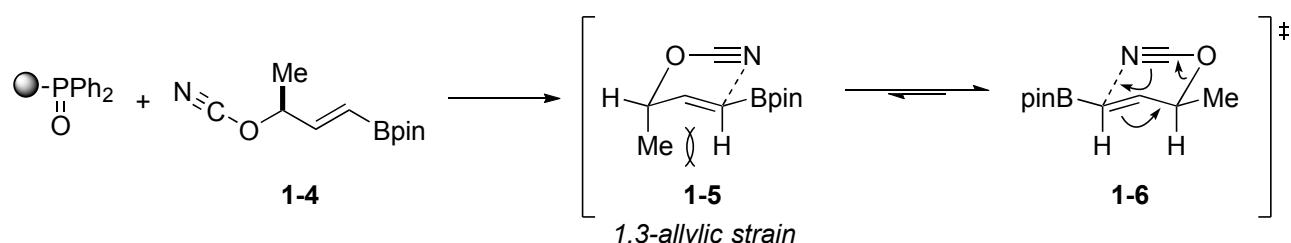
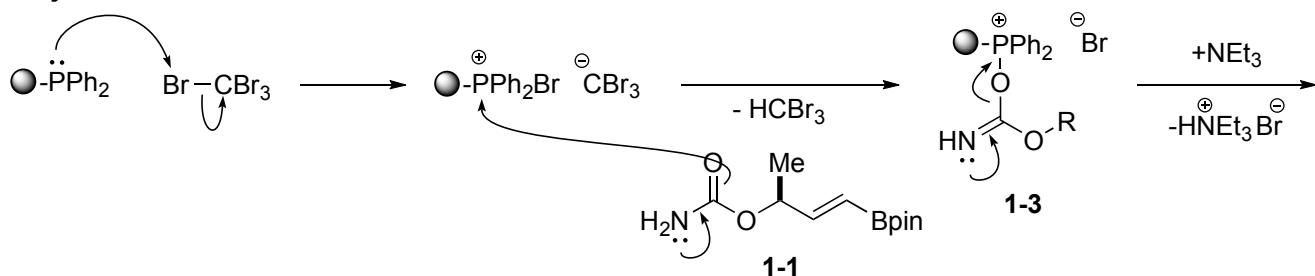
Problem Session (4) Answer

2015/12/12 Satoshi Hashimoto

1-1. Synthesis of Seven-Membered-Ring Carbamates



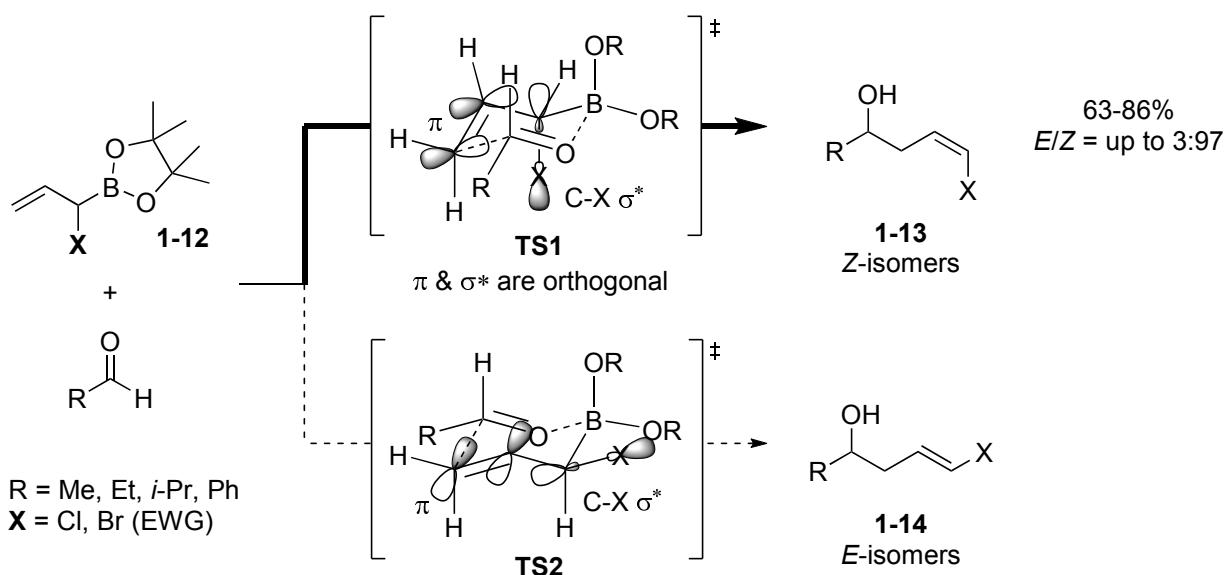
Macé, A.; Touchet, S.; Andres, P.; Cossío, F.; Dorcet, V.; Carreaux, F.; Carboni, B. *Angew. Chem. Int. Ed. ASAP*.
Dehydration



Discussion: Z-selectivity on Addition of α -substituted allylboronates to aldehyde

1. Dipole effects & Stereoelectronic effects

TS to Z-isomer minimizes dipole repulsion (described in the previous page)

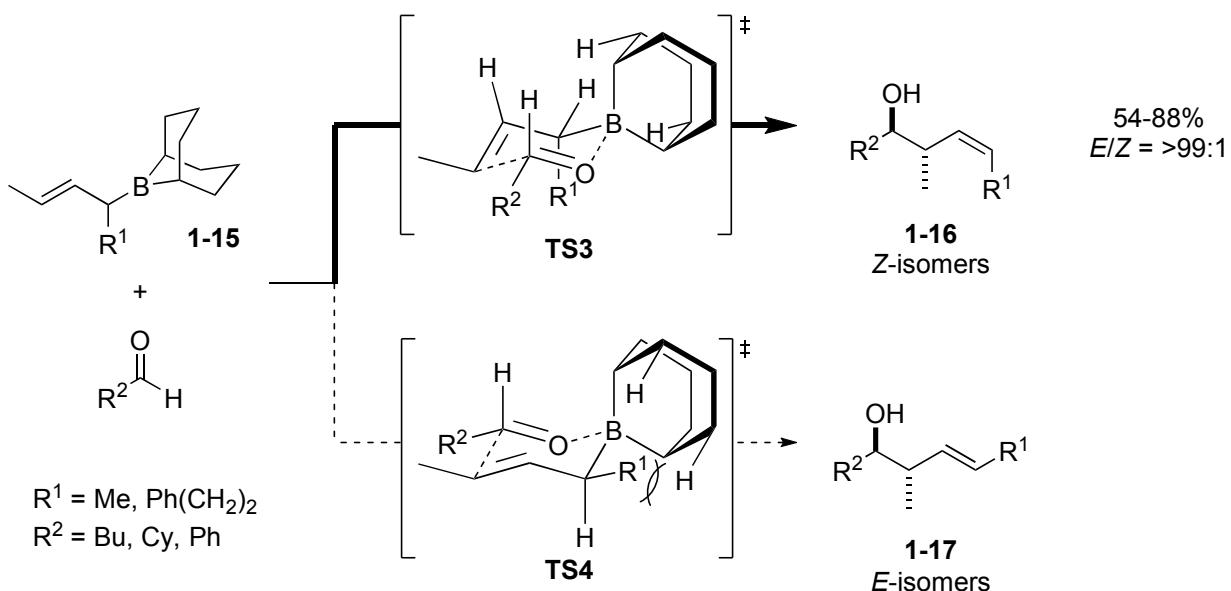


$\pi \rightarrow \sigma^*$ electron density were transferred: nucleophilicity was diminished.

Hoffmann, R. W.; Landmann, B. *Chem. Ber.* **1986**, 119, 1039.

2. Steric effects

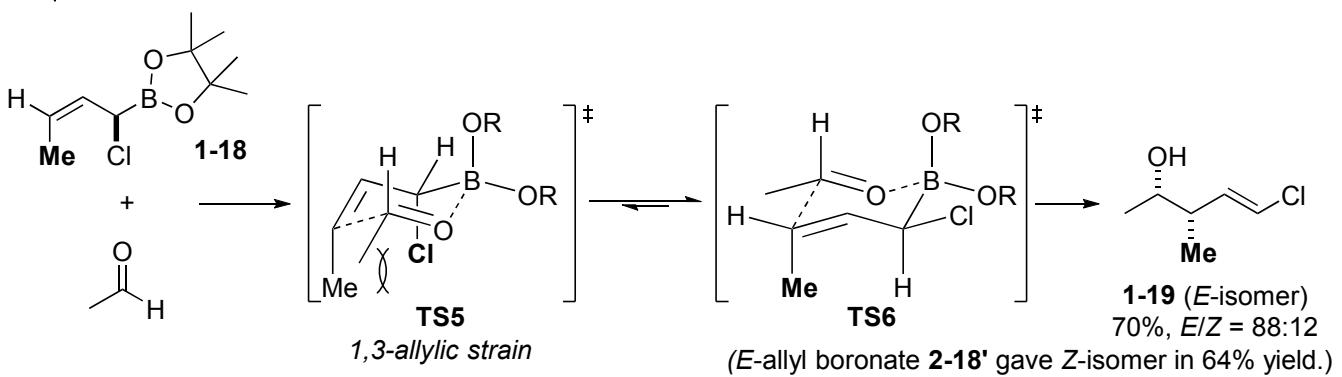
Hindered borane & boronate esters



borane: 9-BBN, boronate ester: tetraphenyl-1,2-ethanediol, etc.

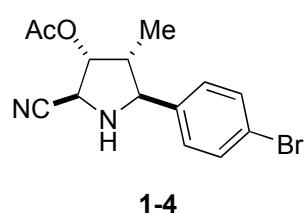
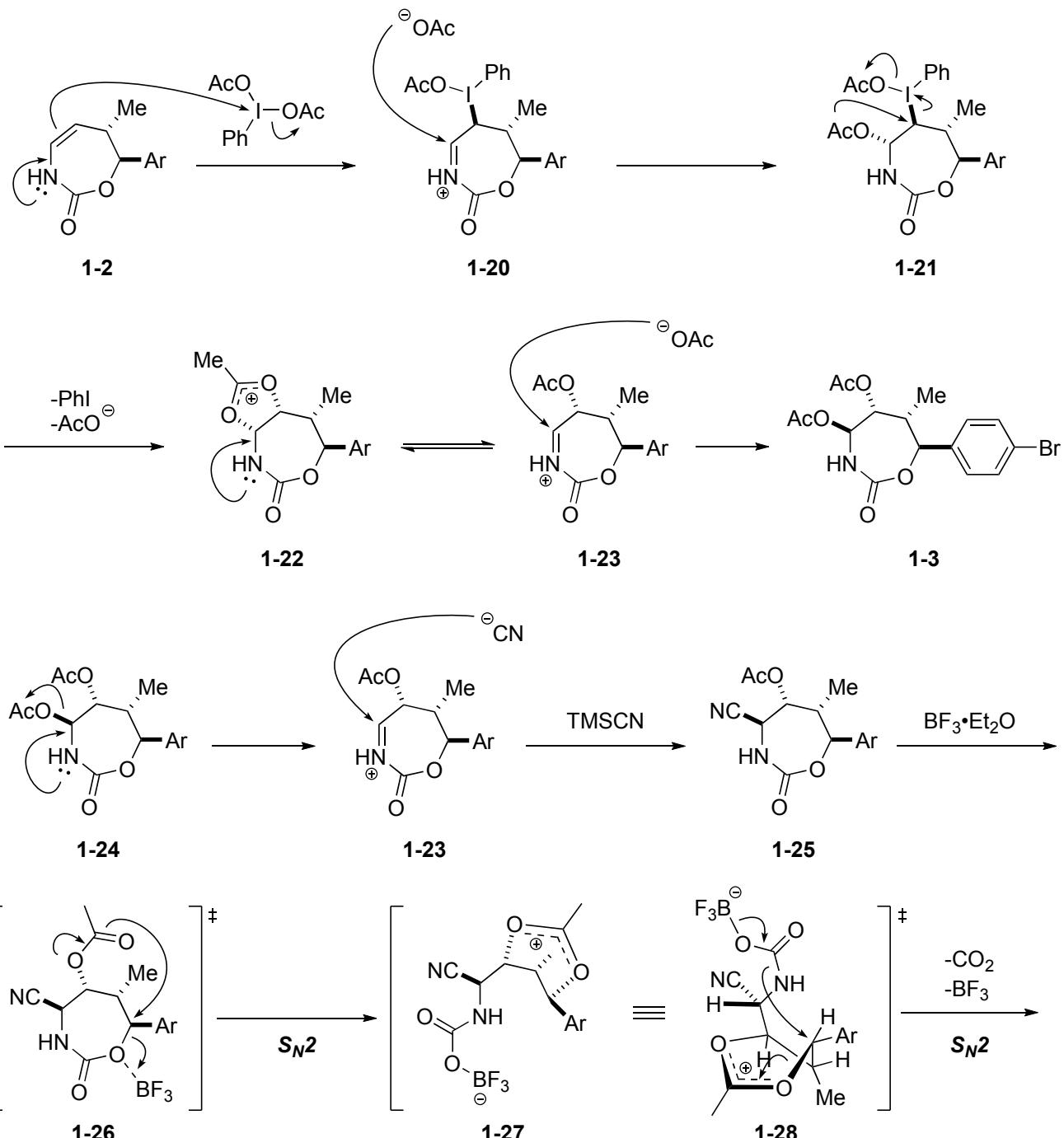
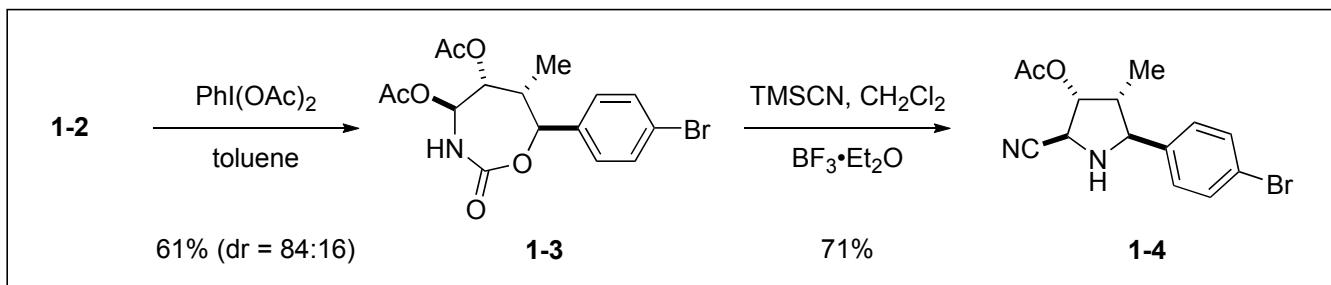
Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, 132, 4025.

3. γ -Substituent should be H in order to reduce 1,3-diaxial like interaction for formation of Z-isomers.



Hoffmann, R. W.; Dresely, S.; Lanz, J. W. *Chem. Ber.* **1988**, 121, 1501. 2

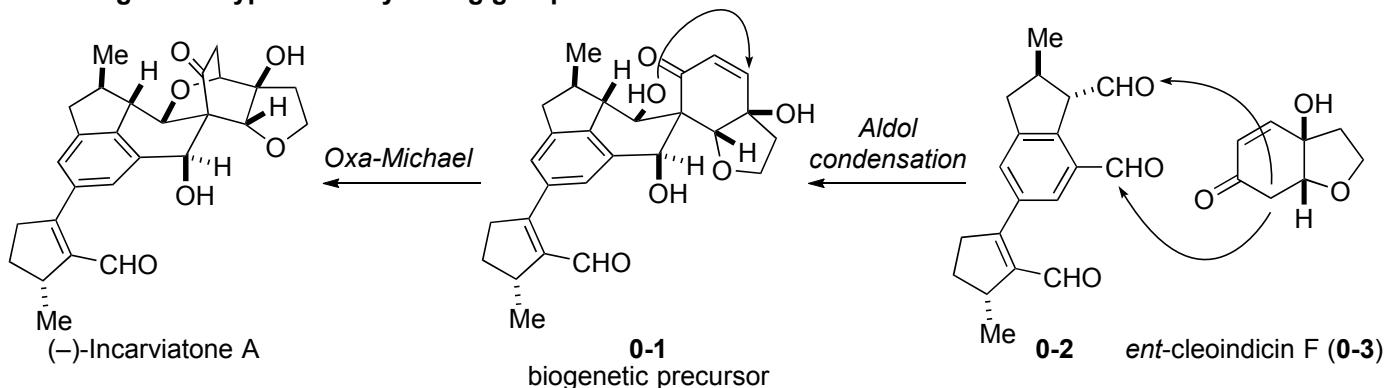
1-2. Ring contraction to pyrrolidine



2. Total Synthesis of (-)-Incarviatone A

Hong, B.; Li, C.; Wang, Z.; Chen, J.; Li, H.; Lei, X. *J. Am. Chem. Soc.* **2015**, *137*, 11946.

Biogenetic hypothesis by Zhang group

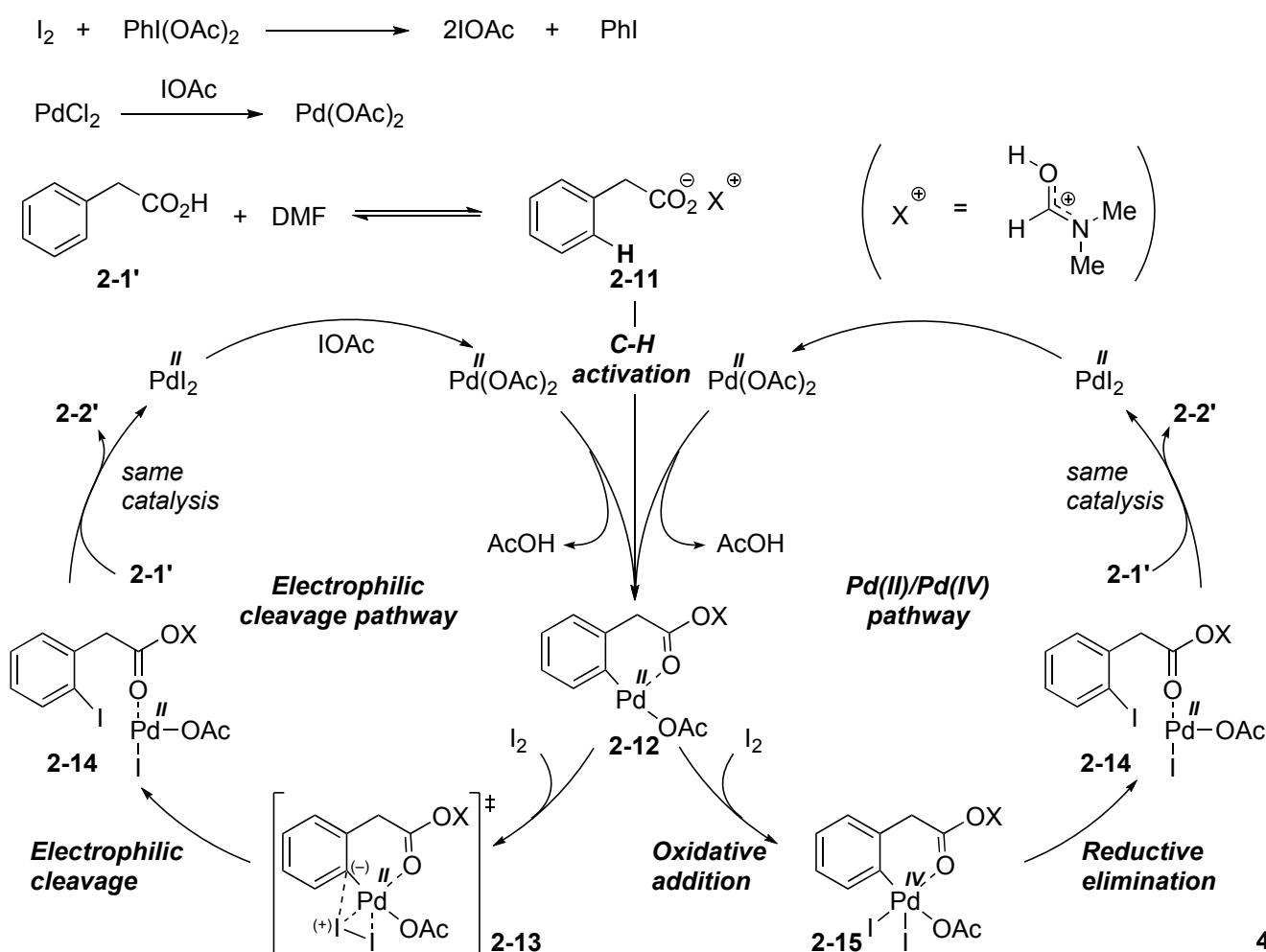
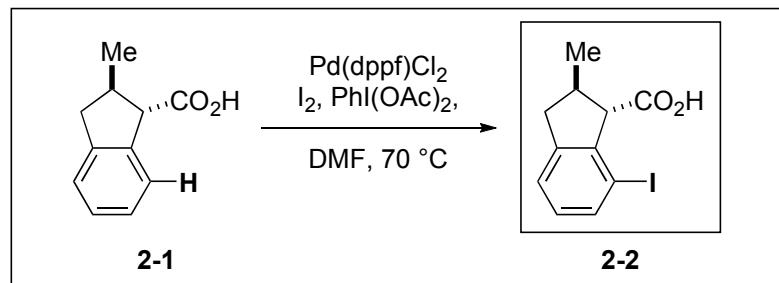


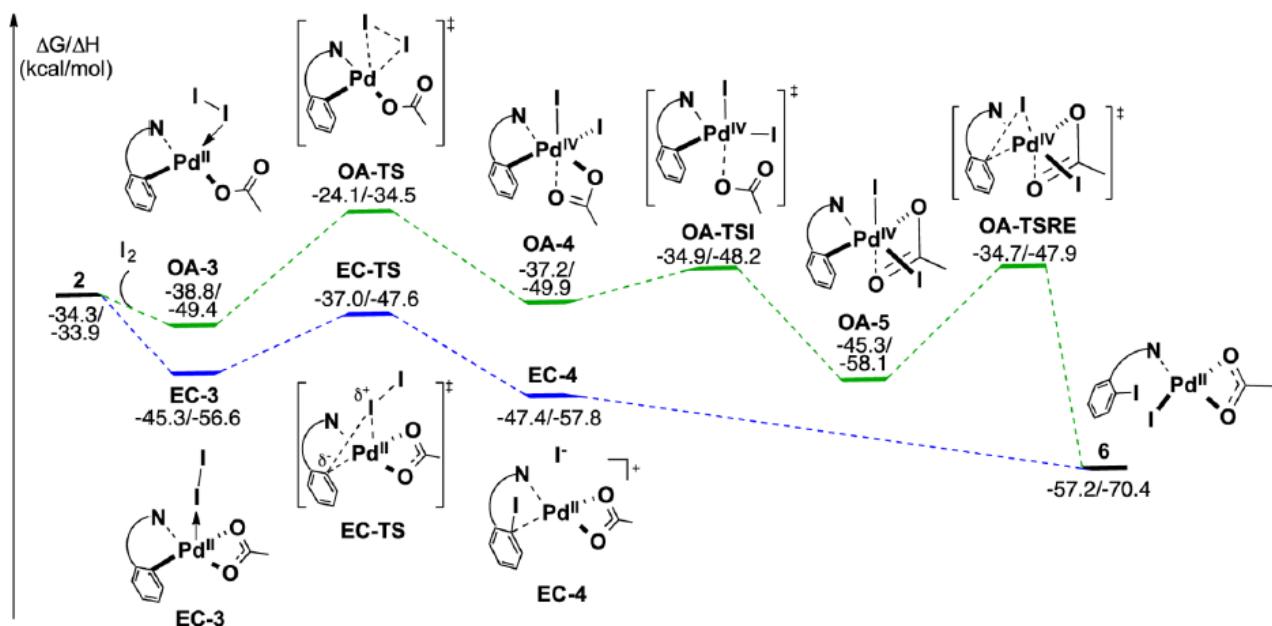
Isolation: Zhang, W.-D. et al. *RSC Advances*, **2012**, *2*, 4175.

Biological Activity: monoamine oxidase (MAO) inhibitor (IC_{50} 29 nM against monoamine oxidase A)

But attempted biomimetic aldol reaction led to racemization of **0-3** and decomposition of dialdehyde moiety.

2-1. Pd catalyzed *ortho*-C–H Iodination



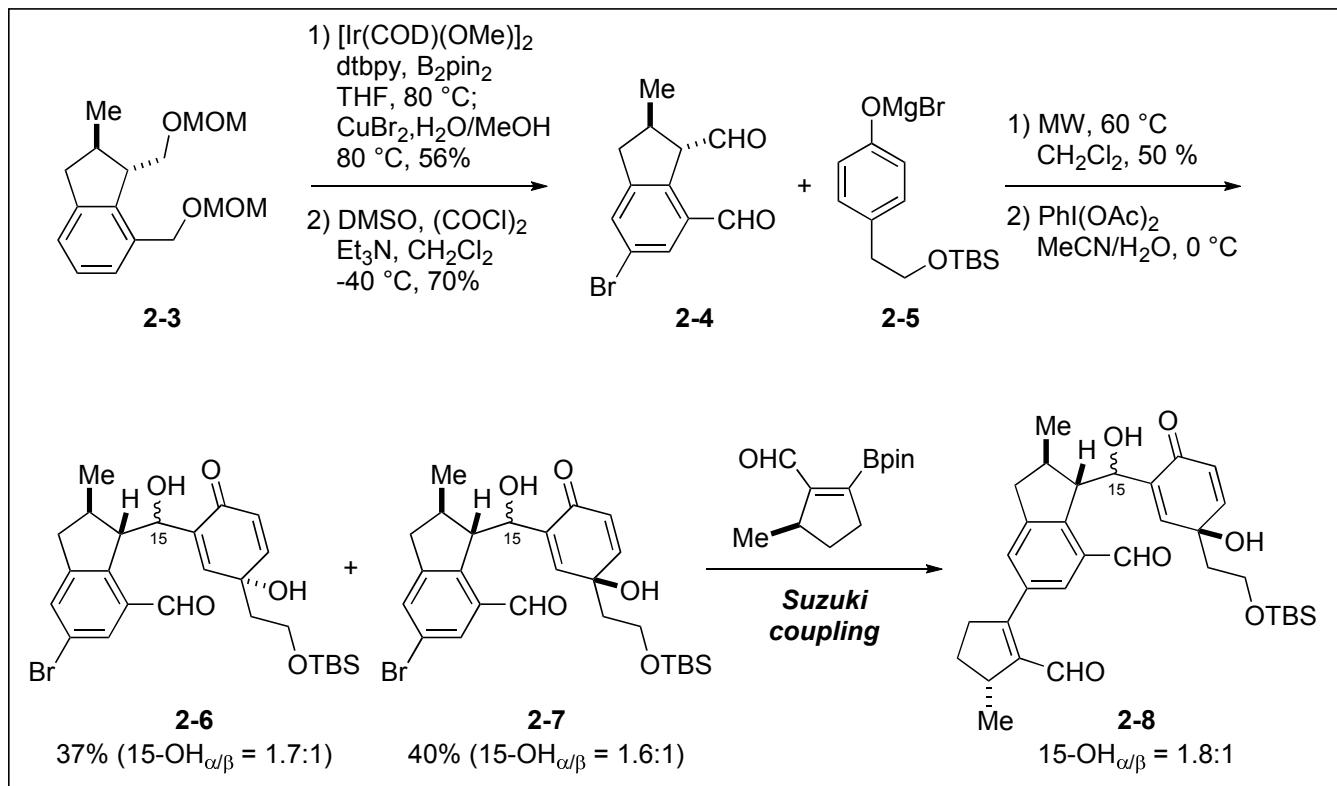


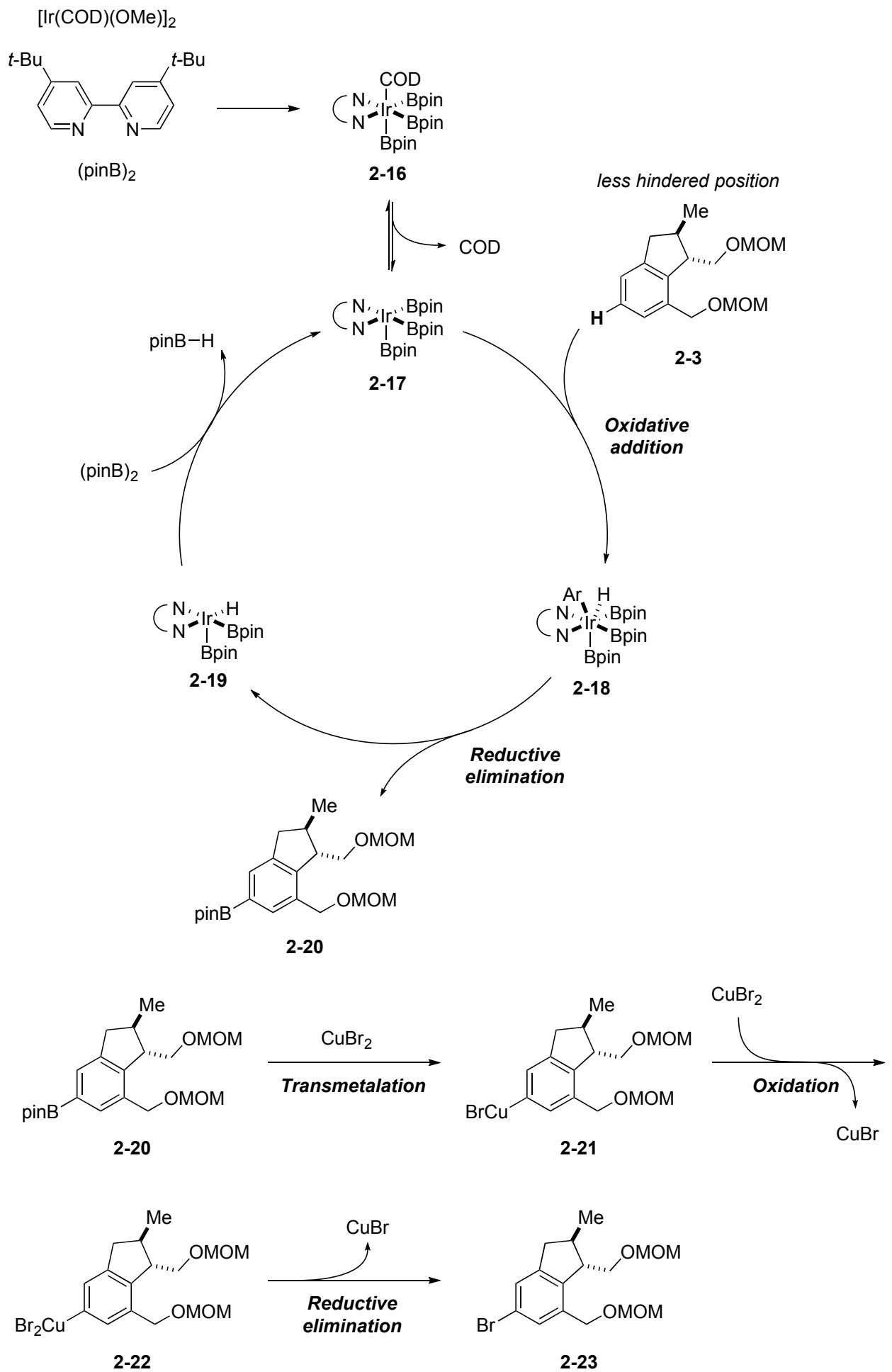
Potential energy surface for C-H iodination via Pd(II)/Pd(IV) and electrophilic cleavage pathways. The reported energies were calculated relative to Pd(OAc)₂ and aryl amide.

2	CONPhCs	CO ₂ K
I ₂ bind free energy (ΔG_{bind})	-11.1	-8.7
energy barrier for EC ($\Delta G^{\ddagger}_{\text{EC}}$)	8.4	9.4
energy barrier for OA ($\Delta G^{\ddagger}_{\text{OA}}$)	21.2	19.2
($\Delta \Delta G^{\ddagger}$) _{EC-OA}	-12.8	-9.8
		(kcal/mol)

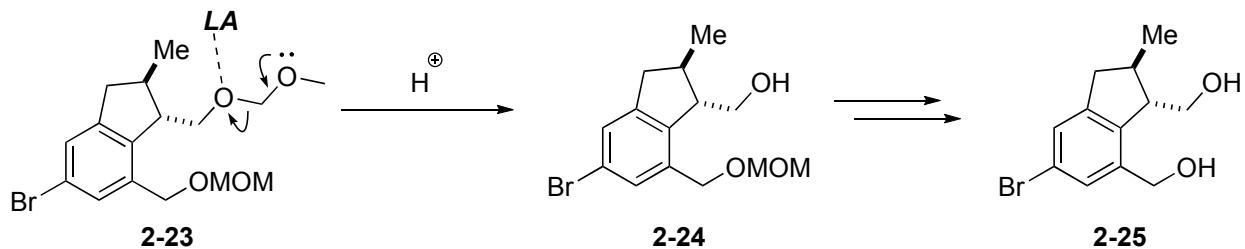
Yu, J.-Q.; Musaev, D.G. et al. *J. Am. Chem. Soc.* **2015**, *137*, 9022.

2-2. One pot meta-borylation, bromination & aldol condensation

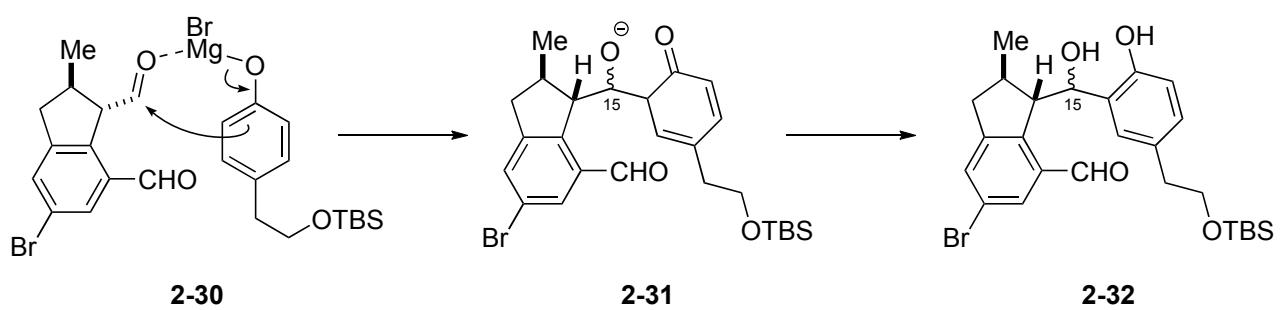
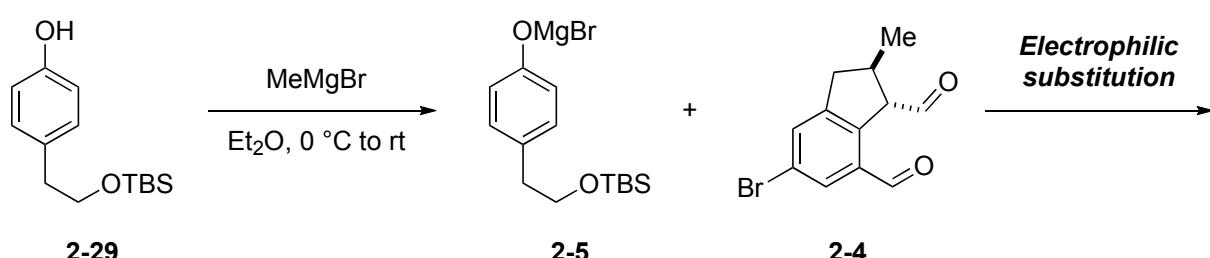
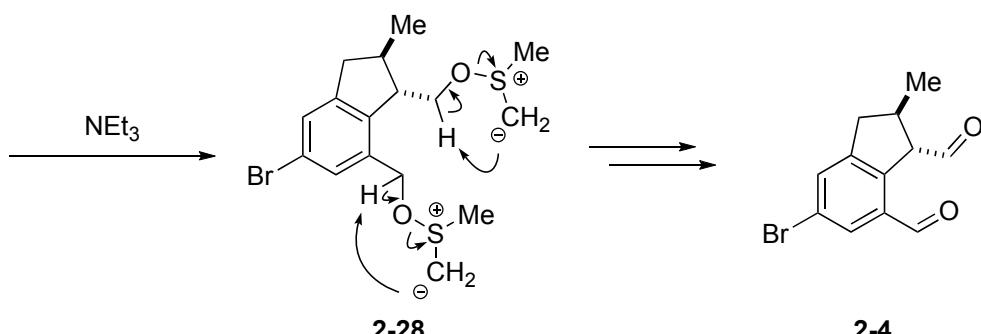
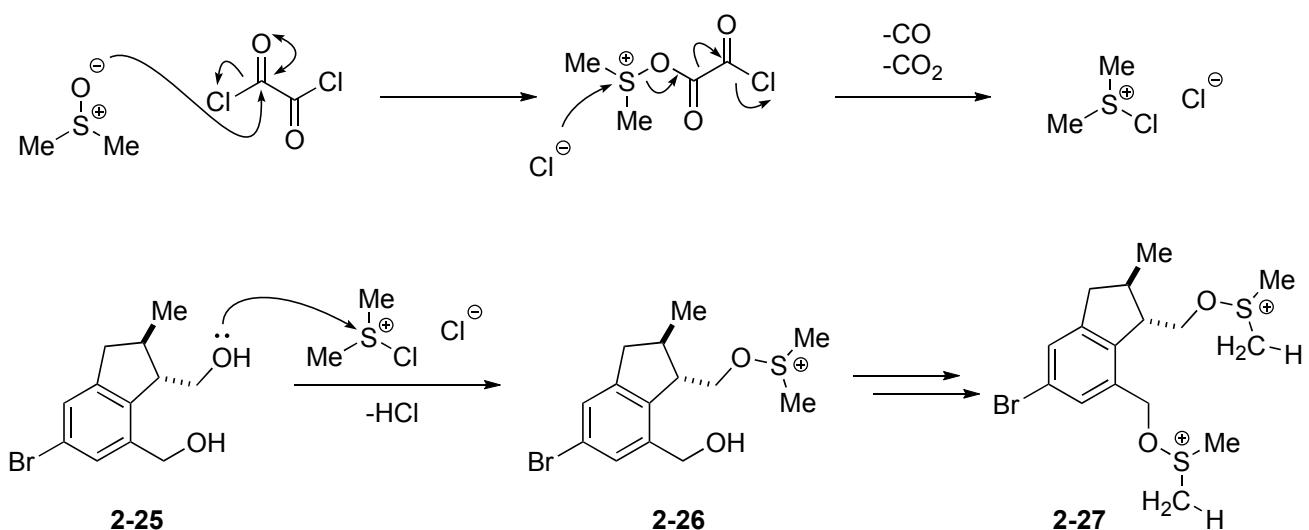




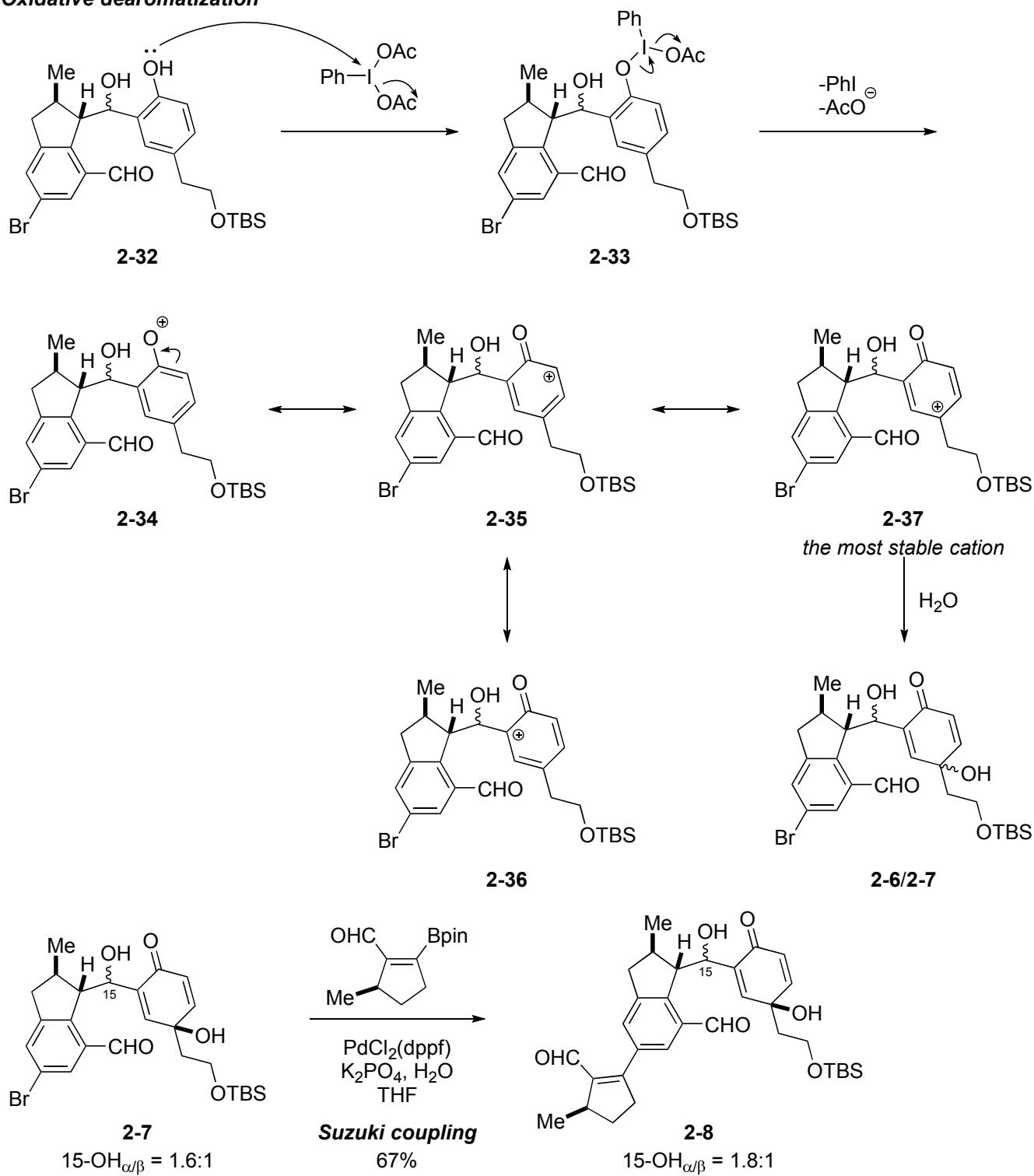
Deprotection



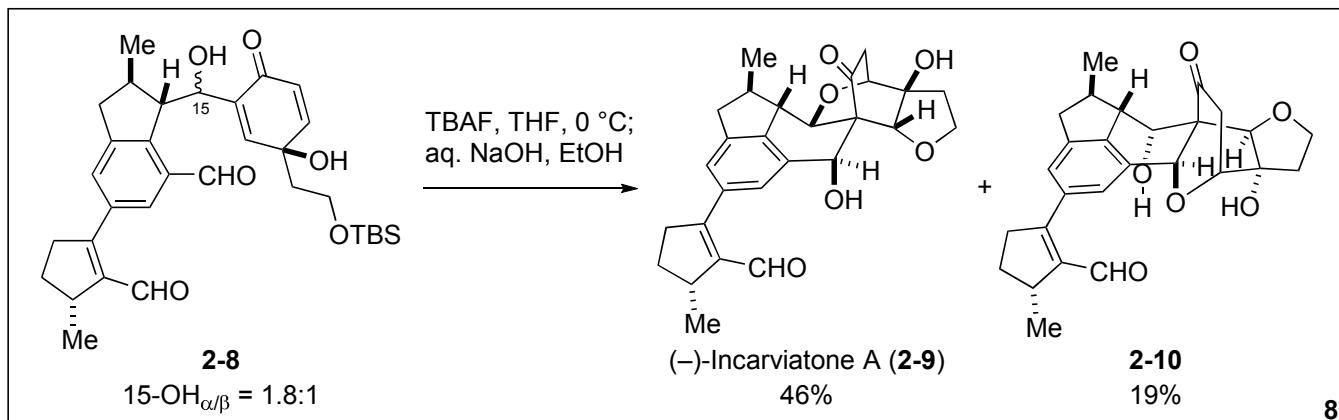
Swern oxidation

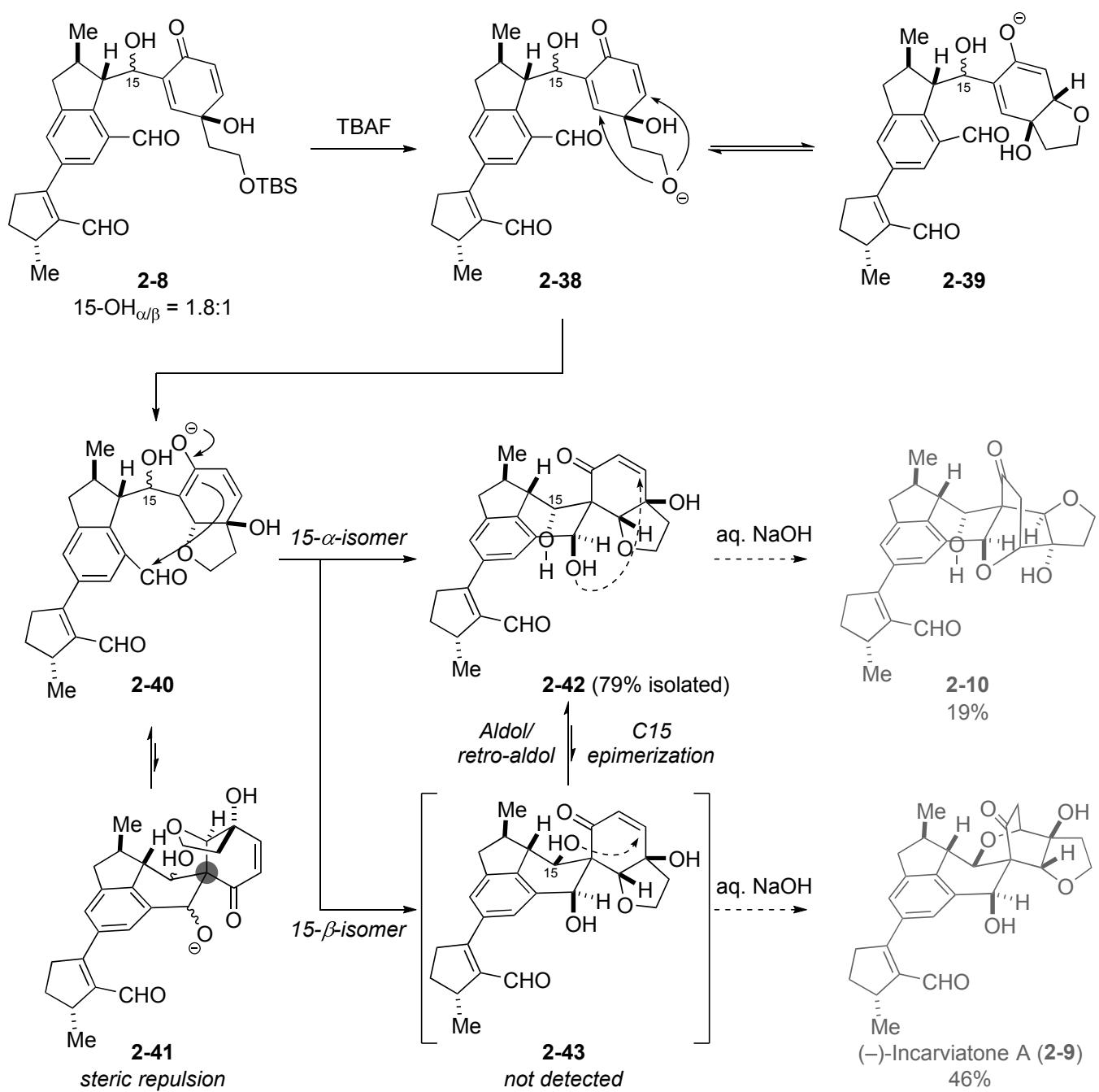


Oxidative dearomatization



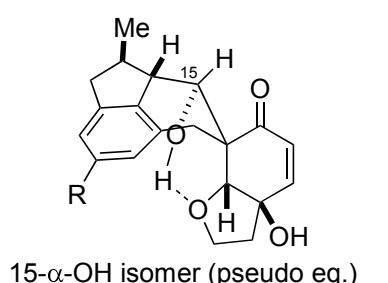
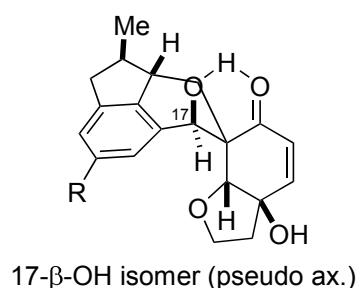
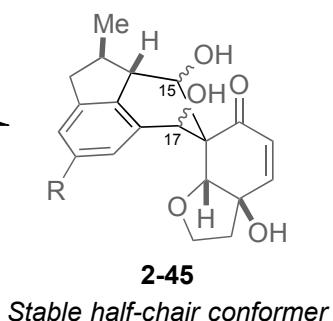
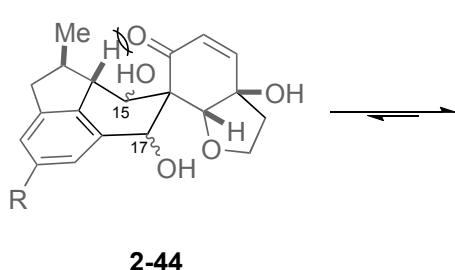
2-3. Biomimetic cascade reaction





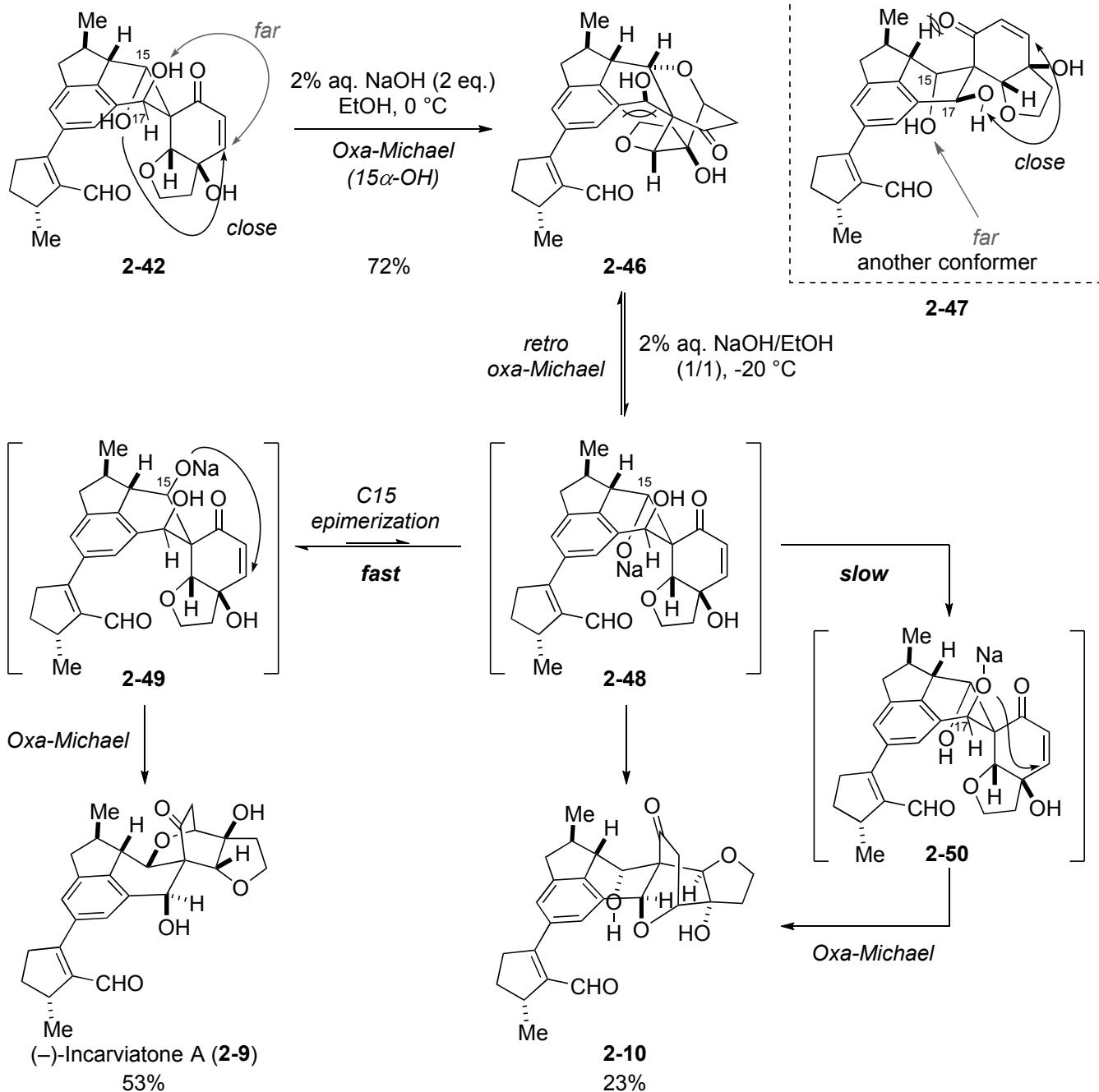
Proposed stereoselectivity at C15-OH & C17-OH

Presumably conformation

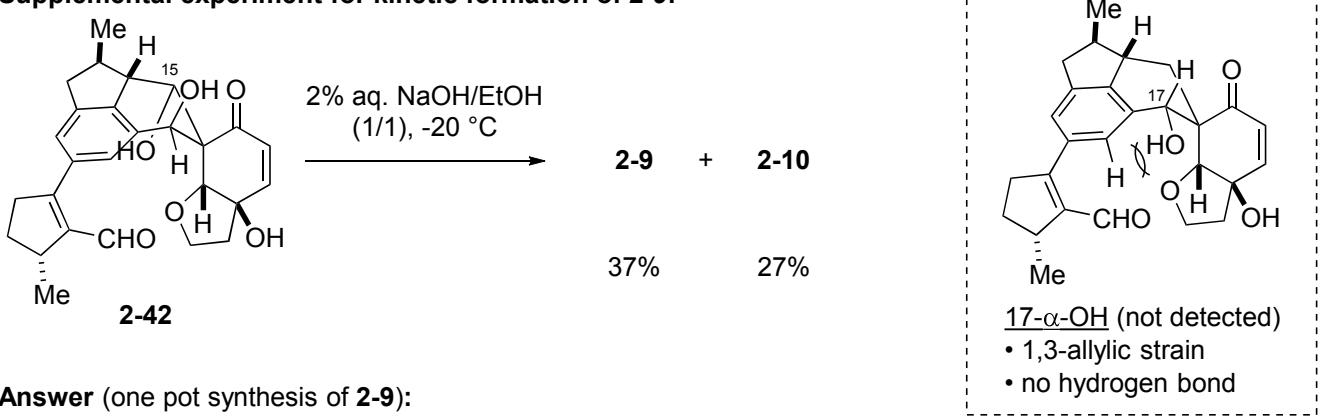


Hydrogen bonds may stabilize the 15- α & 17- β isomer.

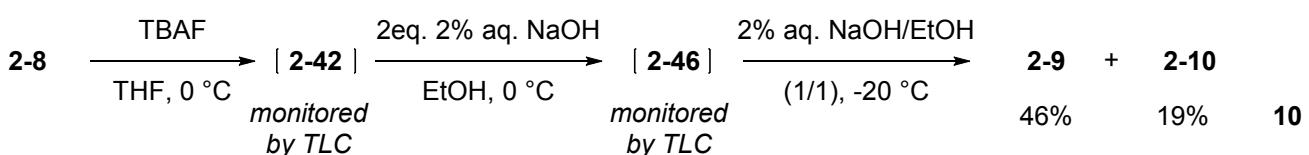
Experimental result:



Supplemental experiment for kinetic formation of 2-9:



Answer (one pot synthesis of 2-9):



Supplemental: proposed reaction pathways of Pd catalyzed iodination

