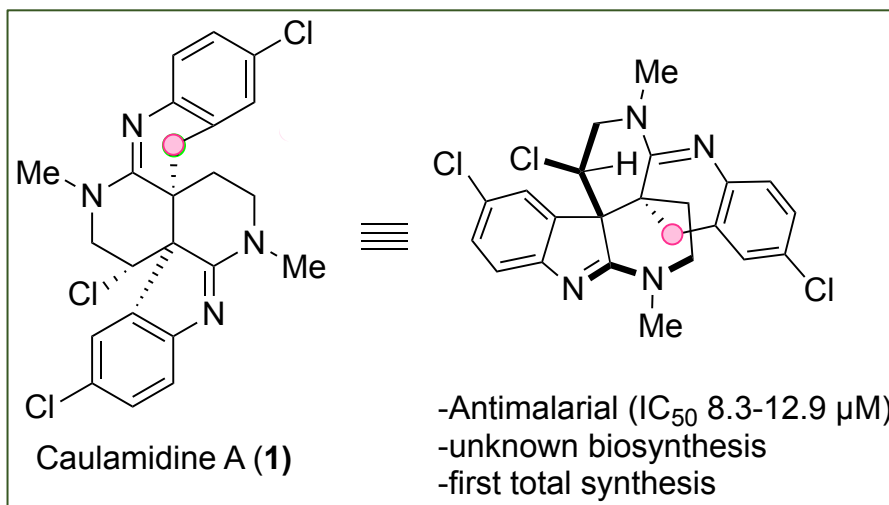
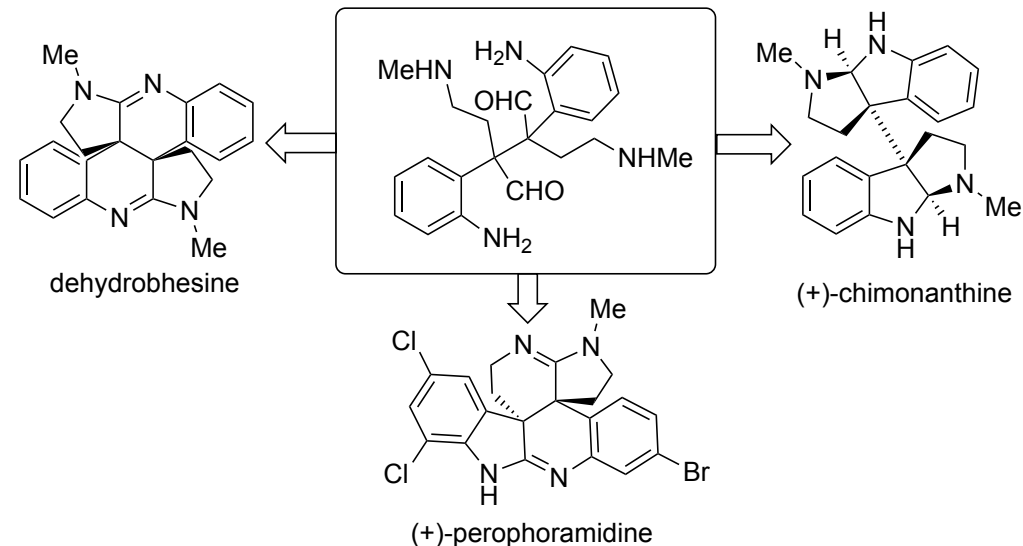


Enantioselective Total Synthesis of (–)-Caulamidine A

Zhouyang Zhu and Thomas J. Maimone*



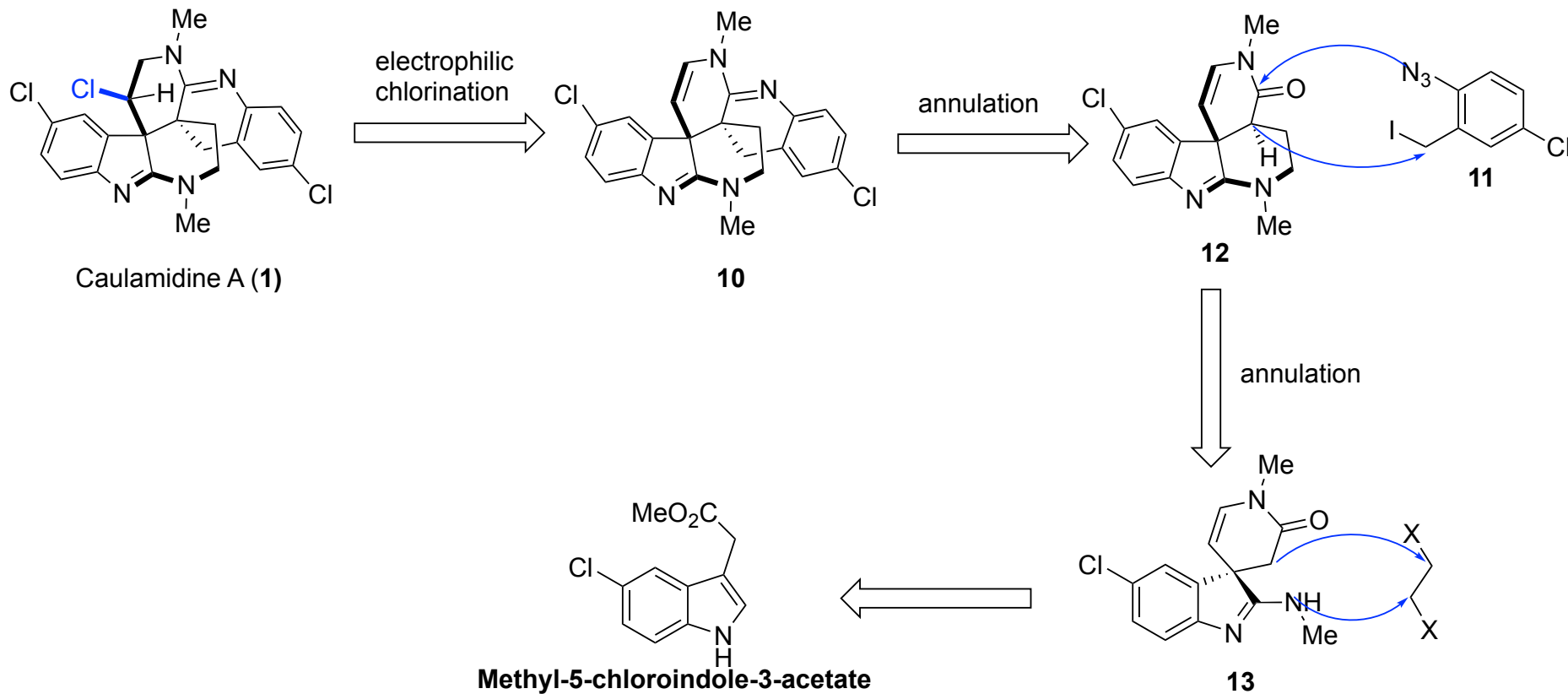
dimeric cyclotryptamine alkaloids

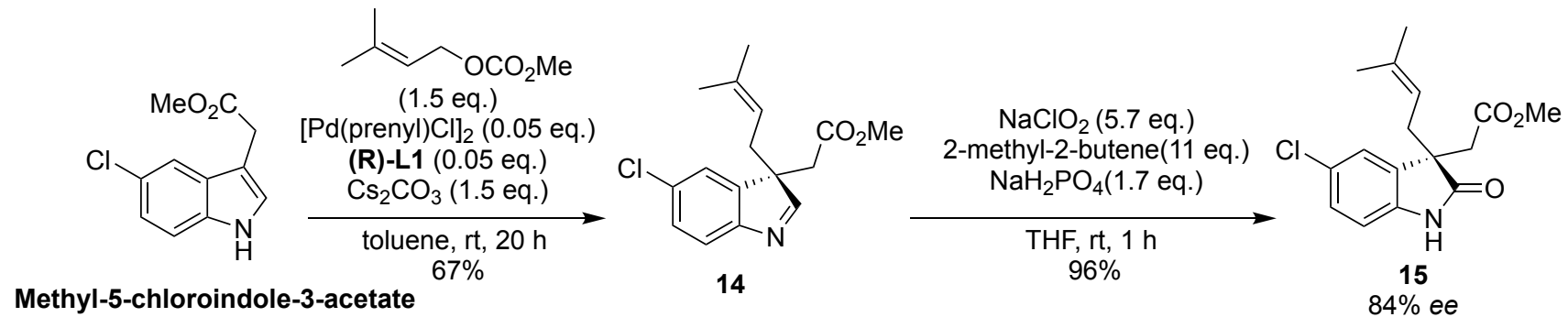
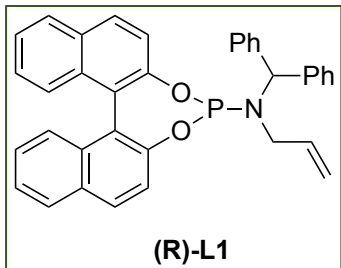


- Marine bryozoans continue to provide architecturally fascinating halogenated alkaloids
- The antimalarial alkaloids caulamidines A and B, recently isolated from *Caulibugula intermis*, contain an intricate bis-amidine core and a chlorine-bearing neopentylic stereocenter
- Compared to topologically similar C20 bis- (cyclotryptamine) alkaloids, caulamidines possess an additional carbon atom of unknown biosynthetic origins, which renders their entire skeleton nonsymmetric and nondimeric

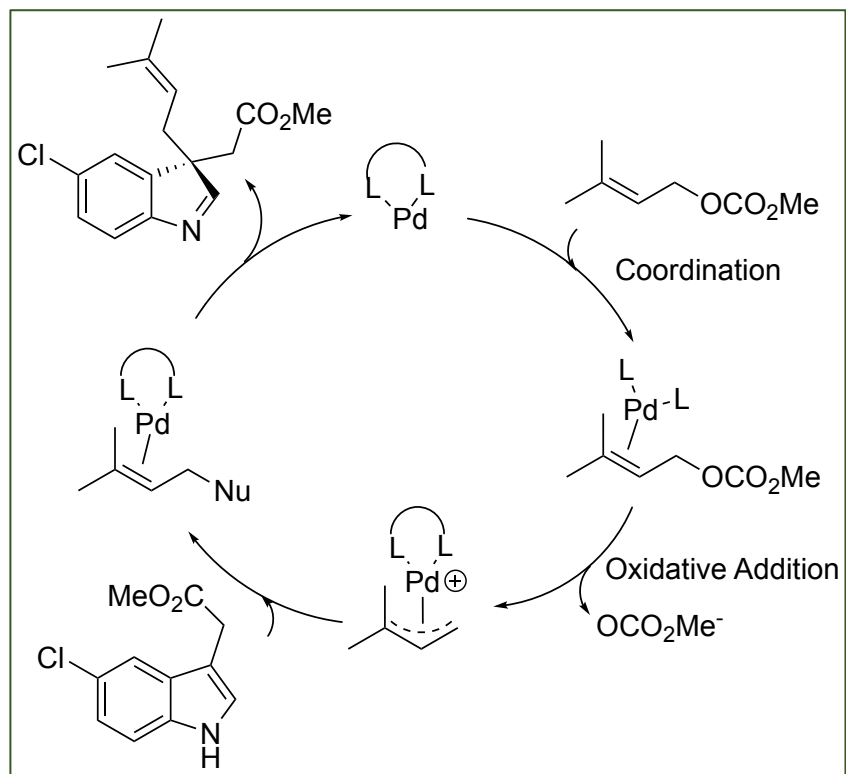
Hannah Robichaud
Liu Lab
November 8, 2023

Retrosynthesis/ Synthetic Plan

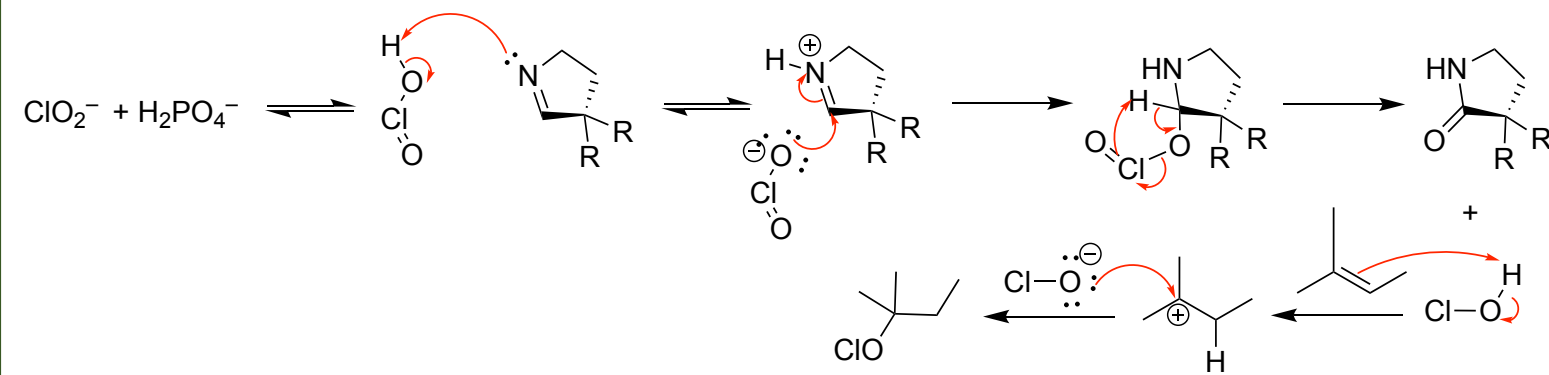


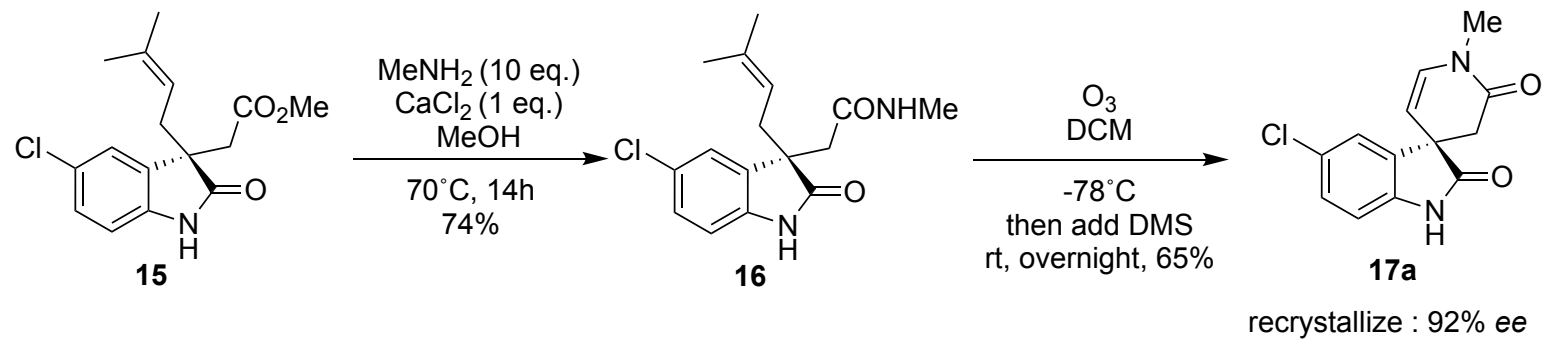


Pd. Cat. Prenylation

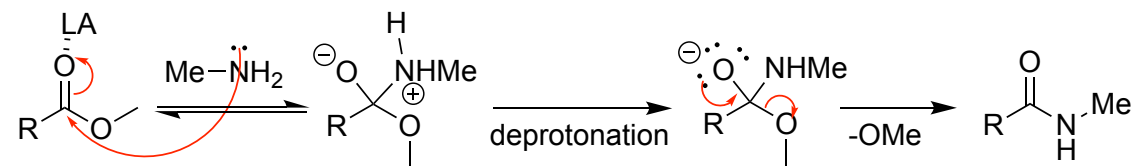


Lindgren-Kraus oxidation conditions to form oxindole 15

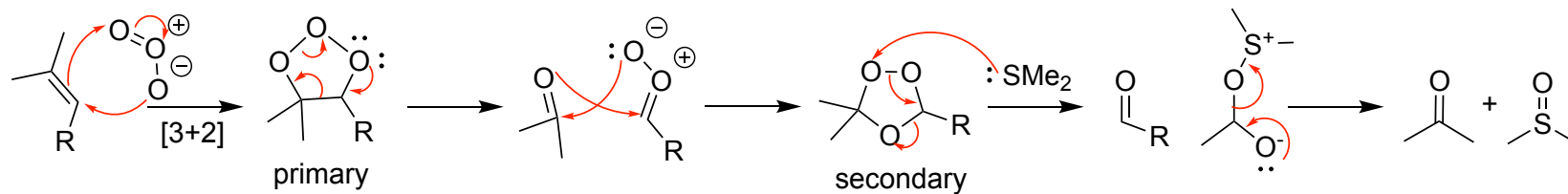




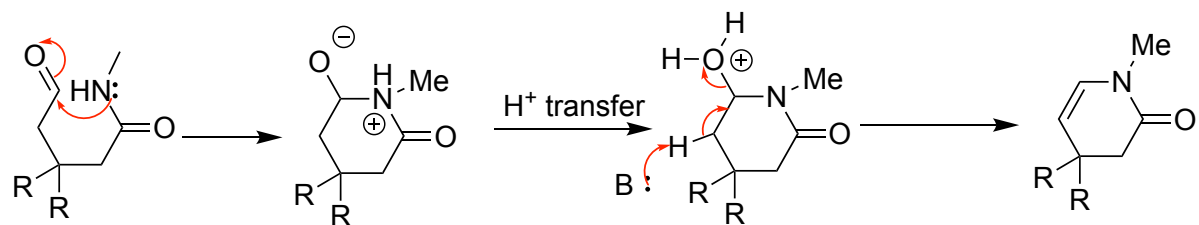
Conversion of ester 15 to amide 16 using methylamine

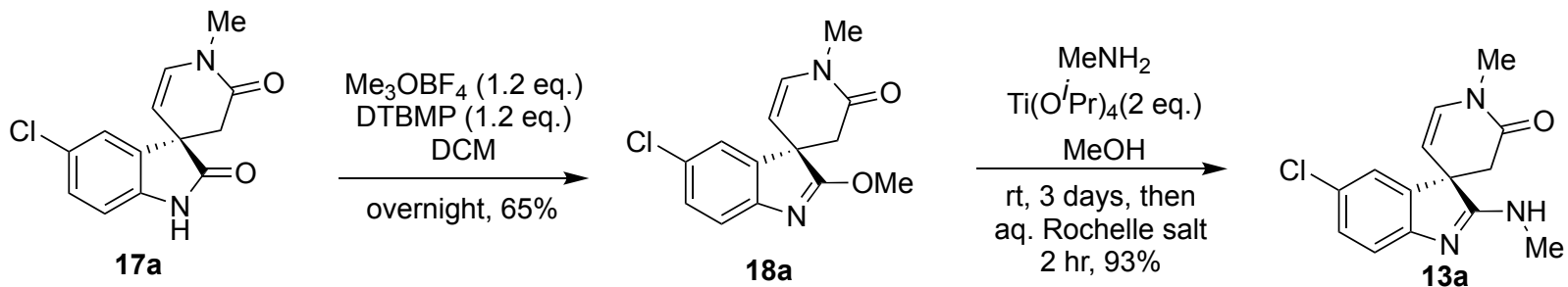


Ozonolysis

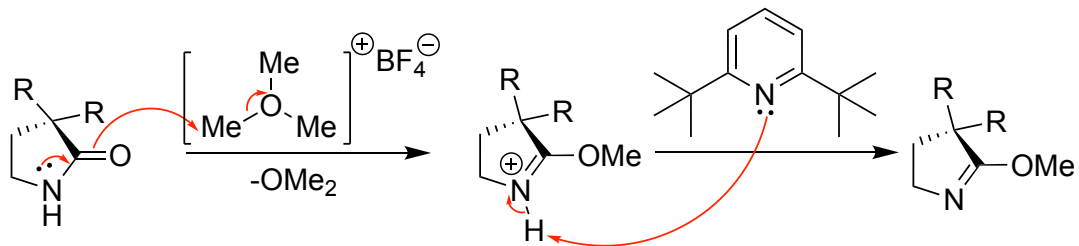


Condensation of aldehyde with secondary amide

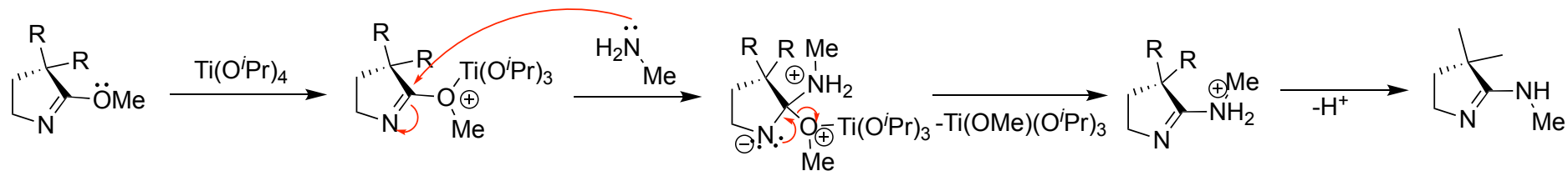


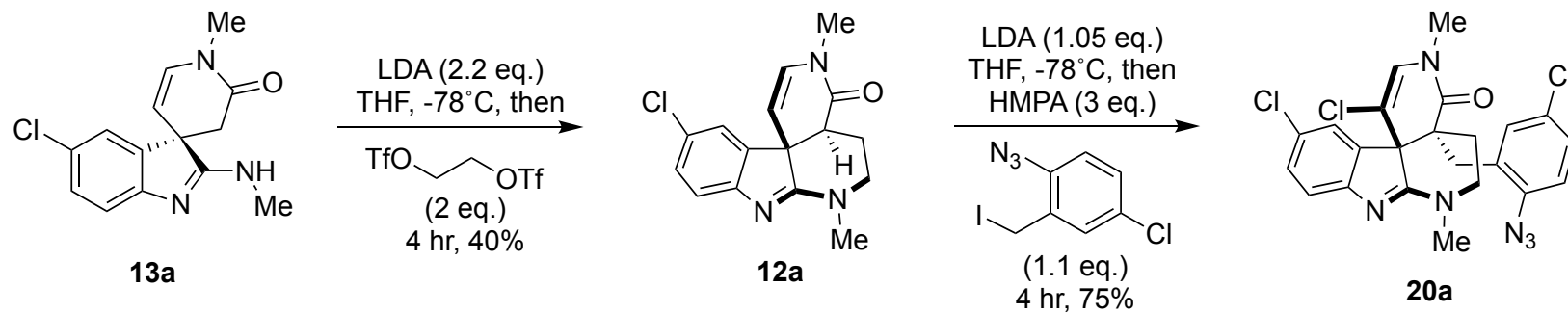


O-alkylation using Meerwein's salt to form to imidate 18a

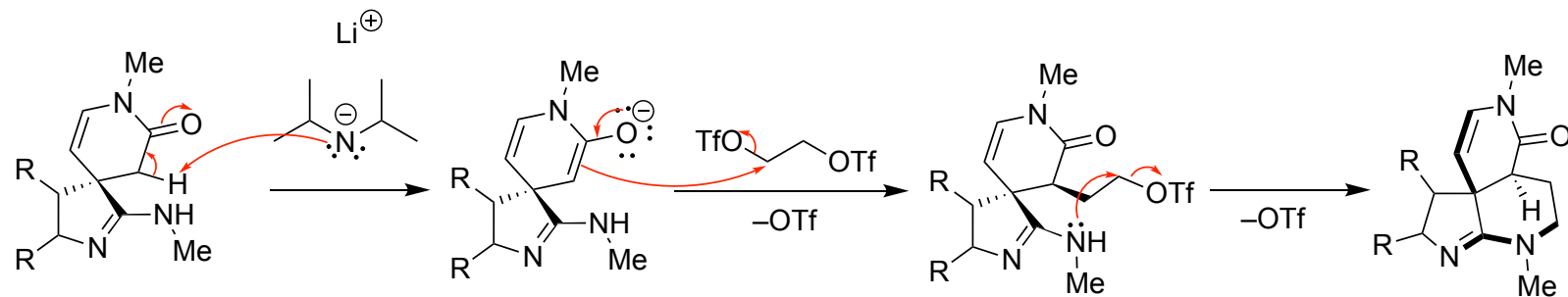


Converting imidate 18a to secondary amine 13a with methylamine and Ti(Oi-Pr)4

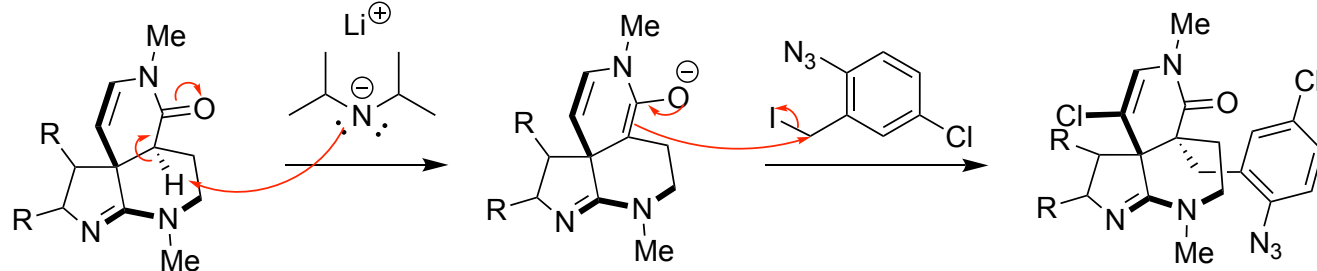


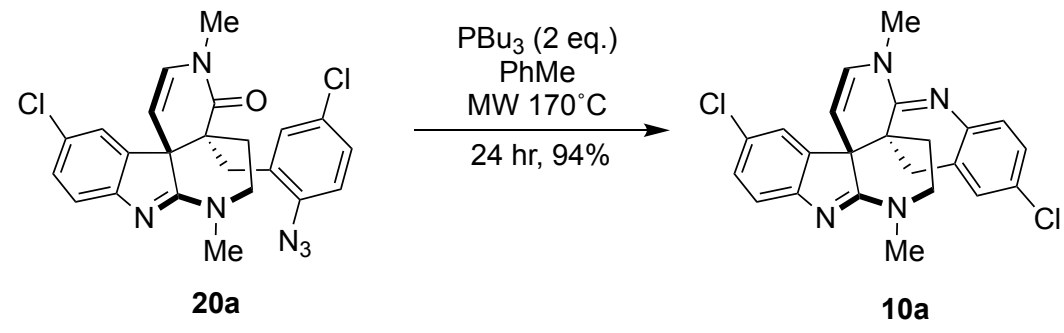


Annulation to form tetracycle

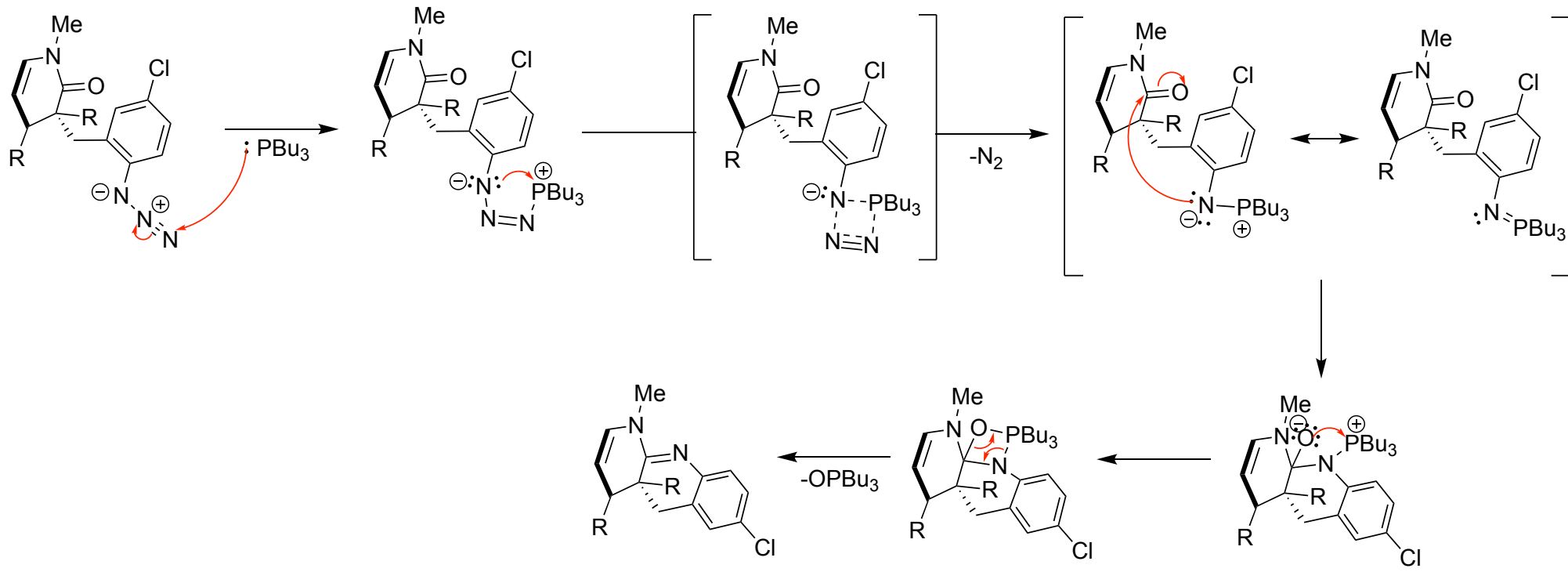


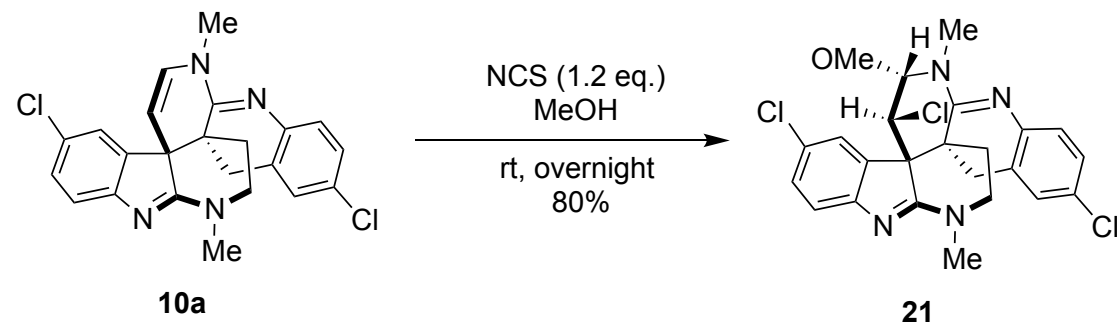
Enolization with LDA and reaction fo benzyl iodide



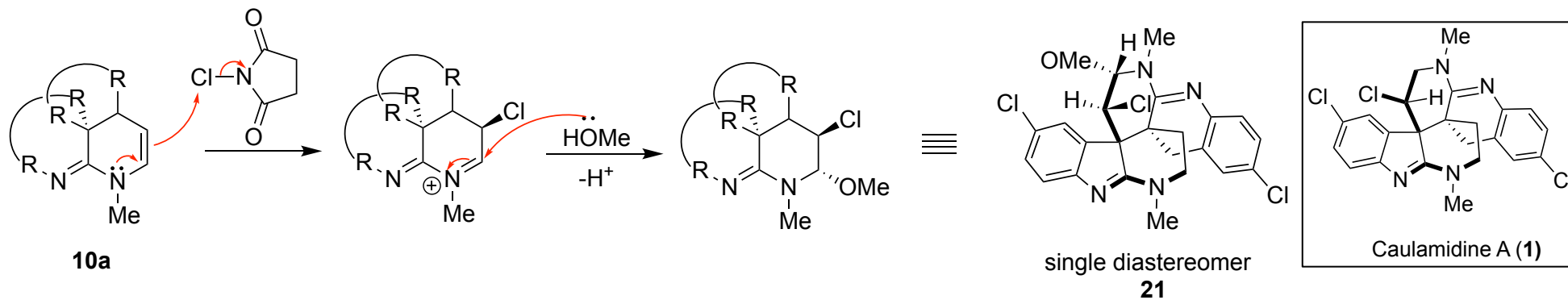


Staudinger-aza-Wittig reaction to form heexacyclic core



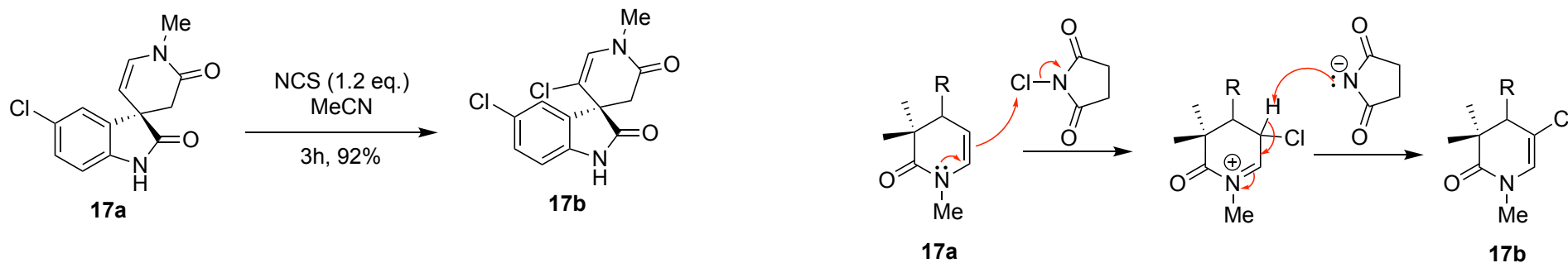


Electrophilic chlorination of enamine

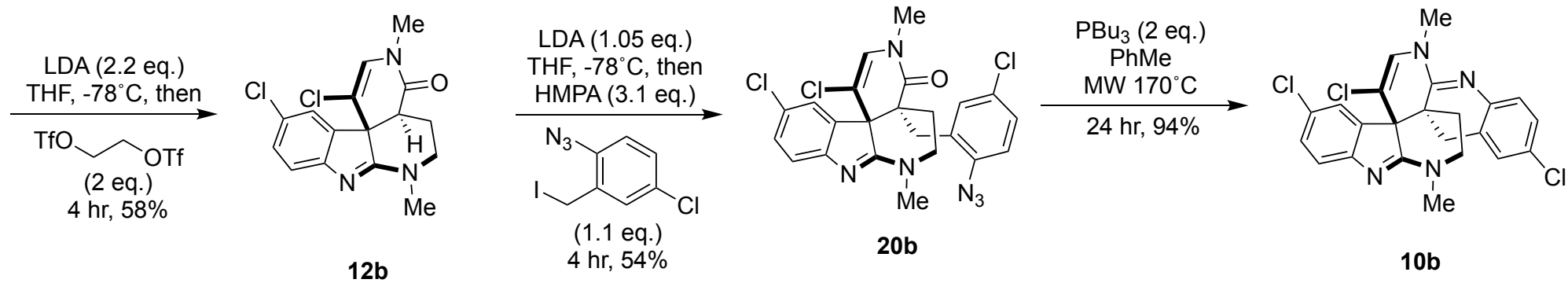
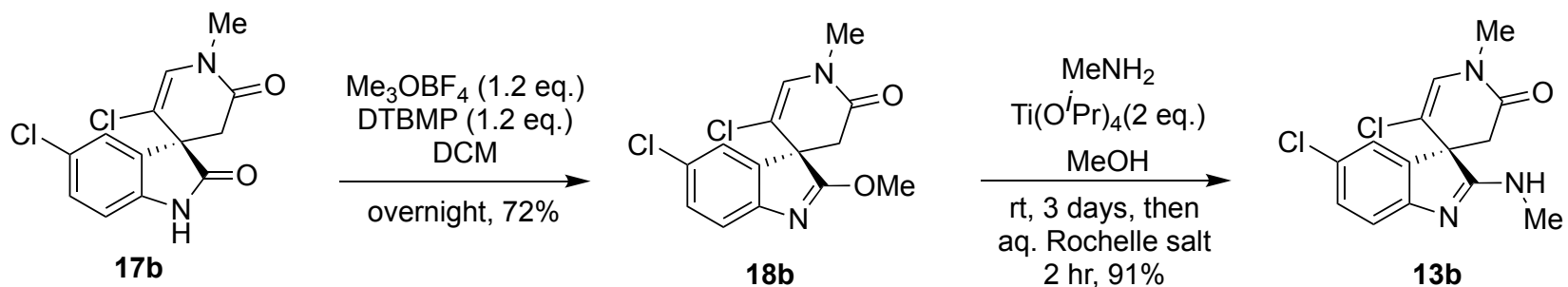


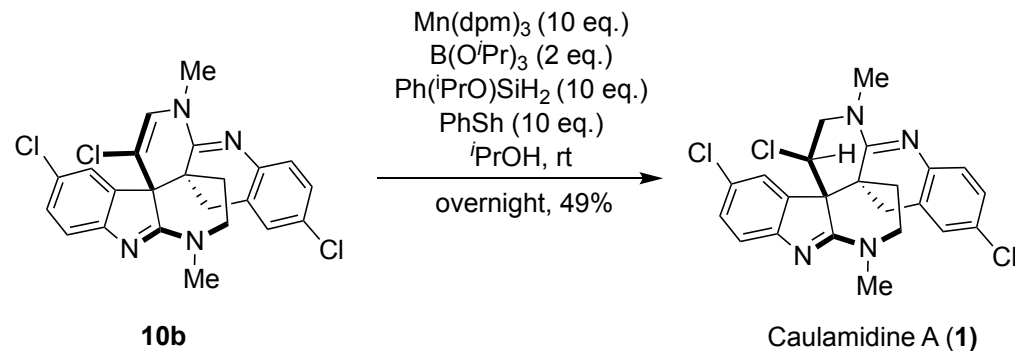
Wrong Diastereomer

Chlorination to install the β -chloro enamine moiety in an earlier step in the synthesis



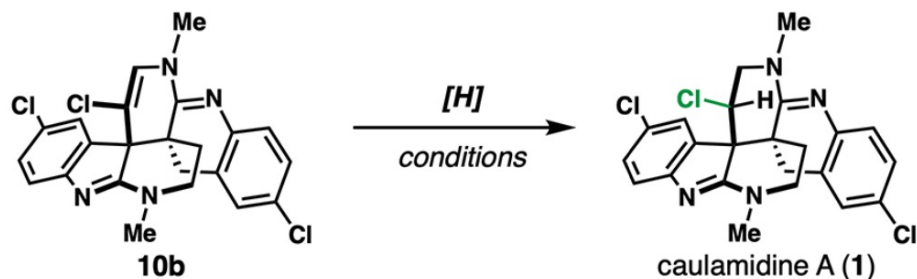
Redo of synthesis



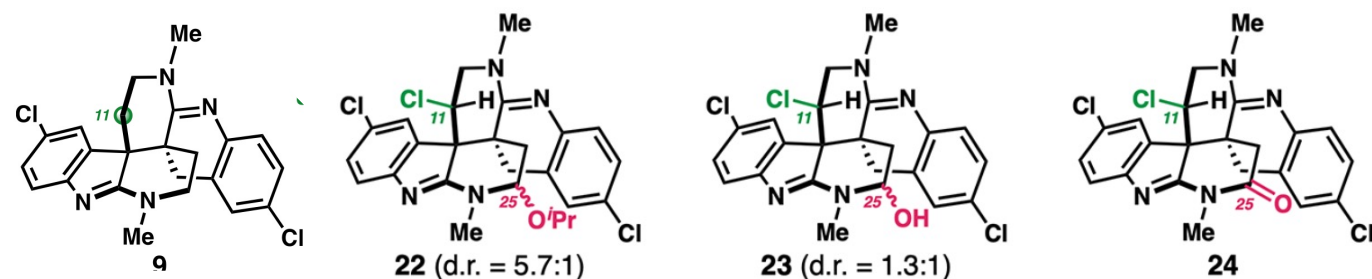


Diastereoselective hydrogen atom transfer: Optimization and Mechanistic studies

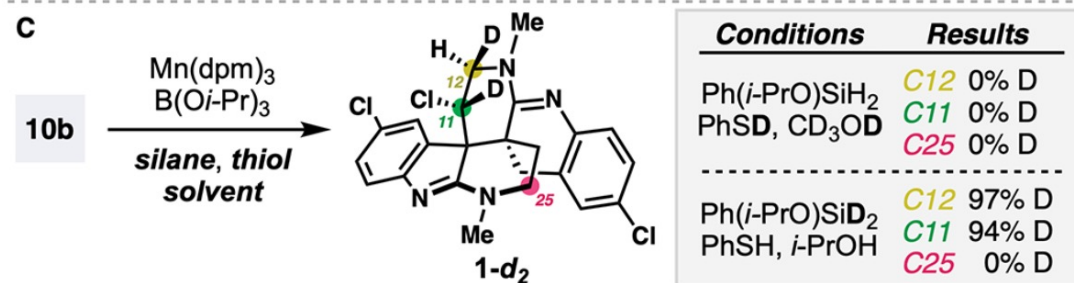
A



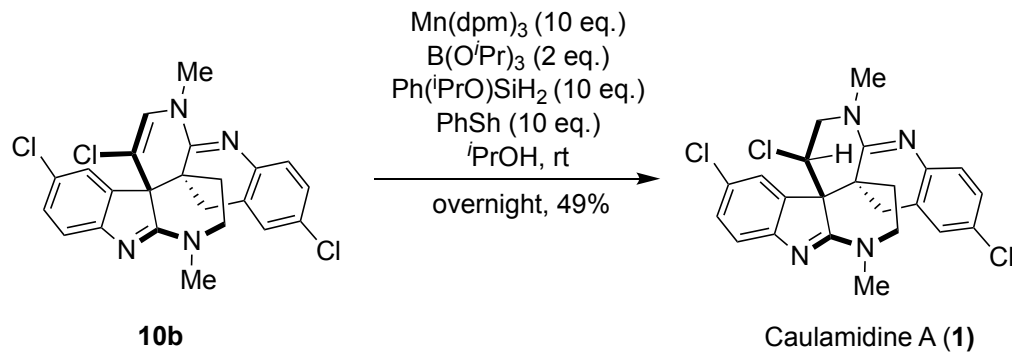
Entry	Conditions	Reaction Products ^a
1	TFA, Et ₃ SiH, DCM	10b
2	H ₂ , PtO ₂ , AcOH/EtOAc	10b , 9 (14%), 1 (6%)
3	Fe ₂ (ox) ₃ , NaBH ₄ , EtOH/H ₂ O	10b
4	Co(acac) ₂ , Et ₃ SiH, 1,4-CHD, TBHP, <i>n</i> -PrOH, air	10b
5	Fe(acac) ₃ , PhSiH ₃ , PhSH, EtOH	10b
6	Mn(dpm) ₃ , PhSiH ₃ , TBHP, <i>i</i> -PrOH	10b
7 ^b	Mn(dpm) ₃ , Ph(<i>i</i> -PrO)SiH ₂ , TBHP, <i>i</i> -PrOH	10b , 1 (trace)
8 ^c	Mn(dpm) ₃ , Ph(<i>i</i> -PrO)SiH ₂ , TBHP, <i>i</i> -PrOH	10b (21%), 1 (15%), 22 (16%), 23 (9%), 24 (7%)
9 ^d	Mn(dpm) ₃ , Ph(<i>i</i> -PrO)SiH ₂ , PhSH, <i>i</i> -PrOH	10b (62%), 1 (12%)
10 ^e	Mn(dpm) ₃ , Ph(<i>i</i> -PrO)SiH ₂ , PhSH, B(O <i>i</i> -Pr) ₃ , <i>i</i> -PrOH	10b (24%), 1 (49%) ^f



C

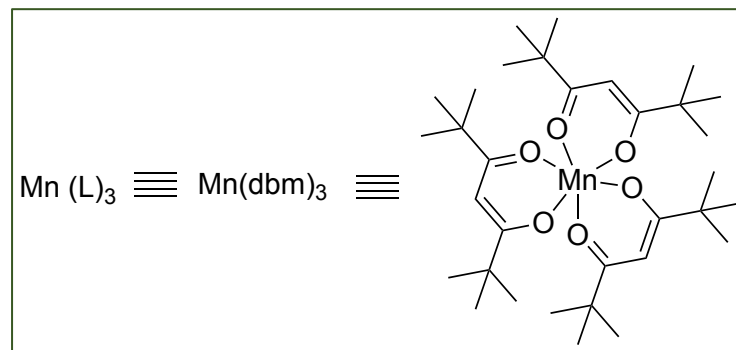
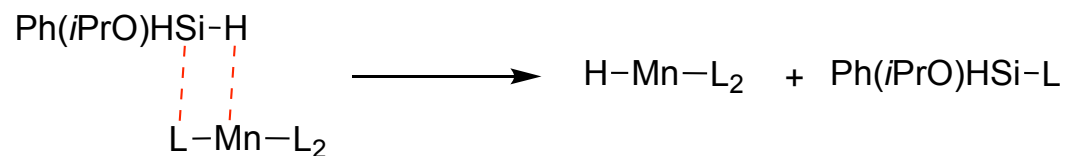


Suspected after the initial HAT, the resulting α -chloro radical underwent a 1,5-HAT to deliver a carbon-centered radical

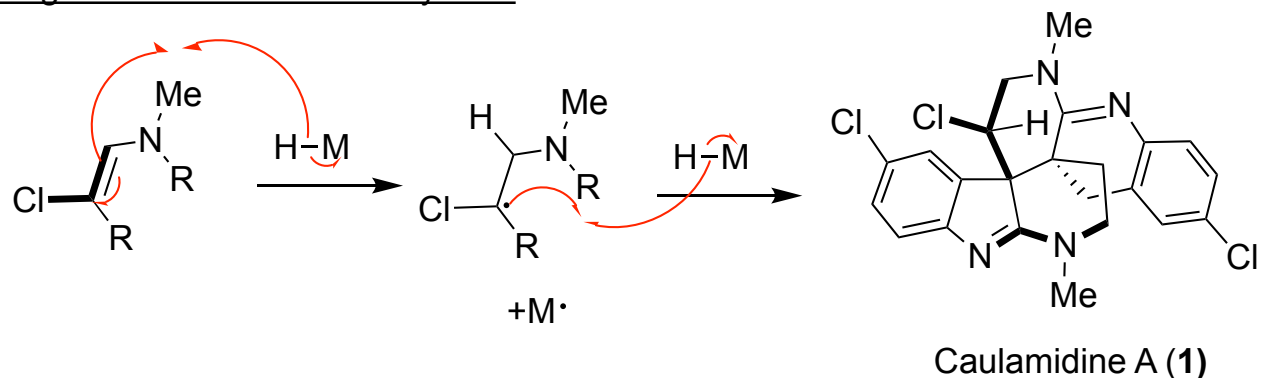


Diastereoselective Metal catalyzed Hydrogen Atom Transfer

Formation of Metal hydride through ligand exchange

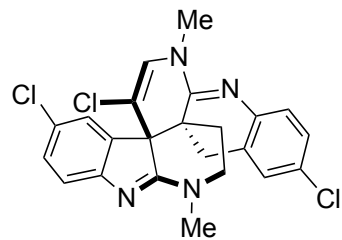


Hydrogen transfer with metal hydride

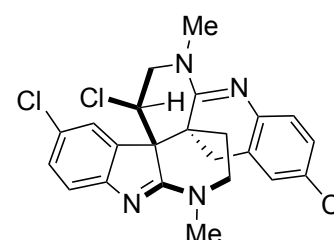
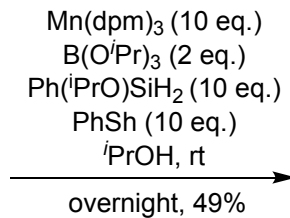


Role of Lewis acid

-could coordinate to lewis basic N's that could be interfering with Mn

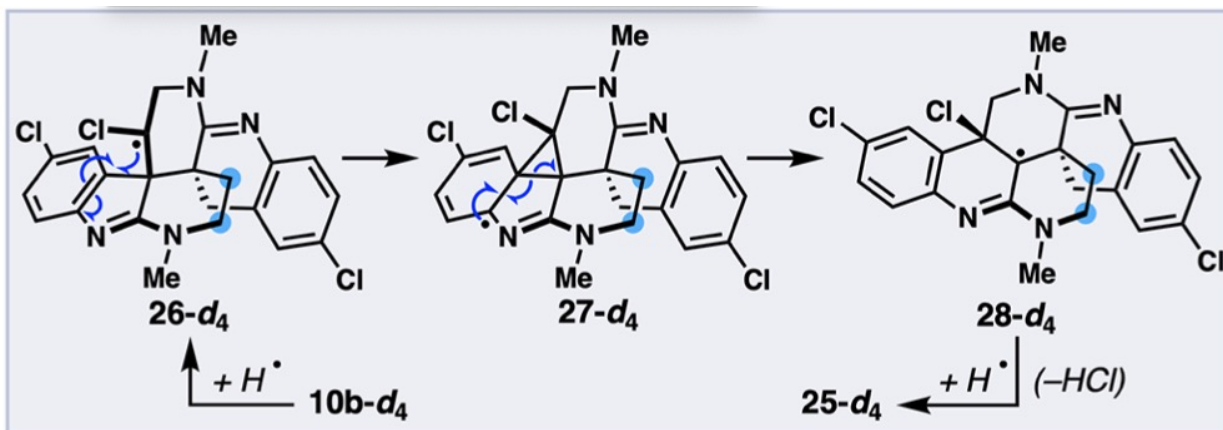
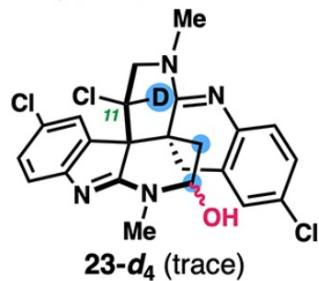
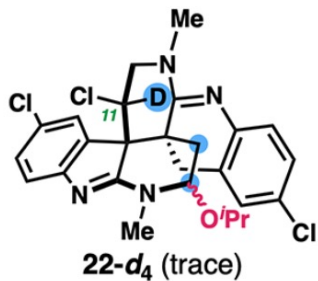
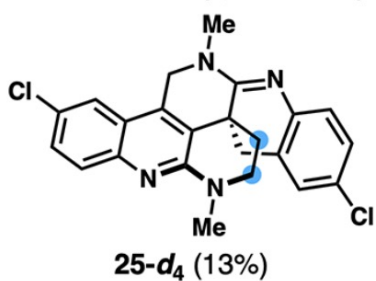
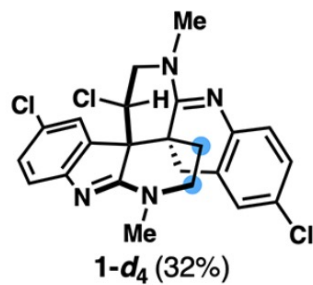
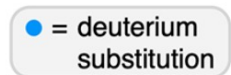
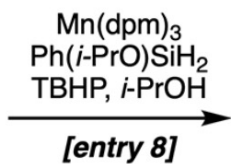
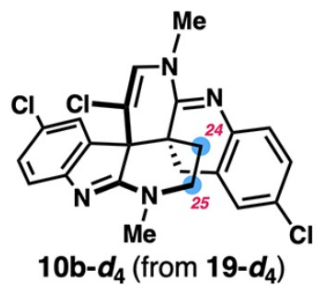


10b

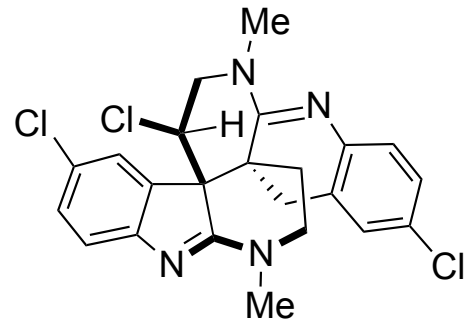


Caulamidine A (1)

B



Question?



Caulamidine A (1)