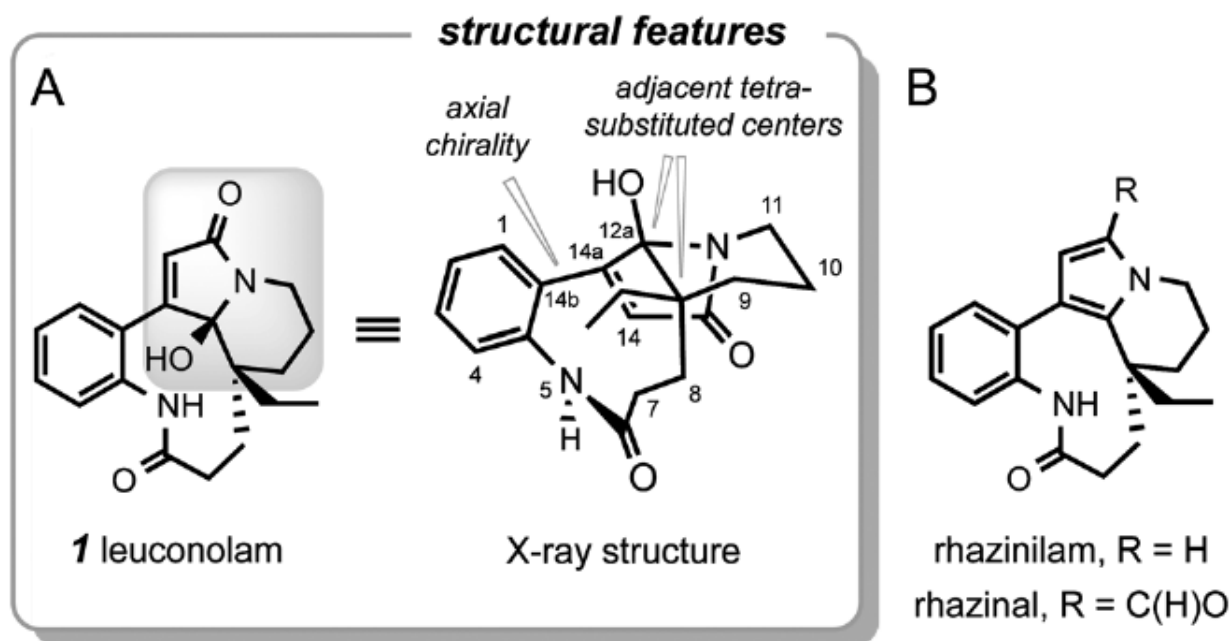


Total synthesis of (+/-)-leuconolam: intramolecular allylic silane addition to a maleimide carbonyl group

Enver Cagri Izgu and Thomas R. Hoye,
Chem. Sci., **2013**, 4, 2262-2266

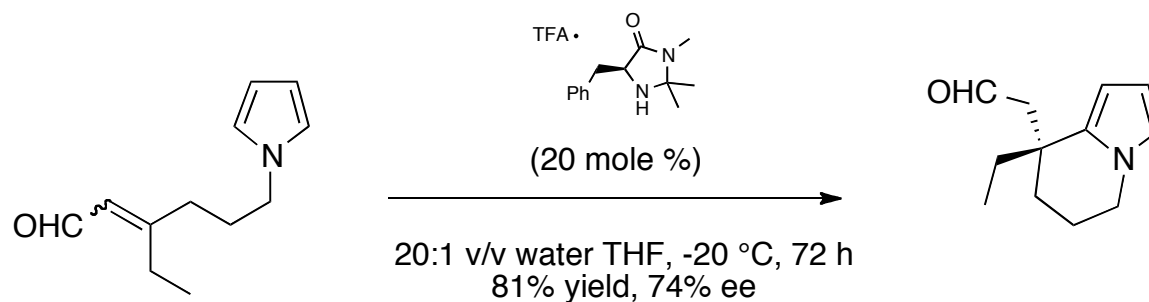
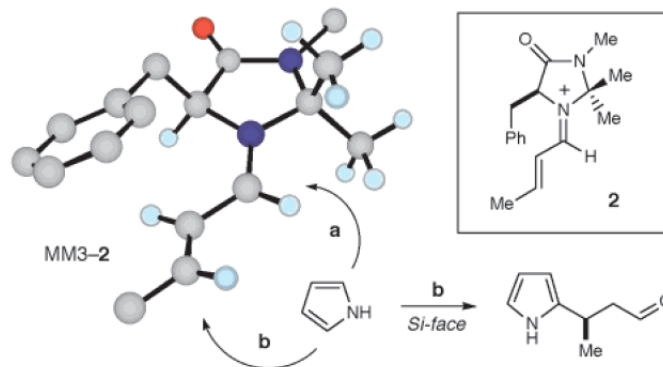
Leuconolam

- Isolated from the *Leuconotis* plants *L. griffithi* and *L. eugenifolia* located in Malaysia
- Open ring indole member of the *aspidosperma* class of anti-mitotic alkaloids closely related to *rhazinilam* and *rhazinal*
- New functionalized α - β -unsaturated carbinolamide subunit

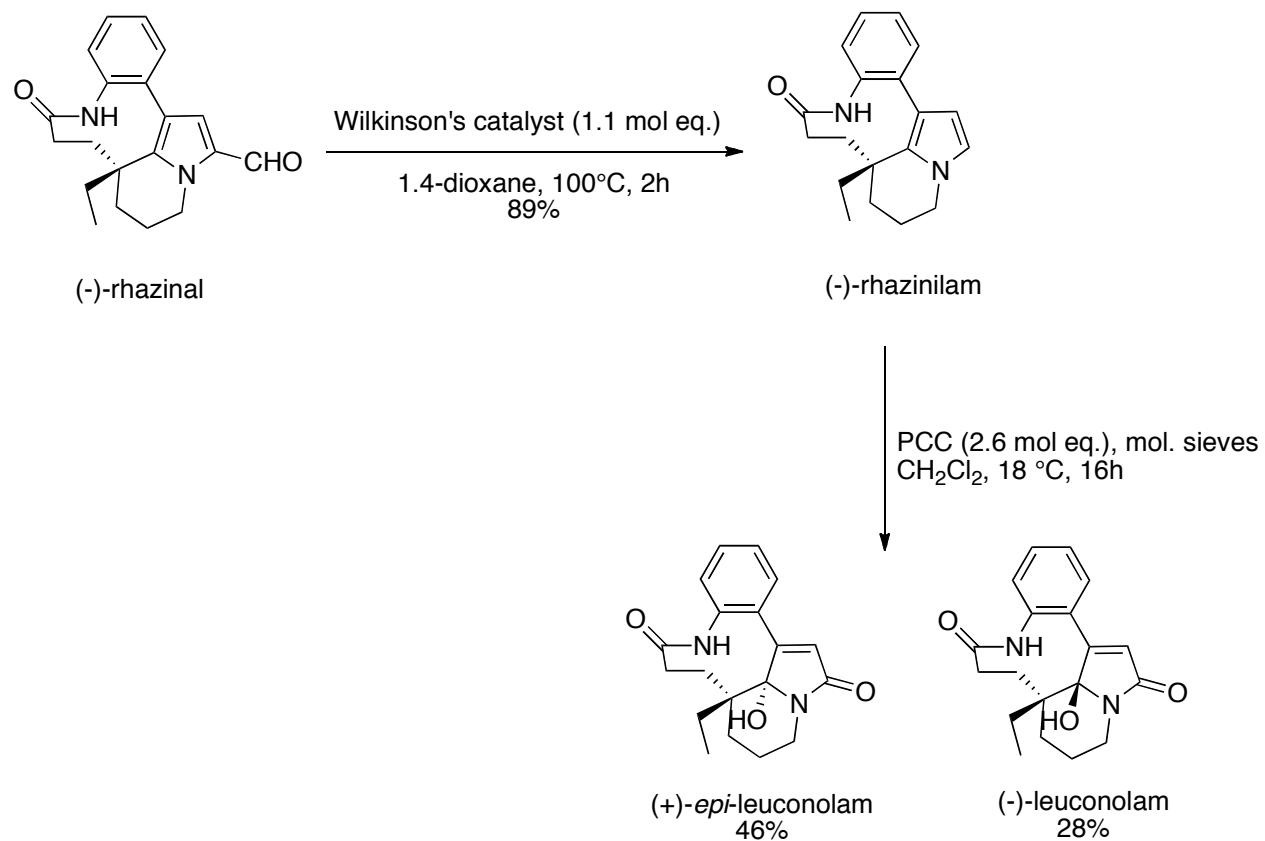


Previous synthesis

- Only 1 synthesis via PCC oxidation of parent (-)-rhazinilam
- Key step of the previous asymmetric synthesis

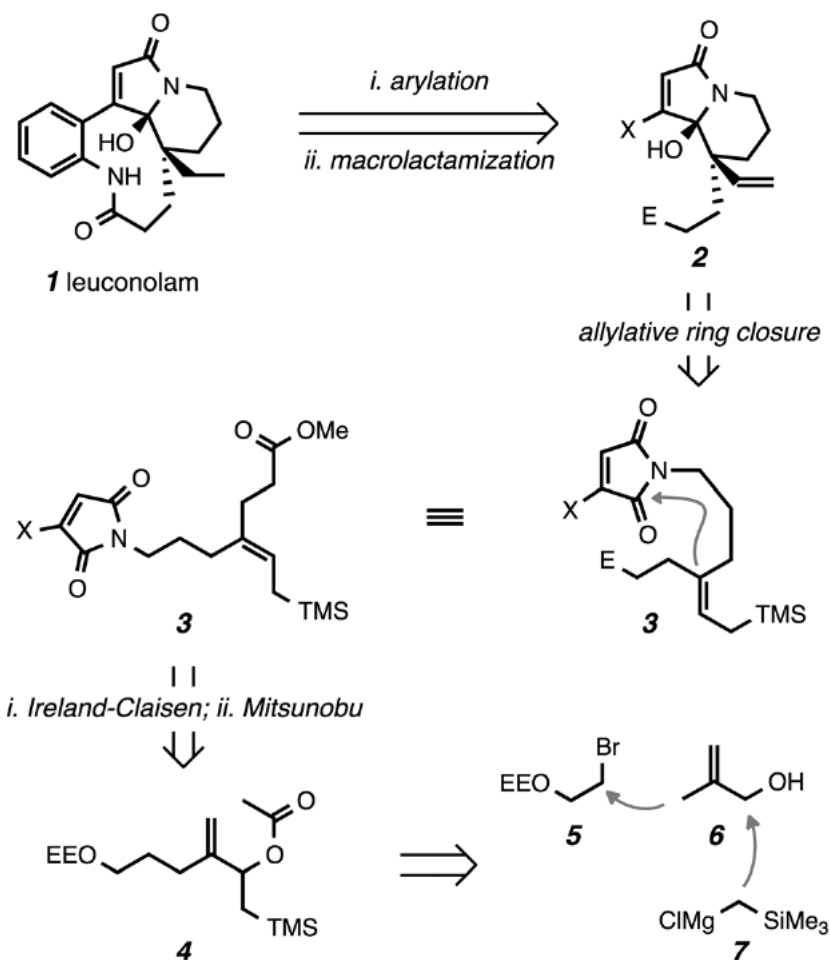


Previous synthesis



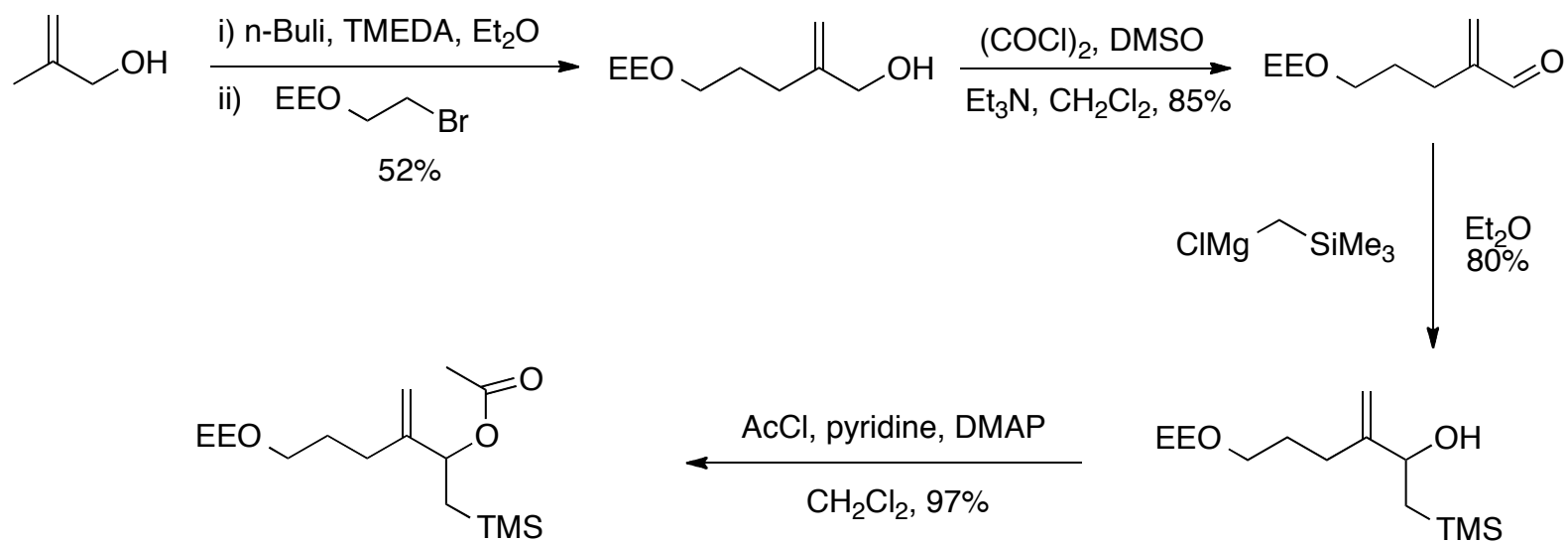
Synthesis of (+/-)-leuconolam

- Retrosynthesis



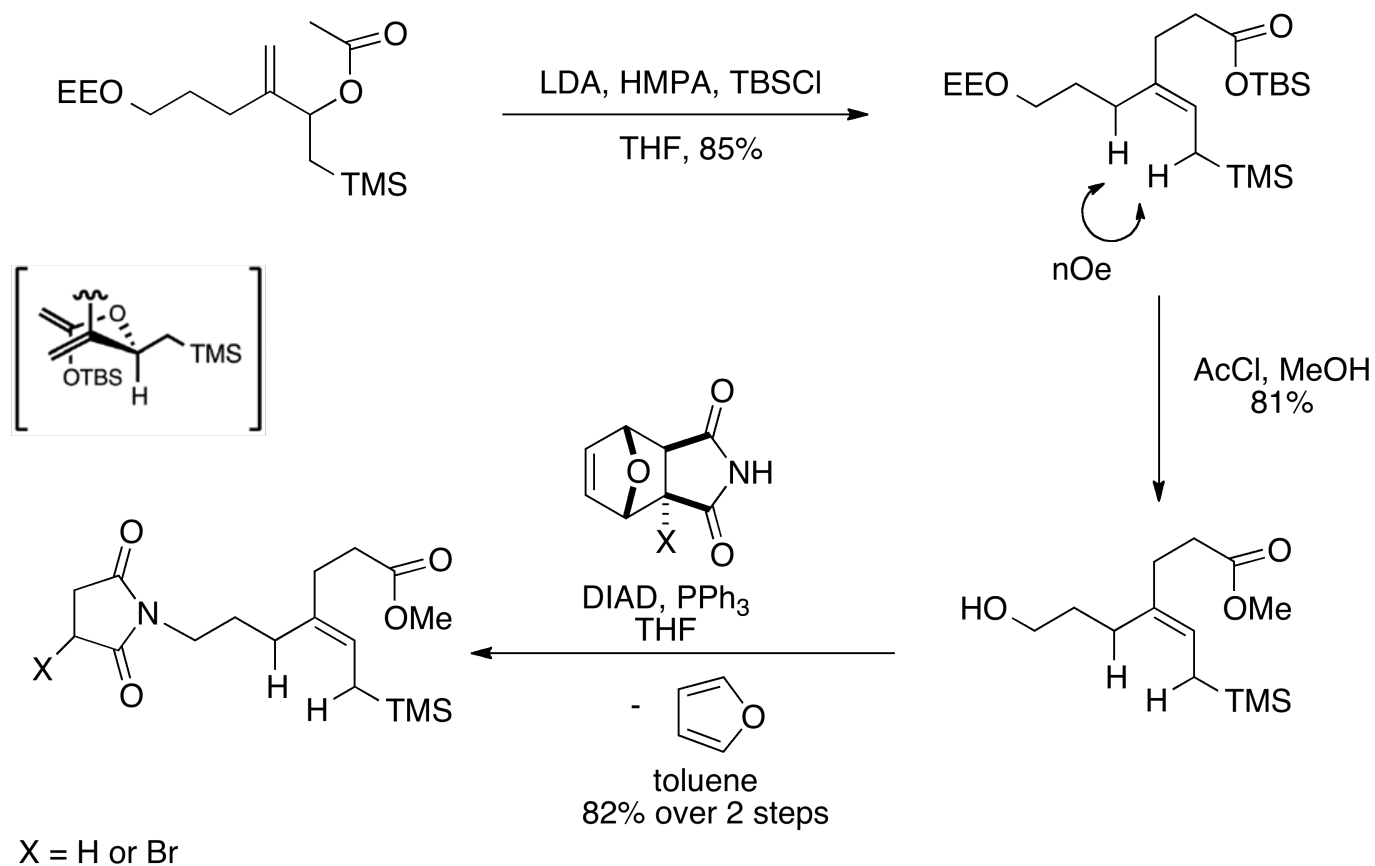
Scheme 1 Retrosynthetic analysis of 1.

Synthesis



prepared on 10 g scale

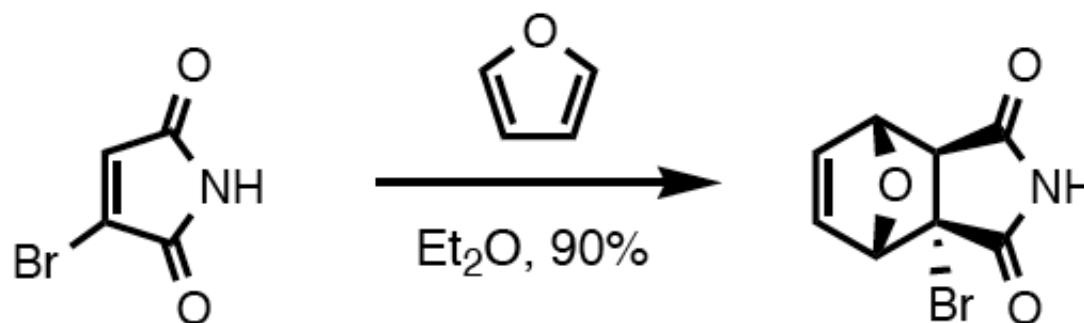
Synthesis



Ireland-Claisen with TMSCl was not successful

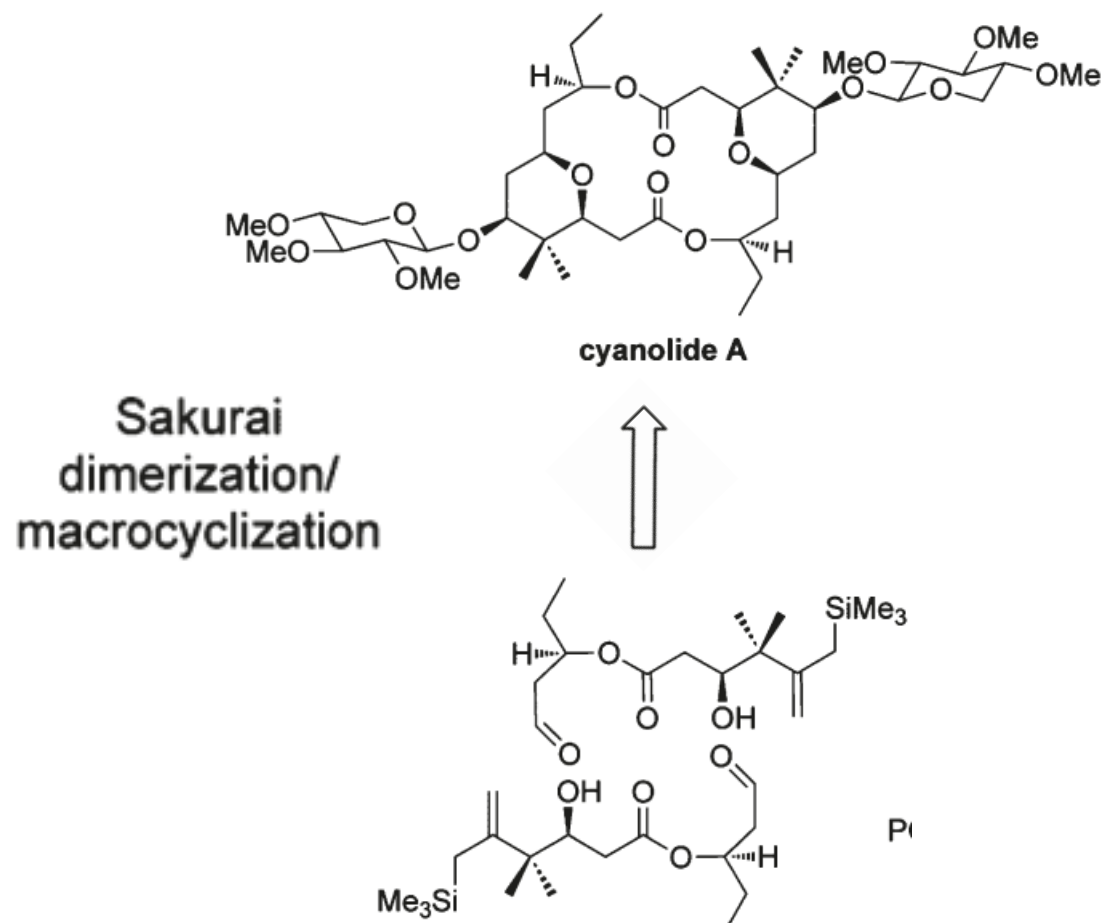
Mitsunobu with maleimide: low yield due to oligomerization

Synthesis

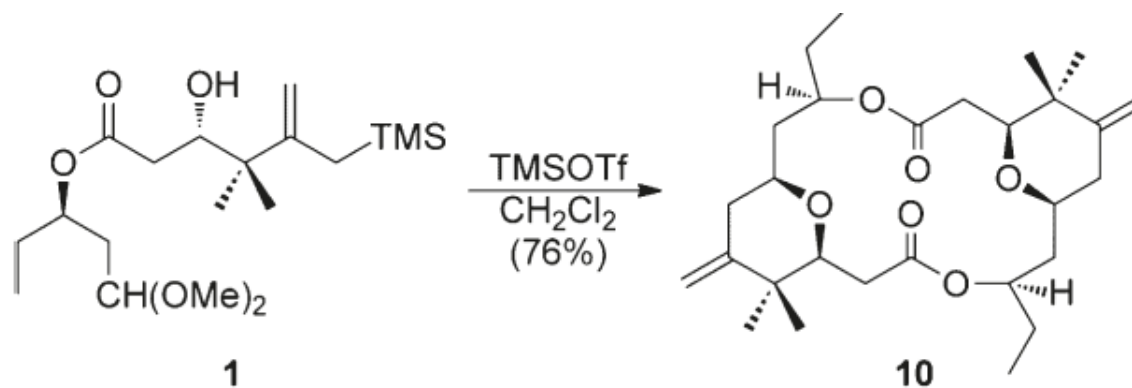


Mitsunobu with maleimide: low yield due to oligomerization

Intramolecular Sakurai reaction

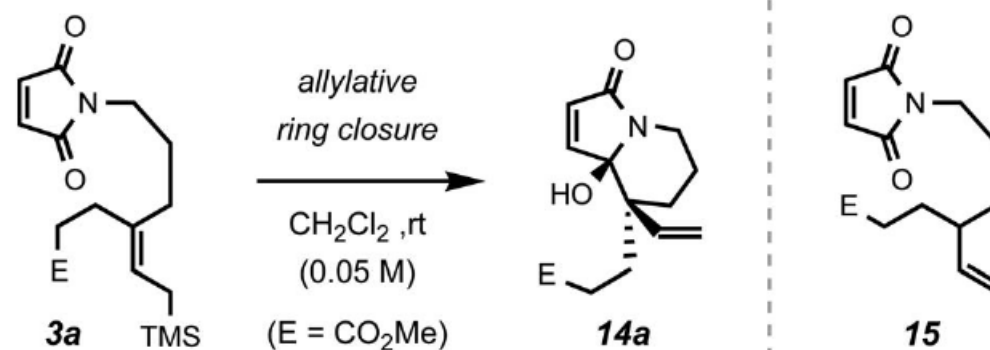


Intramolecular sakurai reaction



Model Study: cyclization

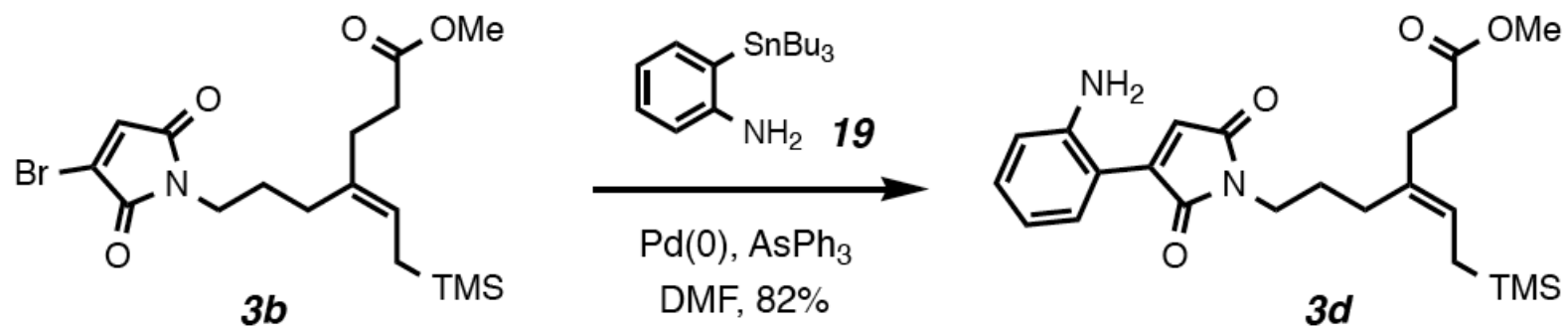
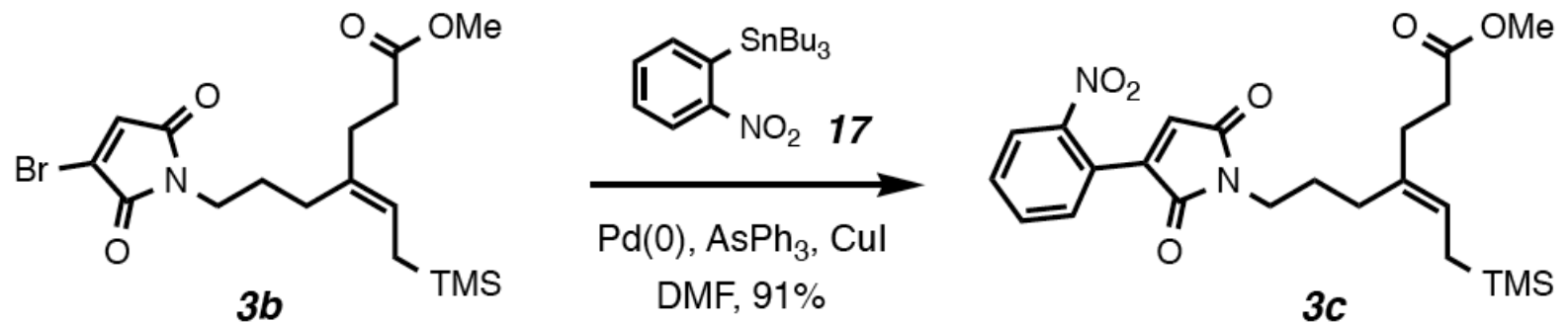
Table 1 Screening Lewis acids for the key allylative cyclization



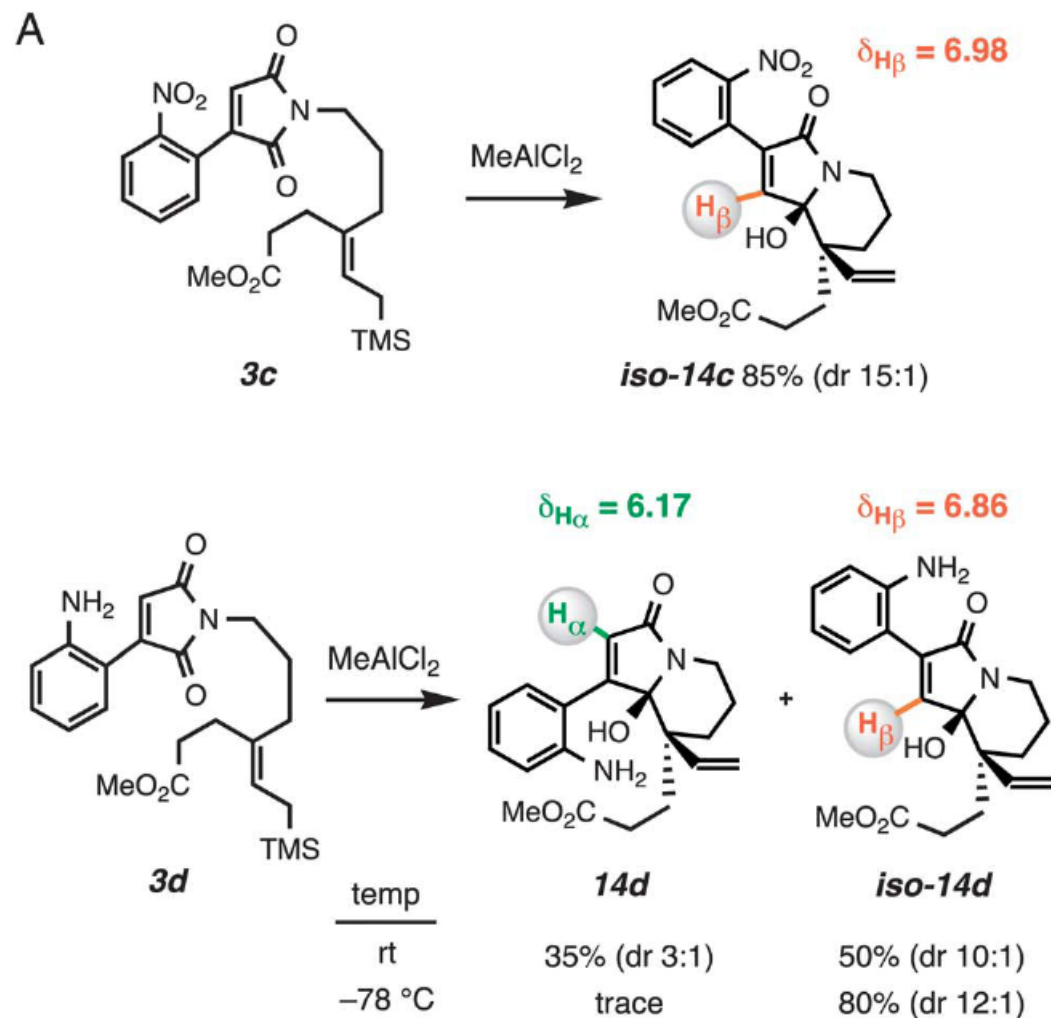
Entry	LA (equiv.)	Time (min)	14a	15
1	Ti(O- <i>i</i> Pr) ₄ (10)	60	no reaction	
2	TiCl ₄ (2)	15	0%	43%
3	TMSOTf (2)	15	0%	95%
4	BF ₃ ·OEt ₂ (2)	15	0%	80%
5	MeAlCl ₂ (4)	10	88% (<i>dr</i> 42 : 1)	0%

Me₂AlCl was also effective and TBAF induced decomposition

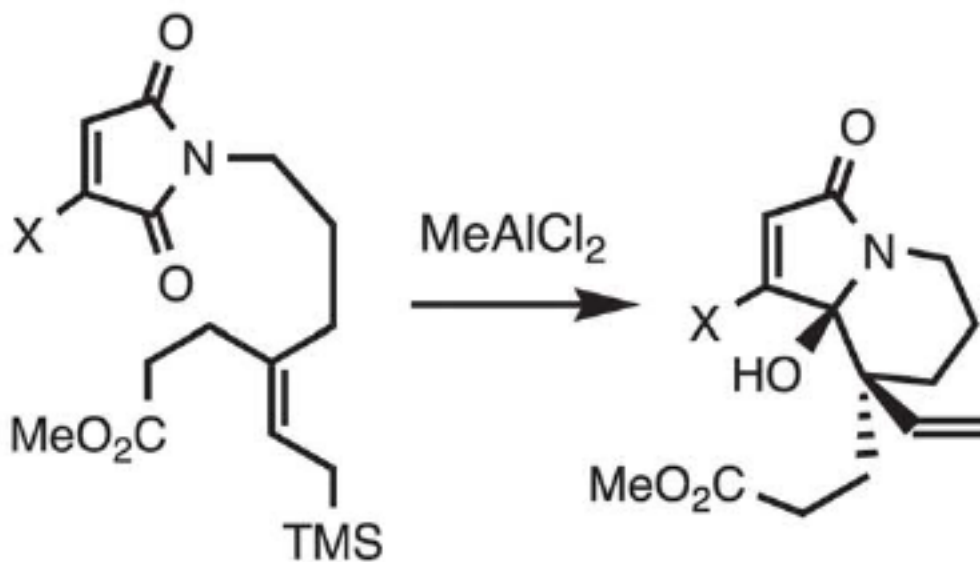
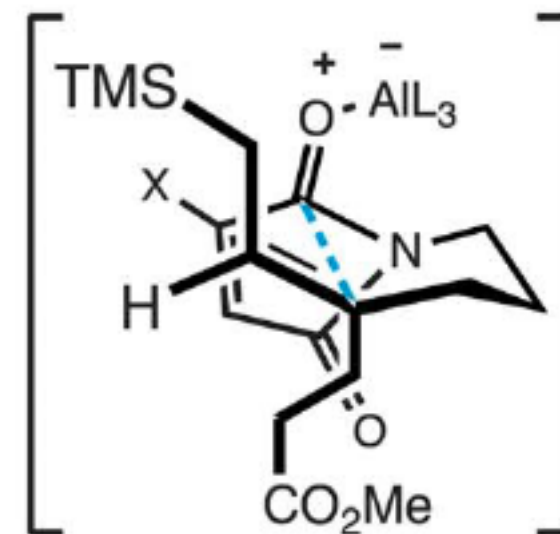
Preparation of cyclization precursor



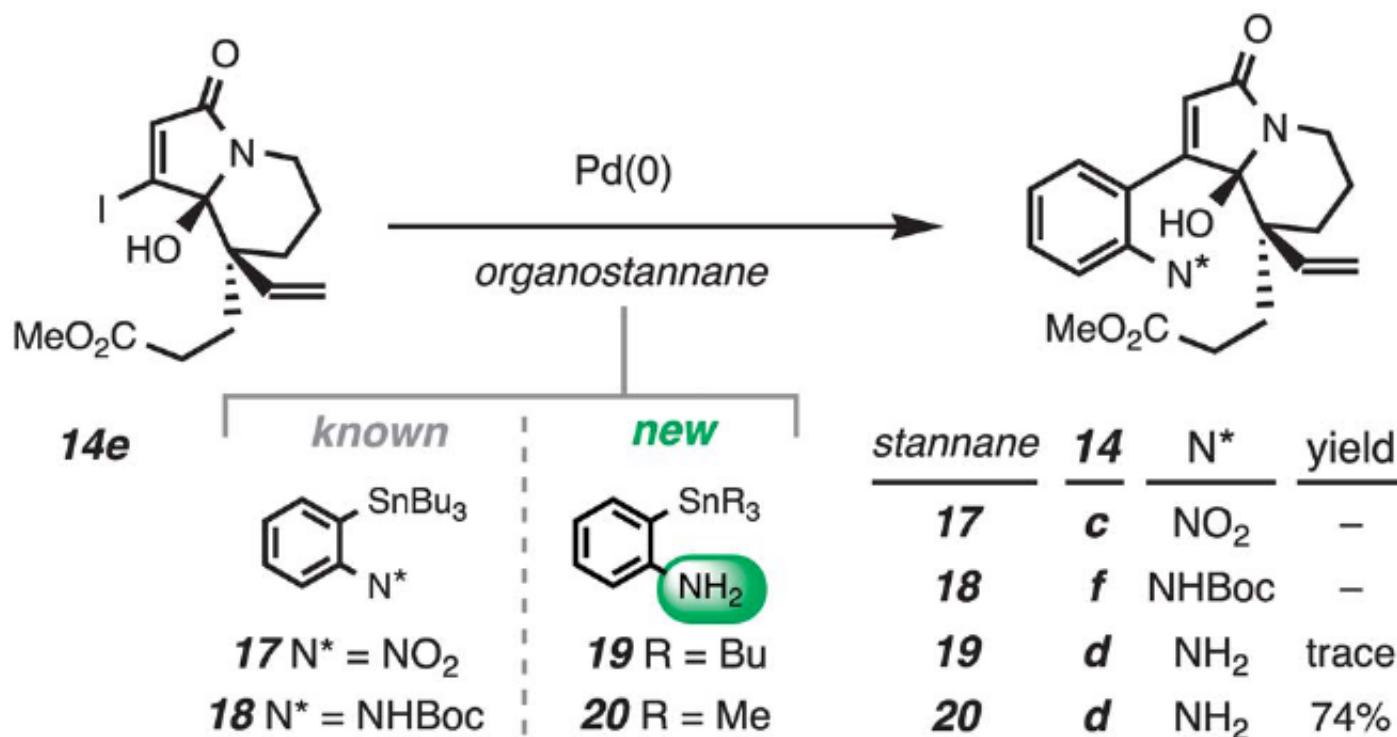
Cyclization study



Cyclization study

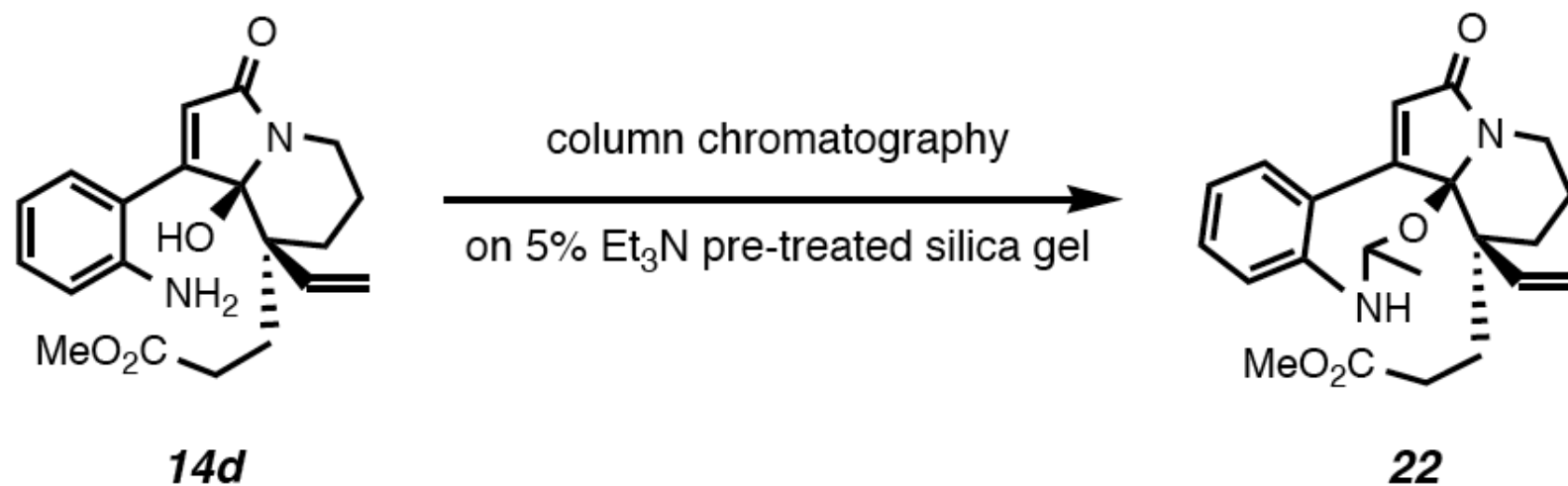
B**3b** X = Br**3e** X = I**14b** X = Br, 87% (dr 15:1)**14e** X = I, 83% (dr 15:1)**C****16** X = Br, I

Cyclization study



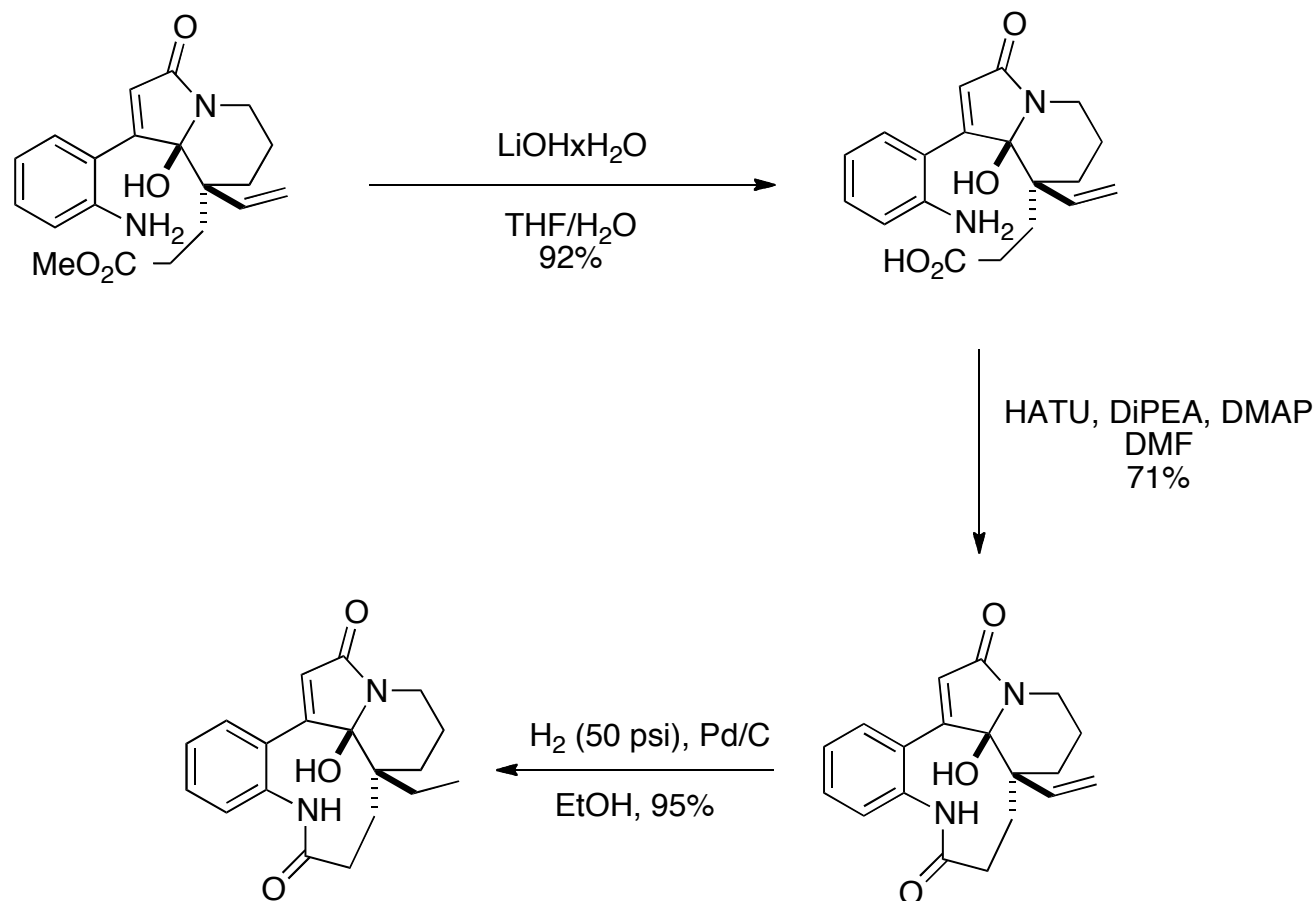
Scheme 4 Arylation (cross-coupling) studies of the iodoalkene **14e** to provide the anilino esters **14c-d**. Reagents and conditions for the synthesis of **14d**: **20** (1.2 equiv.), Pd₂(dba)₃·CHCl₃ (0.1 equiv.), AsPh₃ (0.4 equiv.), DMF, rt, 74%.

Unexpected isolated side product



Acetaldehyde could be an auto-oxidation product of Et₃N

Completion of the synthesis



Tricky hydrolysis due to sensitivity of carbinolamide moiety

Conclusion

- Elegant retrosynthesis/synthesis
- Regio- and diastereoselective intramolecular cyclization yielding 2 contiguous quaternary centers
- Development of (trimethylstannyl)anniline coupling
- Development of an enantioselective method is needed

Effect of CuI in Stille coupling

