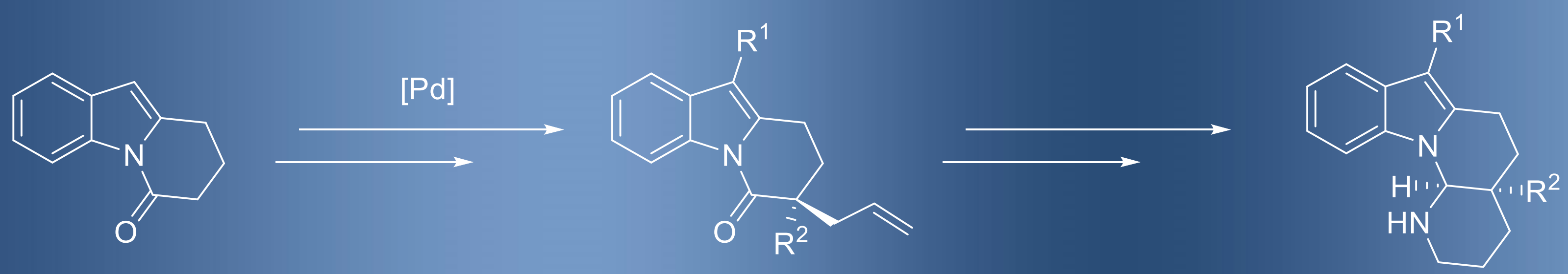
Enantioselective Pd-Catalyzed Allylic Alkylation Reactions of Dihydropyrido[1,2-*a*]indolone Substrates: Efficient Syntheses of (-)-Goniomitine, (+)-Aspidospermidine, and (-)-Quebrachamine

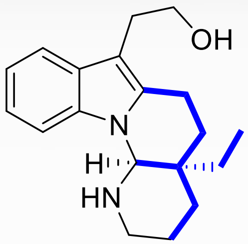
Beau P. Prirchett, Jun Kikuchi, Yoshitaka Numajiri, Brian M. Stoltz

Angew. Chem. Int. Ed., **2016**, *early view*

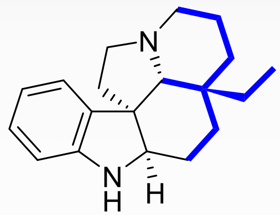
Serene Tai
Current literature 15 Oct 2016



Introduction – Aspidosperma alkaloid

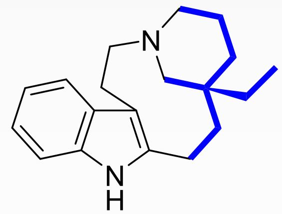


goniomitine



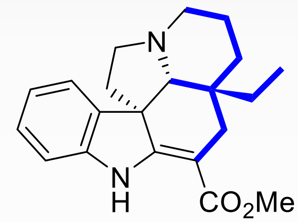
aspidospermidine

good showcase for new synthetic strategies



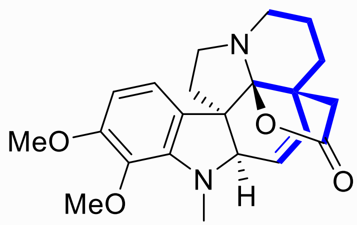
quebrachamine

possess adrenergic blocking activities



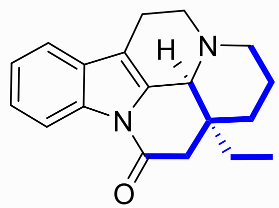
vincadifformine

Cytotoxicity against vincristine-resistant human KB/VJ300 cells



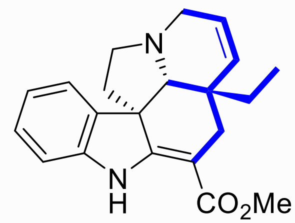
aspidophytine

insecticide particularly effective against cockraches



eburnamonine

vasodilator, cerebral metabolic stimulant



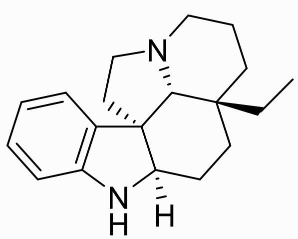
tabersonine

key intermediate for the synthesis of vinblastine

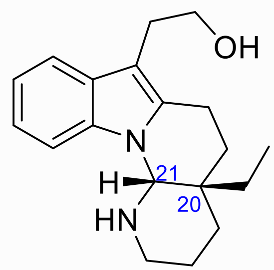
Phytochemicals - Isolation, Characterisation and Role in Human Health, **2015**, 163 – 184.

Introduction – goniomitine isolation & characterization

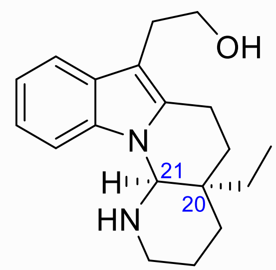
- Isolated from the root bark of *Gonioma Malagasy* found in Madagascar
- Structure and absolute configuration was initially proposed based on its NMR spectra through correlation with other known alkaloids from Aspidosperma found in the same plant
- The absolute stereochemistry was later confirmed to be (20*R*, 21*S*)
- Contains a unique octahydroindolo[1,2-*a*][1,8]naphthyridine core
- Weak antiproliferative activity in several cancer cell lines (IC_{50} = µM range)
- 11 total syntheses (4 asymmetric syntheses) to date



aspidospermidine



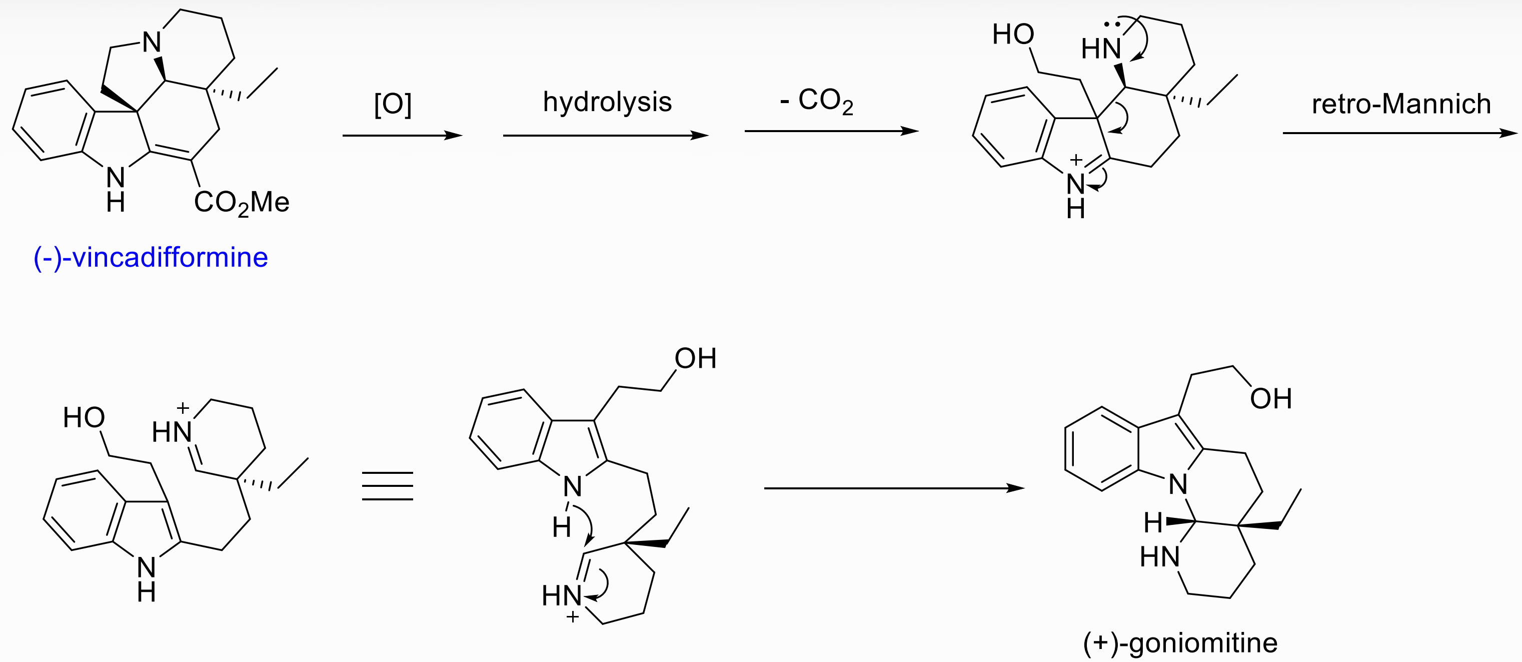
(20*S*, 21*R*)-(+)-goniomitine
unnatural



(20*R*, 21*S*)-(-)-goniomitine
natural

Tetrahedron Lett., **1987**, *28*, 2123-2126
ISRN Org. Chem., **2013**, 292396

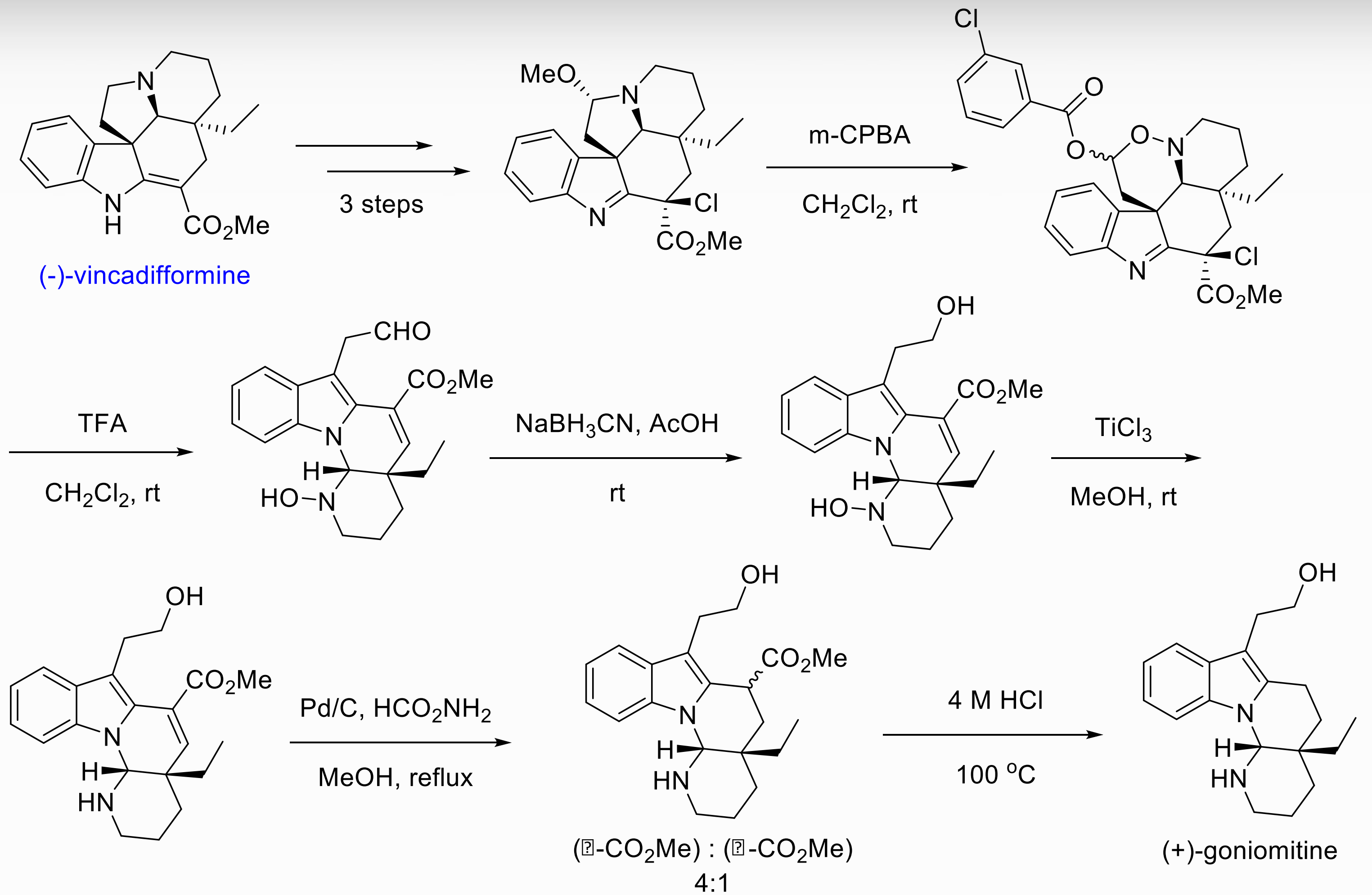
Proposed biogenesis of goniomitine



Tetrahedron Lett., **1987**, *28*, 2123-2126

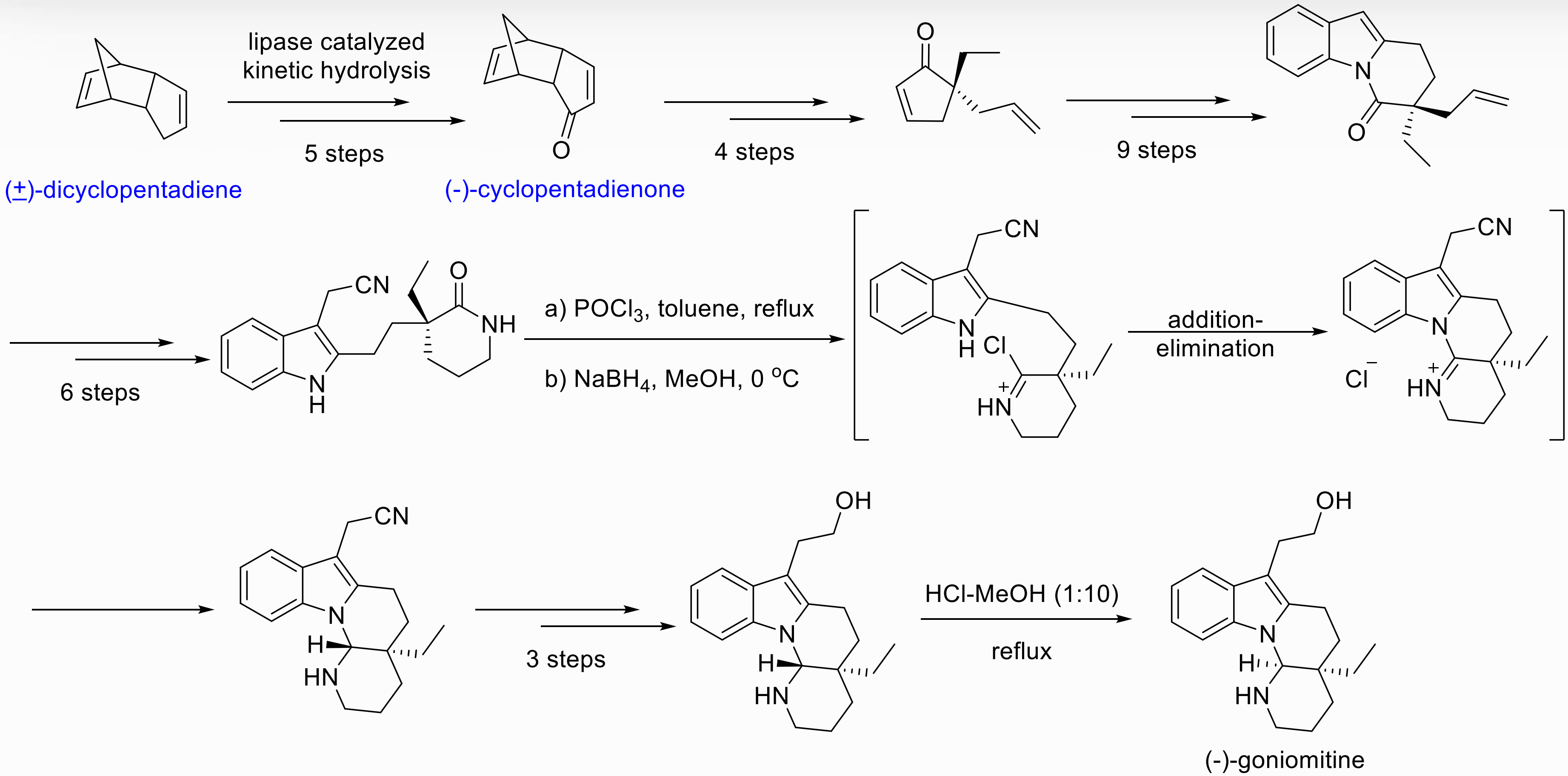
4

Biomimetic semisynthesis of goniomitine (Lewin 2013)



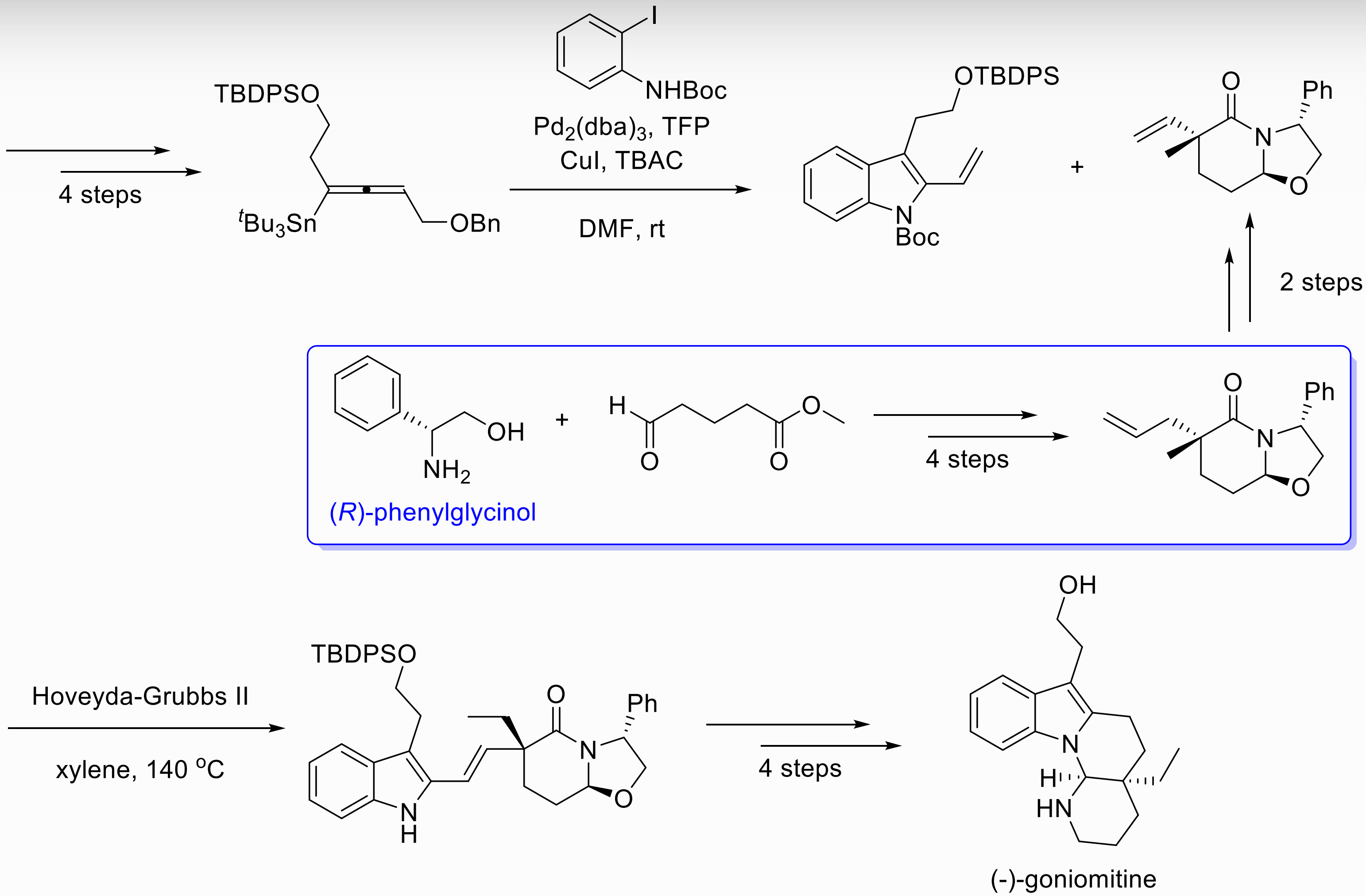
J. Org. Chem., **1995**, *60*, 3282-3287
Tetrahedron, **2013**, *69*, 1622-1627

Asymmetric syntheses of goniomitine (Takano 1991)



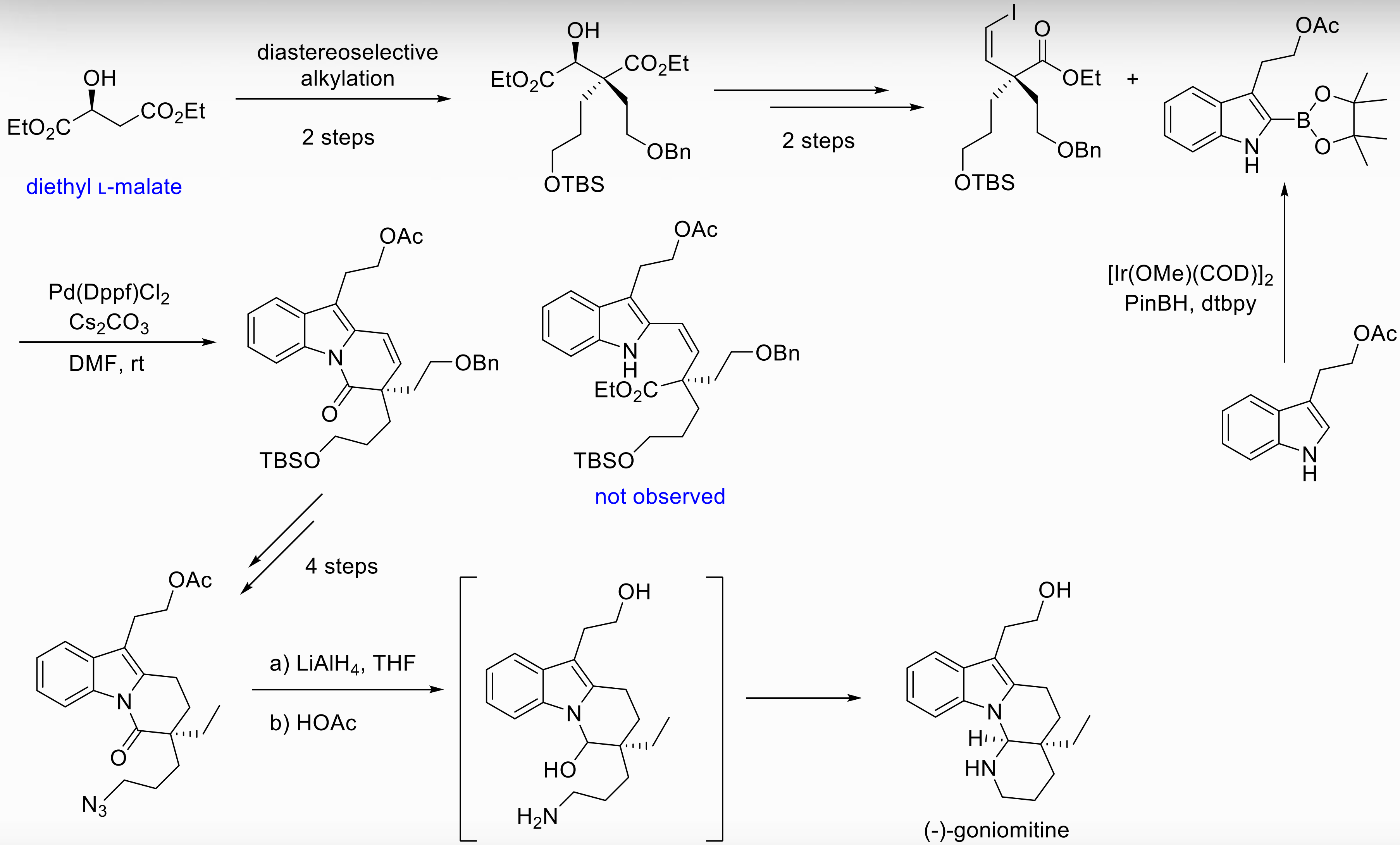
J. Chem. Soc., Chem. Commun., **1991**, 462-464

Asymmetric syntheses of goniomitine (Mukai 2011)



Org. Lett, **2011**, *13*, 1796-1799

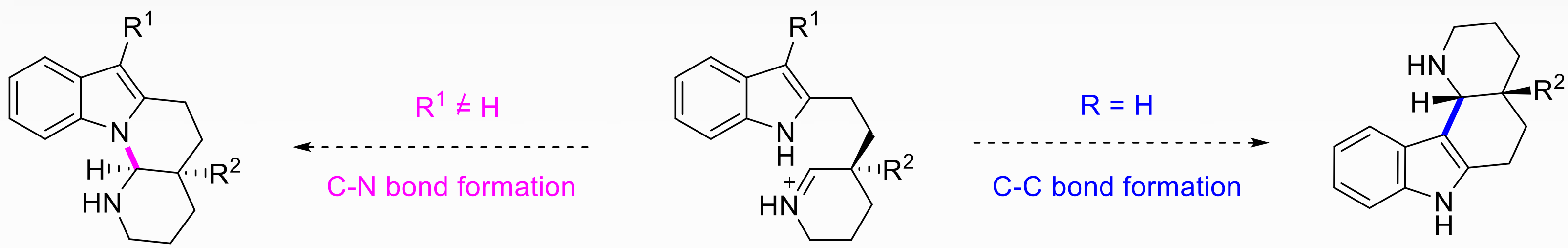
Asymmetric syntheses of goniomitine (Jia 2014)



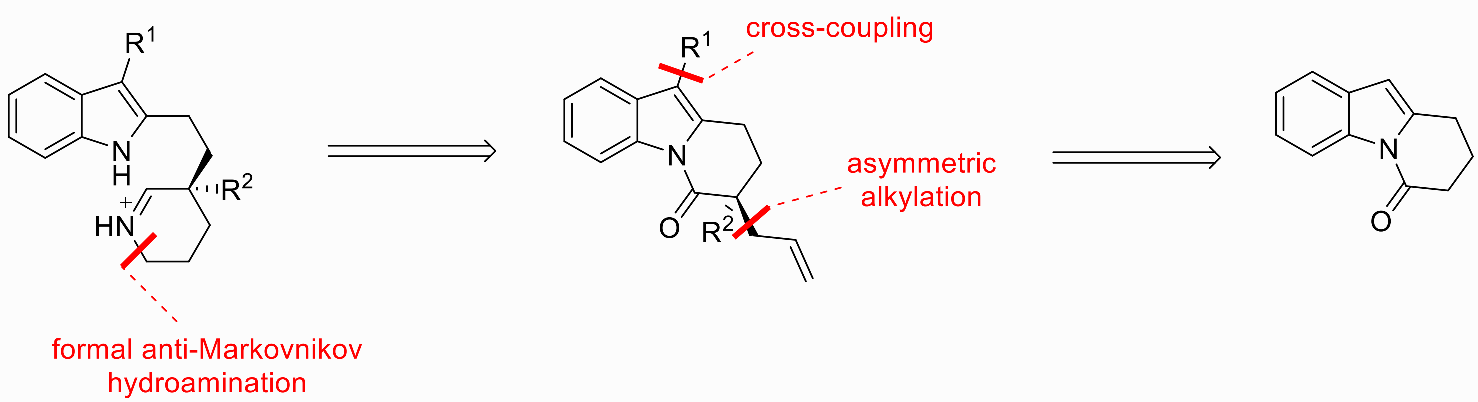
Org. Lett., **2014**, *16*, 3416-3418

Asymmetric syntheses of goniomitine (Stoltz 2016)

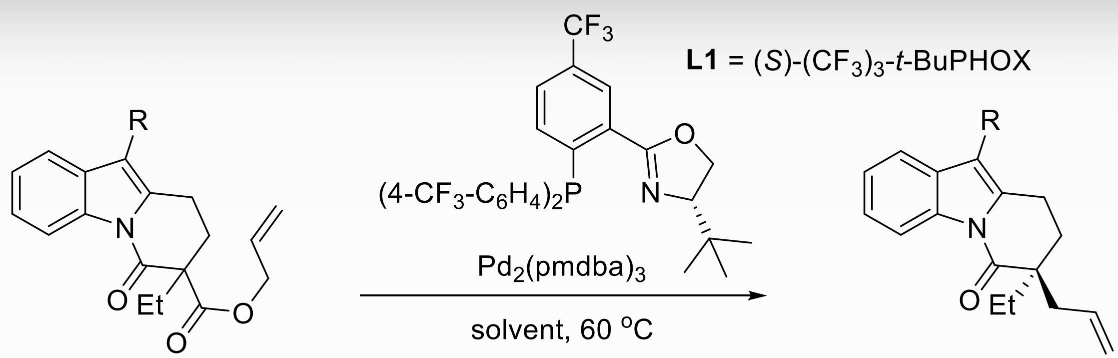
❖ Indole-iminium cyclization chemoselectivity



❖ Retrosynthesis of key iminium intermediate



Pd-catalyzed asymmetric allylic alkylation



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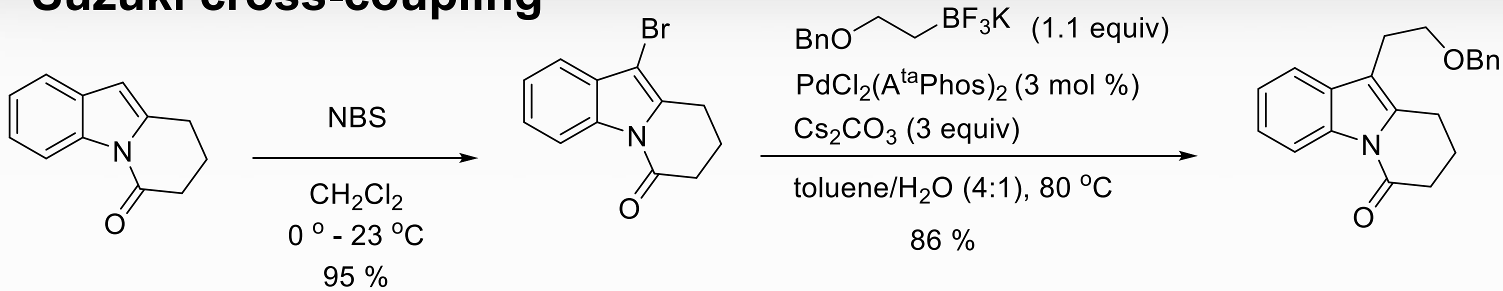
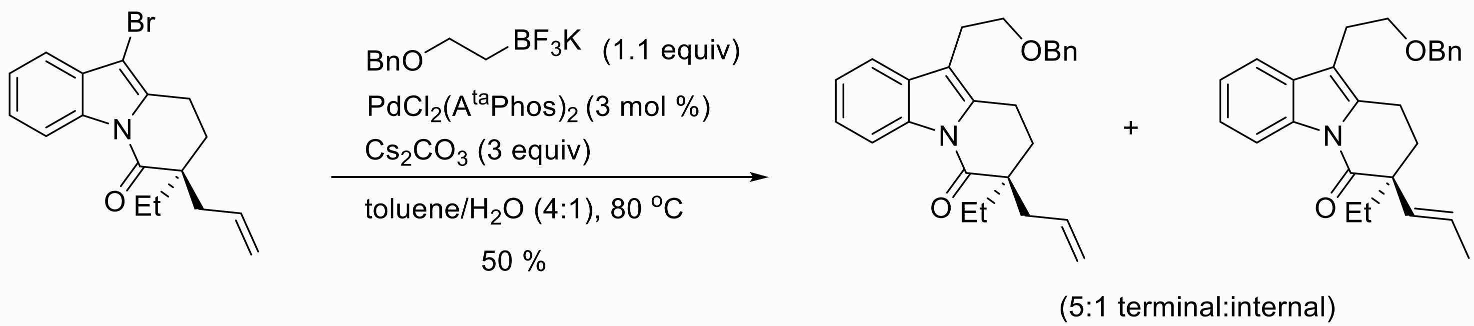
Entry	R	Solvent	$Pd_2(dmba)_3$ [mol %]	Ligand [mol %]	T [h]	Yield [%]	ee [%]
1	CH_2CH_2OBn	toluene	10	25	72	38	89
2	CH_2CH_2OBn	MTBE	10	25	24	59	87
3	Br	toluene	5	12.5	24	21	93
4	Br	MTBE	5	12.5	8	83	96
5	H	toluene	10	25	48	54	92
6	H	MTBE	5	12.5	24	71	94

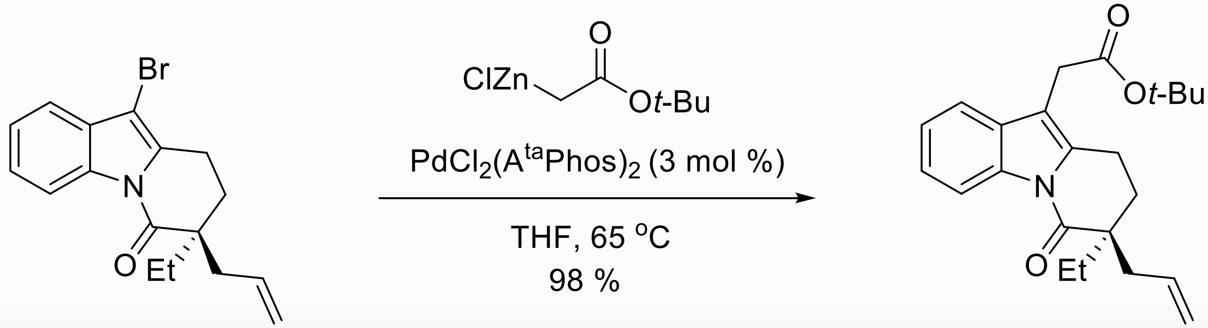
Cross-coupling reactions

❖ Suzuki cross-coupling



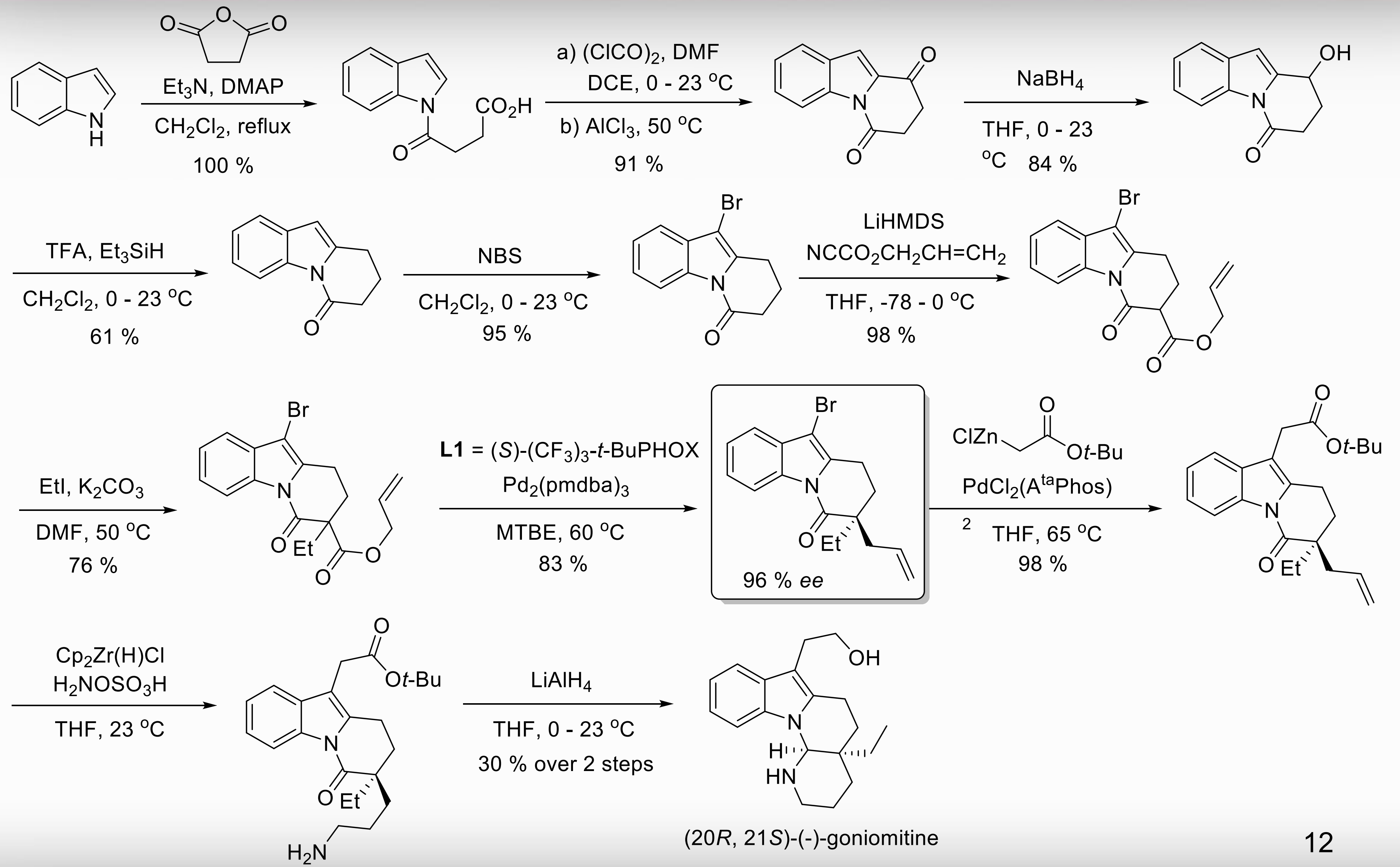


❖ Negishi cross-coupling

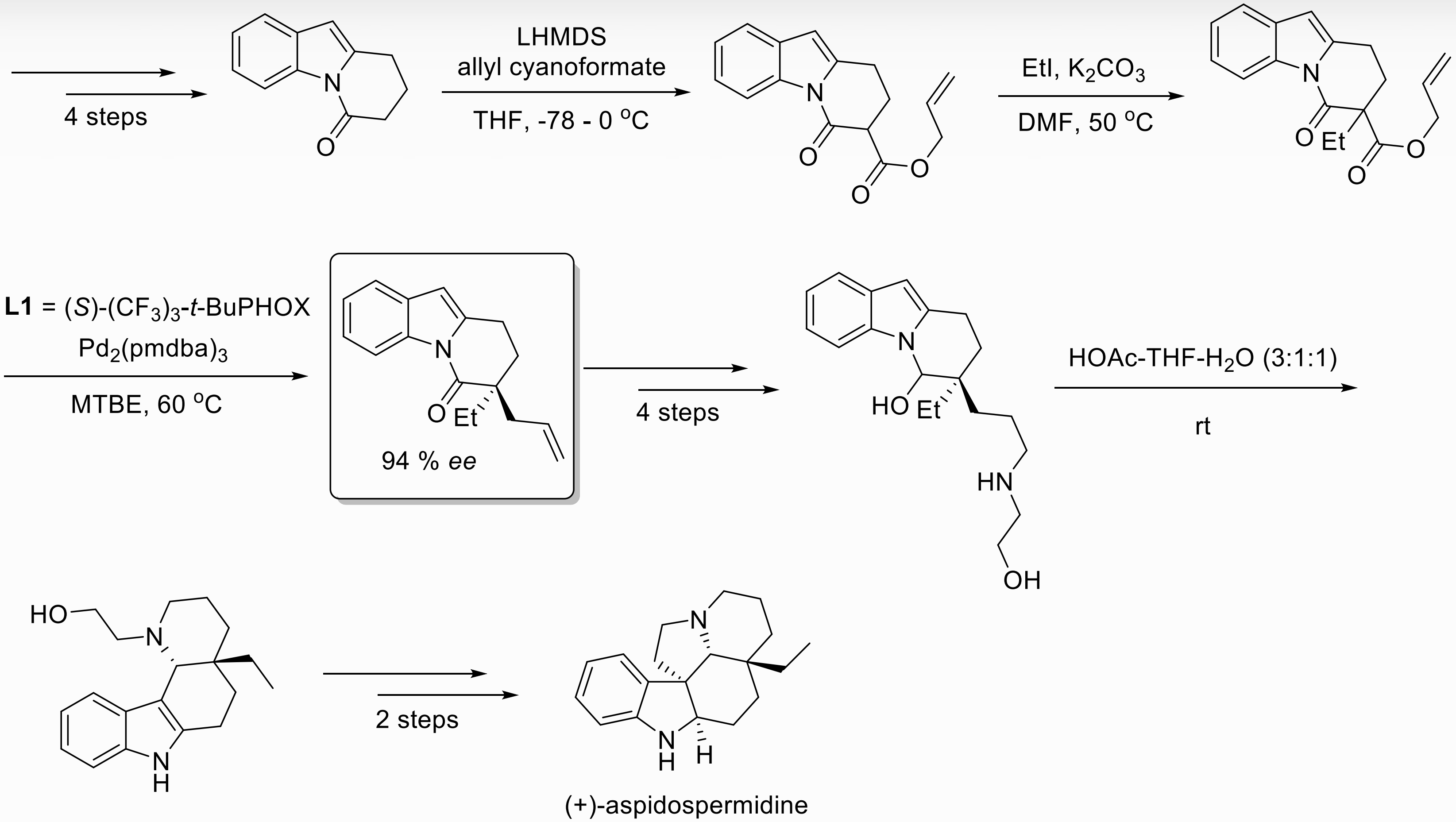


single olefin isomer!

Complete synthesis of (-)-goniomitine

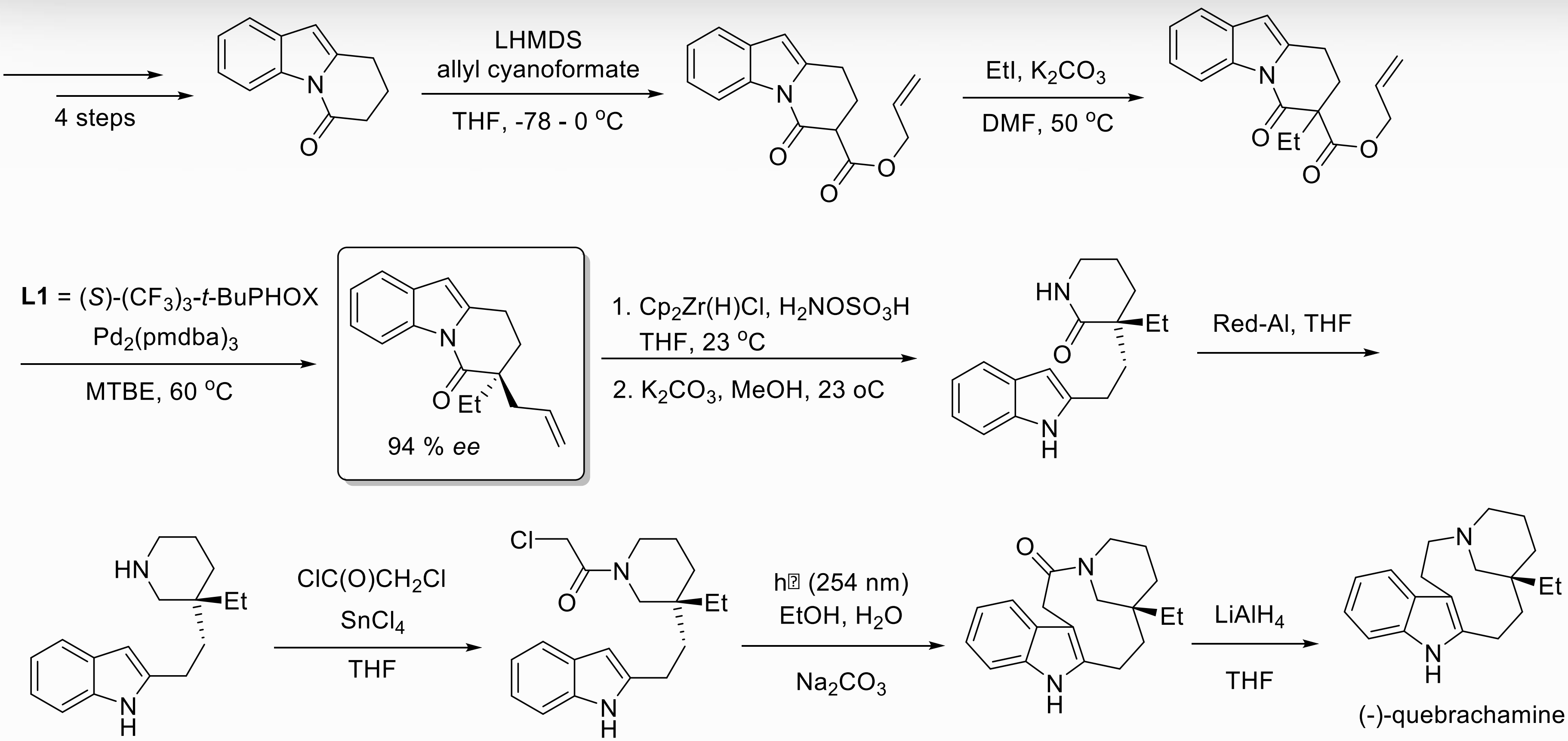


Asymmetric formal synthesis of (+)-aspidospermidine



J. Chem. Soc., **2012**, *134*, 14563-14572

Asymmetric formal synthesis of (-)-quebrachamine



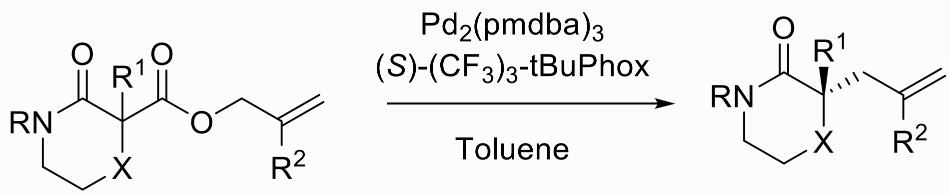
Eur. J. Org. Chem., **2009**, 1072-1077

Conclusions

- ❖ **First catalytic enantioselective total synthesis**
- ❖ **Redox efficiency and freedom from protecting-group manipulations**
- ❖ **DHPI scaffold provides divergent, enantioselective access to other alkaloids**
- ❖ **Overall yield comparison**

	Steps	**Overall yield (%)**	**Quantity (mg)**
Takano (1991)	29	0.25	-
Mukai (2011)	10 (from lit known SM)	12	4.5
Jia (2014)	11	3.4	4.6
Stoltz (2016)	11	8	33

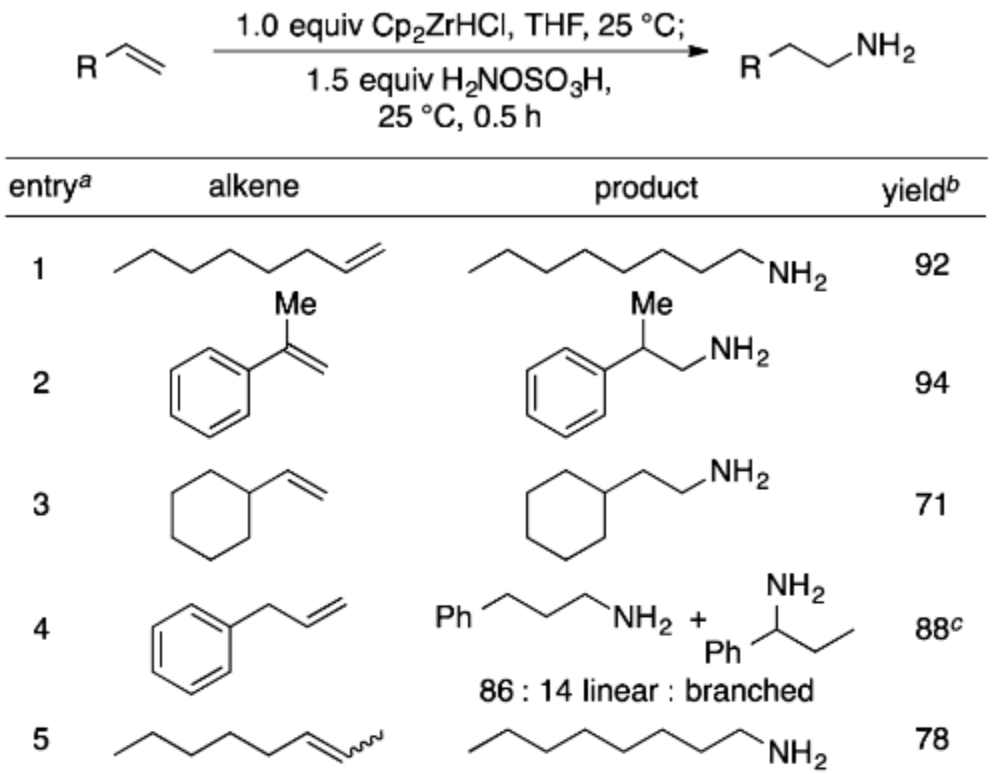
16



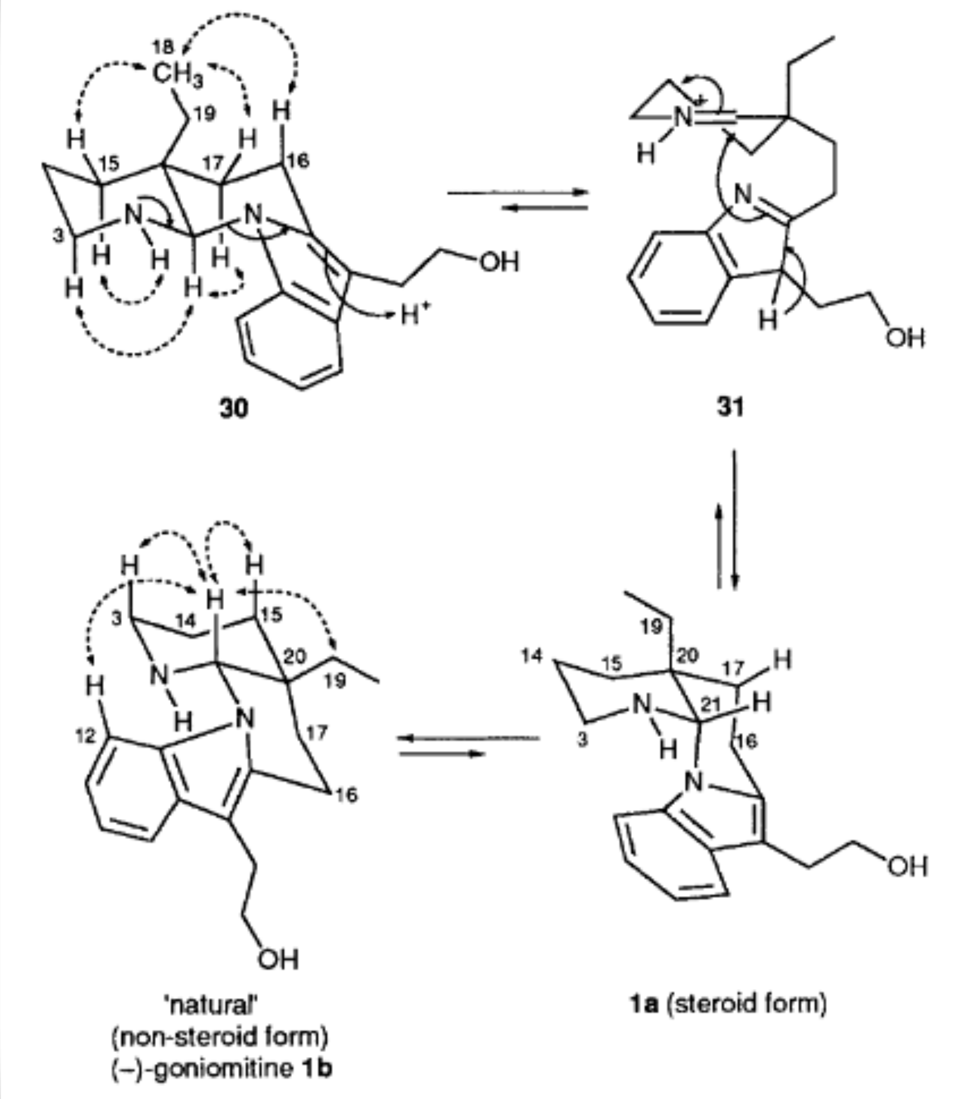
Nat. Chem., **2012**, *4*, 130

17

Table 2. Reactions to Form Primary Amines



J. Org. Chem., **2013**, *78*, 8909-8914


30
31
1a (steroid form)
'natural'
(non-steroid form)
(–)-goniomitine 1b

19