Palladium-Catalyzed Decarboxylative Vinylation of Potassium Nitrophenyl Acetate: Application to the Total Synthesis of (±)-Goniomitine

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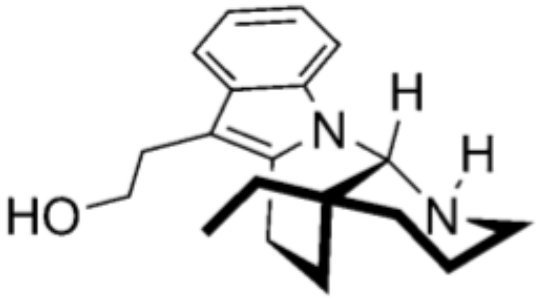
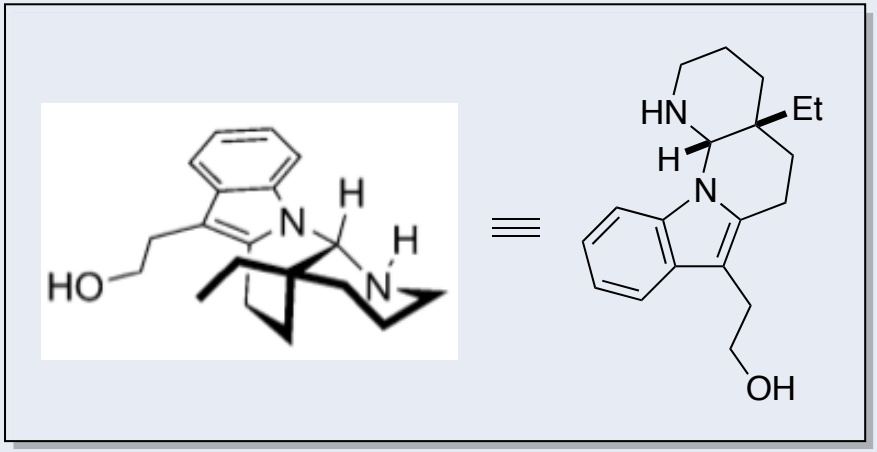


goniomitine **1**

Angew. Chem. Int. Ed. **2013**, *52*, 1-6.

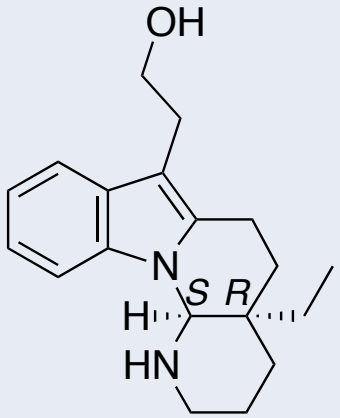
Introduction – Goniomitine

- Isolated from root bark of **Gonioma malagasy** (Madagascar) by Husson and co-workers in 1987 in Gif-sur-Yvette/France
- Unique member of the **aspidosperma alkaloid** family
- First study of biological activity by Waser *et al.* in 2010 → significant **cyctotoxicity** against several cancer cell lines
- To date, only **six total synthesis**

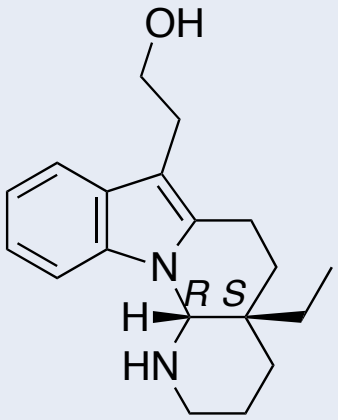


Introduction – Goniomitine

- Octahydroindolo[1,2-α][1,8]naphthyridine skeleton linked to a tryptophol moiety
- Natural occuring is (–)-goniomitine

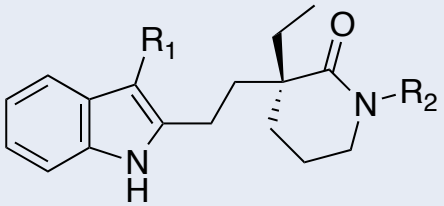


(–)-Goniomitine
(20*R*, 21*S*)

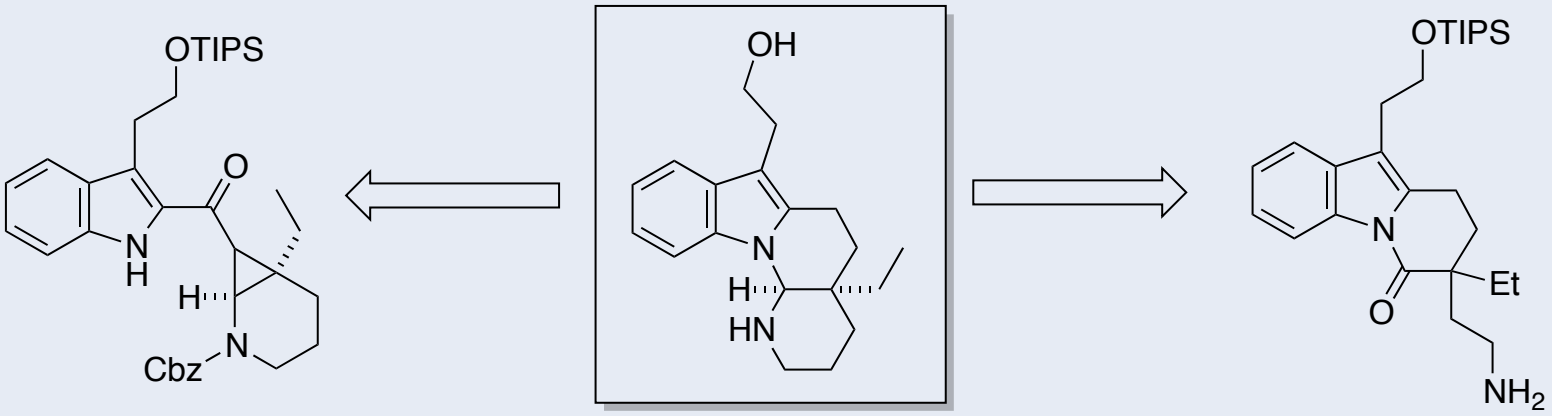


(+)-Goniomitine
(20*S*, 21*R*)

Previous Syntheses



Takano *et al. J. Chem. Soc., Chem. Commun* **1991**, 462.
Pagenkopf *et al. Org. Lett.* **2008**, *10,* 157.
Mukai *et al. Org Lett.* **2011**, *13*, 1796.



Waser *et al. ACIE* **2010**, 49, *5767.*

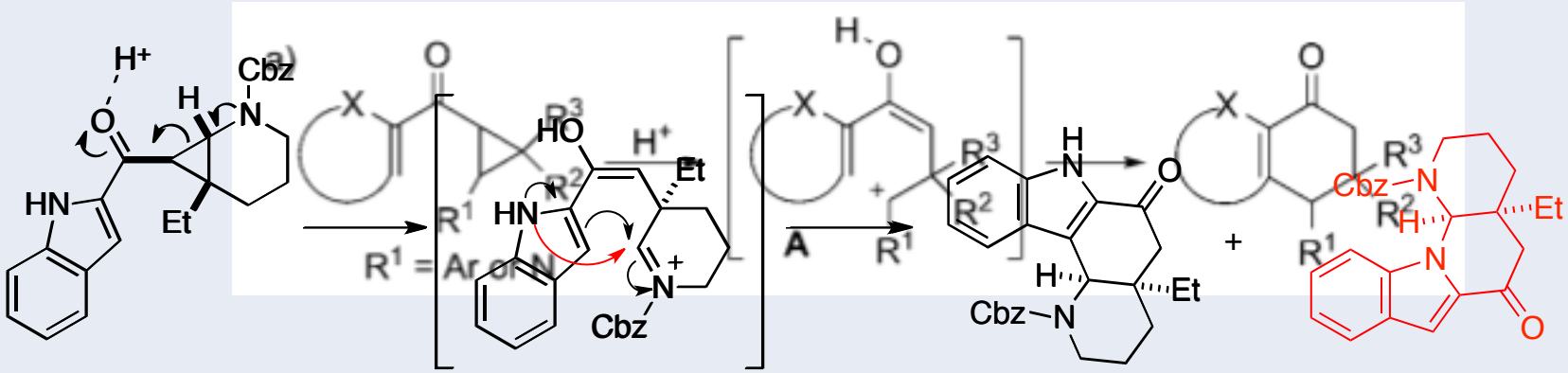
Bach *et al. JACS* **2012**, 134, *14563.*

Common features: building 2,3-functionalized indoles followed by the stepwise formation of rings C and D

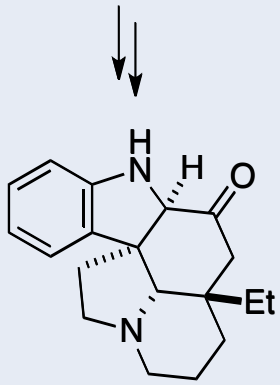
Previous Syntheses

Waser *et al. ACIE* **2010**, *49*, 5767-5770.

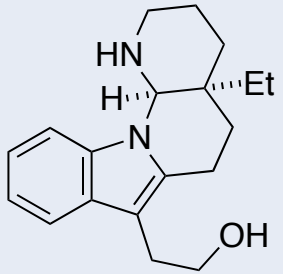
Homo-Nazarov cyclization of vinyl cyclopropyl ketones



Entry	R (**1**)	Catalyst	Solvent	**15/16**	Yield [%]
1	H (**1a**)	TsOH	MeCN	1.6:1[a]	74
2	H (**1a**)	$Cu(OTf)_2$	MeCN	8:1[b]	n.d.[c]
3	H	$Pd(CH_3CN)_4(BF_4)_2$	MeCN	11:1[b]	n.d.
4	H	$Cu(OTf)_2$	MeCN	7:1[a]	91
5	H	TsOH	$MeNO_2$	1.3:1[b]	n.d.
6	H	TsOH	THF	polymers[b]	n.d.
7	H	TsOH	CH_2Cl_2	1:18[b]	n.d.
8	H	TsOH	toluene	1:16[b]	n.d.
9	H	TsOH	CH_2Cl_2	1:21[a]	89
10	4-OMe (**1b**)	TsOH	CH_2Cl_2	1:22[a]	92
11	4-OMe	$Cu(OTf)_2$	MeCN	8:1[a]	88
12	5-OMe (**1c**)	TsOH	CH_2Cl_2	1:20[a]	86
13	5-OMe	$Cu(OTf)_2$	MeCN	8:1[a]	95



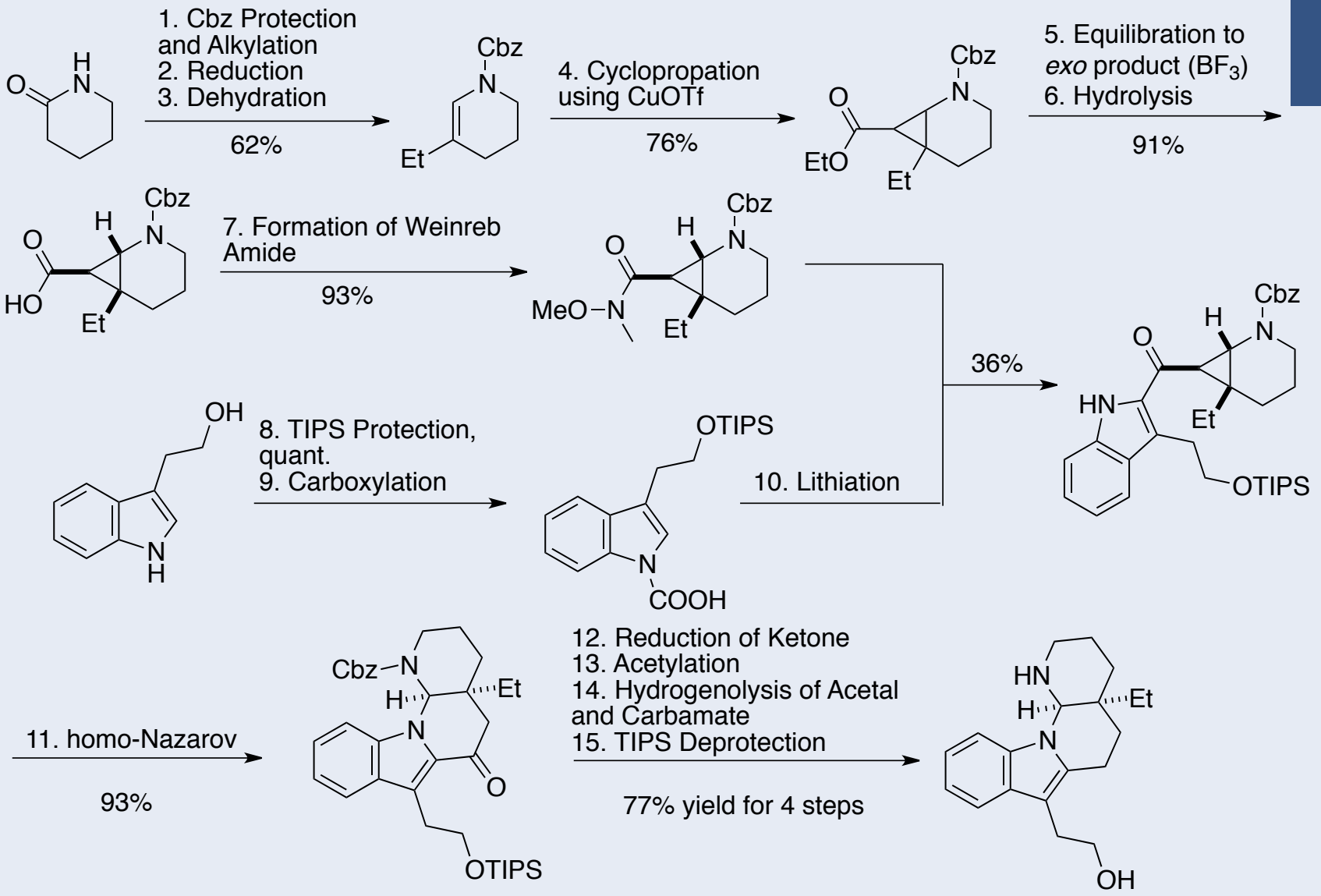
aspidospermidine



goniomitine

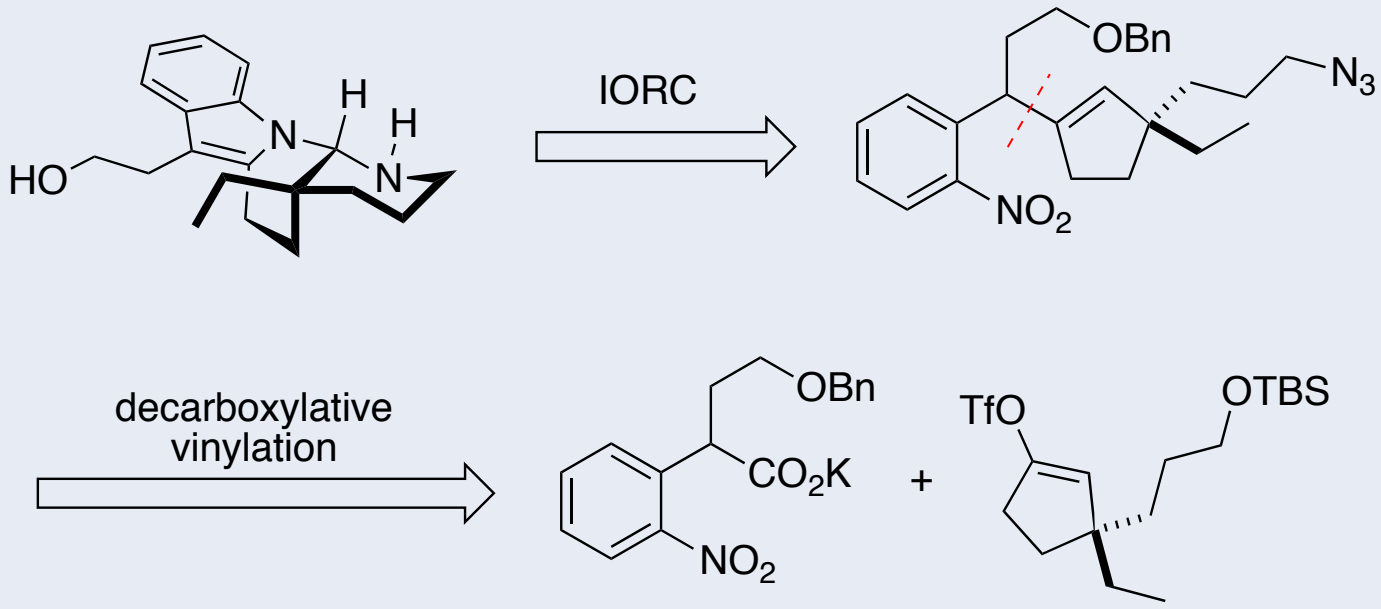
Previous Syntheses

Waser *et al. ACIE* **2010**, *49*, 5767-5770.



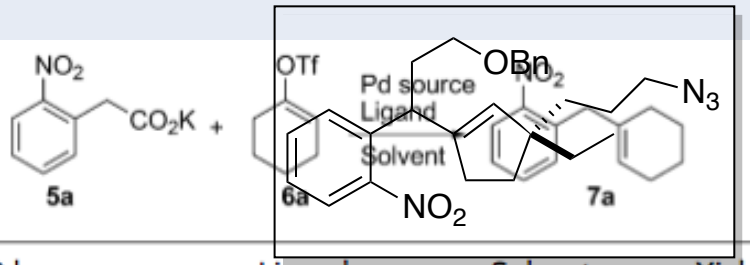
Retrosynthesis

(Jieping Zhu *et al. ACIE* **2013**, *52*, 1-6.)



Decarboxylative Vinylation

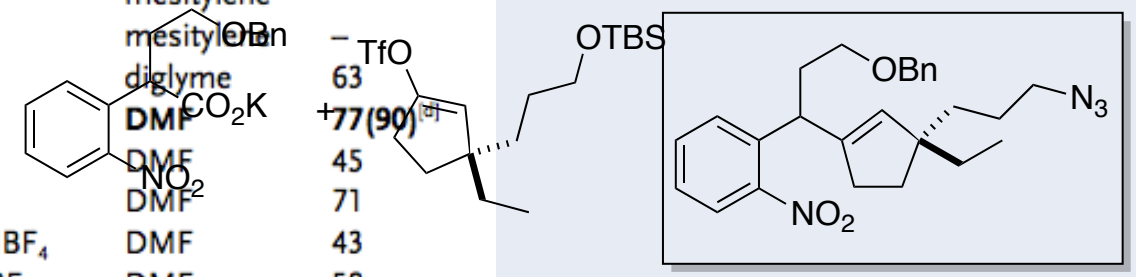
Transition-metal-catalyzed decarboxylative coupling of carboxylic acids



decarboxylative vinylation

Entry	Pd source	Ligand	Solvent	Yield [%][b]
1[c]	[{PdCl(allyl)}$_2$]	X-Phos	mesitylene	–
2	[{PdCl(allyl)}$_2$]	X-Phos	mesitylene	–
3	[{PdCl(allyl)}$_2$]	X-Phos	diglyme	63
4	**[{PdCl(allyl)}$_2$]**	**X-Phos**	**DMF**	**77 (90)[d]**
5[e]	[{PdCl(allyl)}$_2$]	X-Phos	DMF	45
6	[{PdCl(allyl)}$_2$]	S-Phos	DMF	71
7	[{PdCl(allyl)}$_2$]	tBu$_3$P·HBF$_4$	DMF	43
8	[{PdCl(allyl)}$_2$]	Cy$_3$P·HBF$_4$	DMF	58
9	[{PdCl(allyl)}$_2$]	Cy-JohnPhos	DMF	60
10	[{PdCl(allyl)}$_2$]	XantPhos[f]	DMF	51
11	[PdCl$_2$(dppf)]$_2$[g]	–	DMF	54
12	[Pd(Ph$_3$P)$_4$][g]	–	DMF	66

[a] Reaction conditions: **5a** (0.12 mmol), **6a** (0.1 mmol), Pd source (2.0 mol%), ligand (6.0 mol%), in the given solvent (c 0.2 M) at 100 °C for 2 h. [b] Yield of isolated product. [c] Run at 150 °C. [d] Using **6a** (1.5 equiv). [e] Run at 40 °C for 16 h. [f] 3.0 mol%. [g] 4.0 mol%.



Decarboxylative Vinylation

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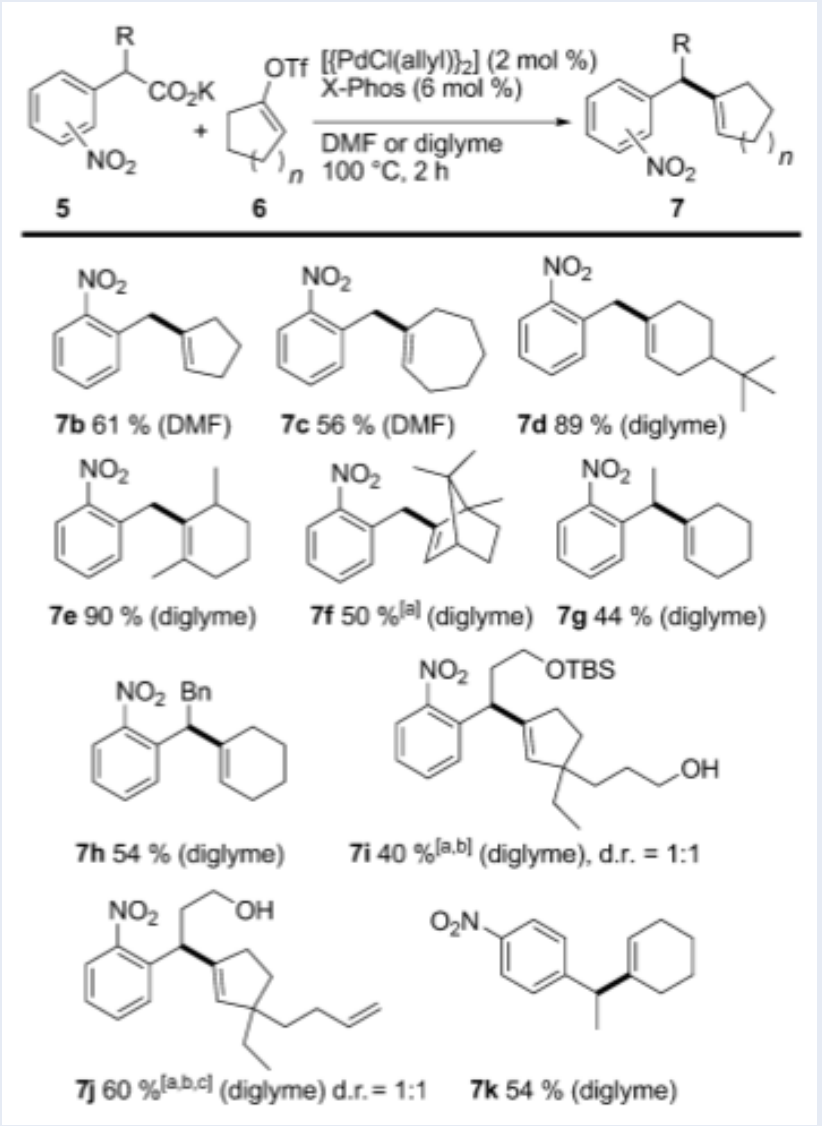
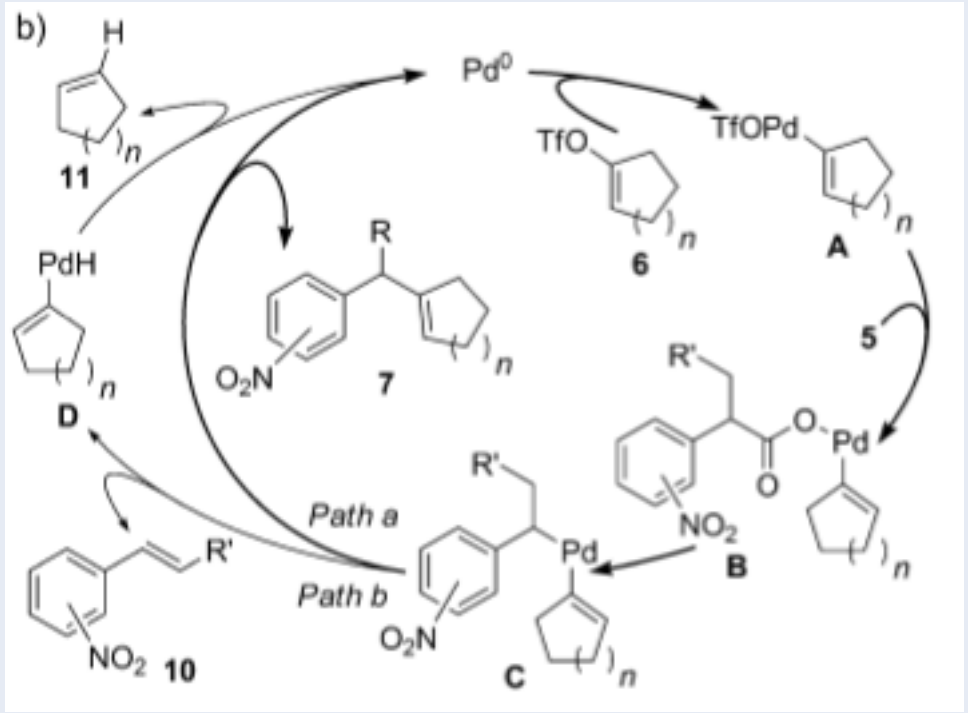
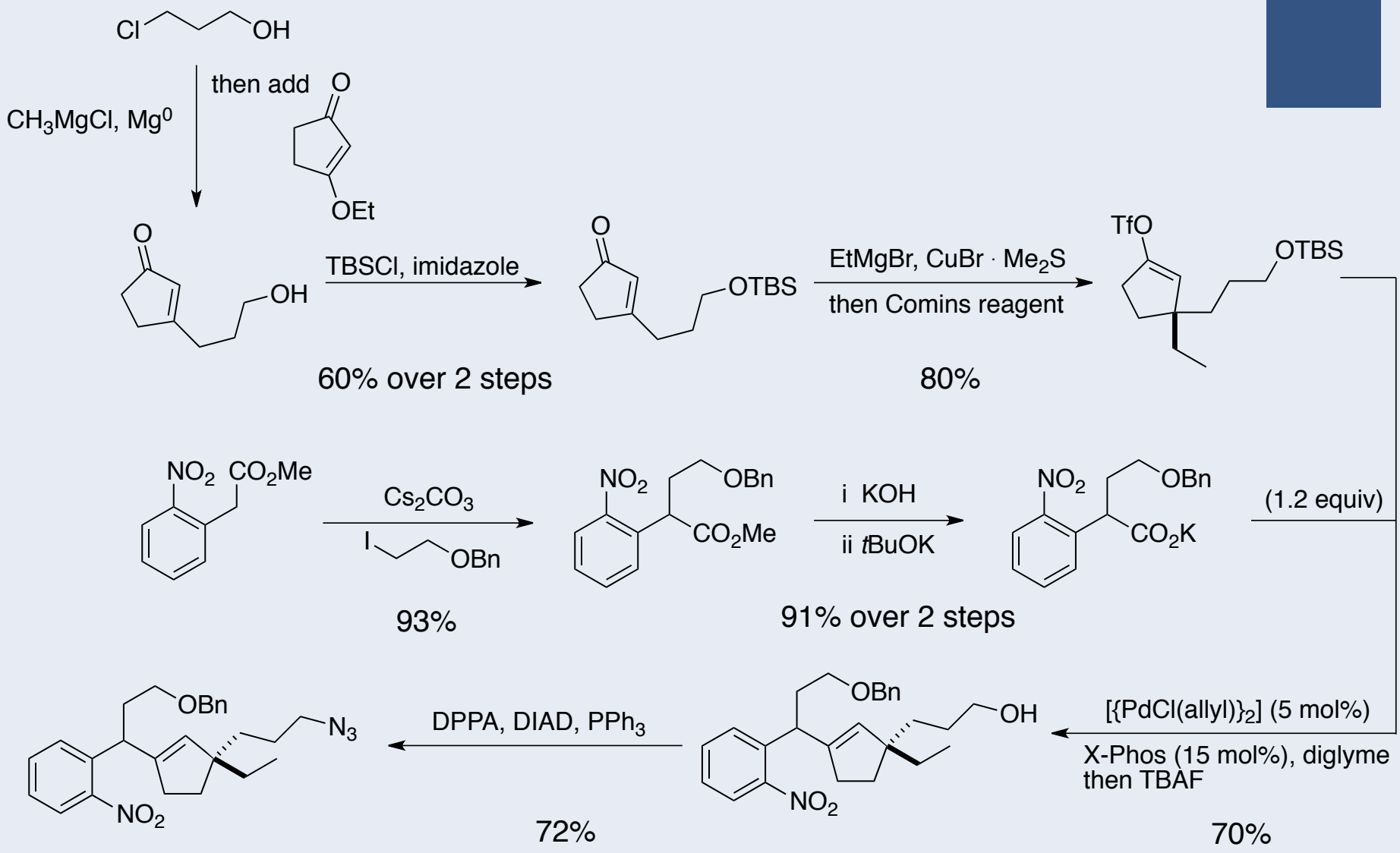




Total Synthesis of (±)-Goniomitine



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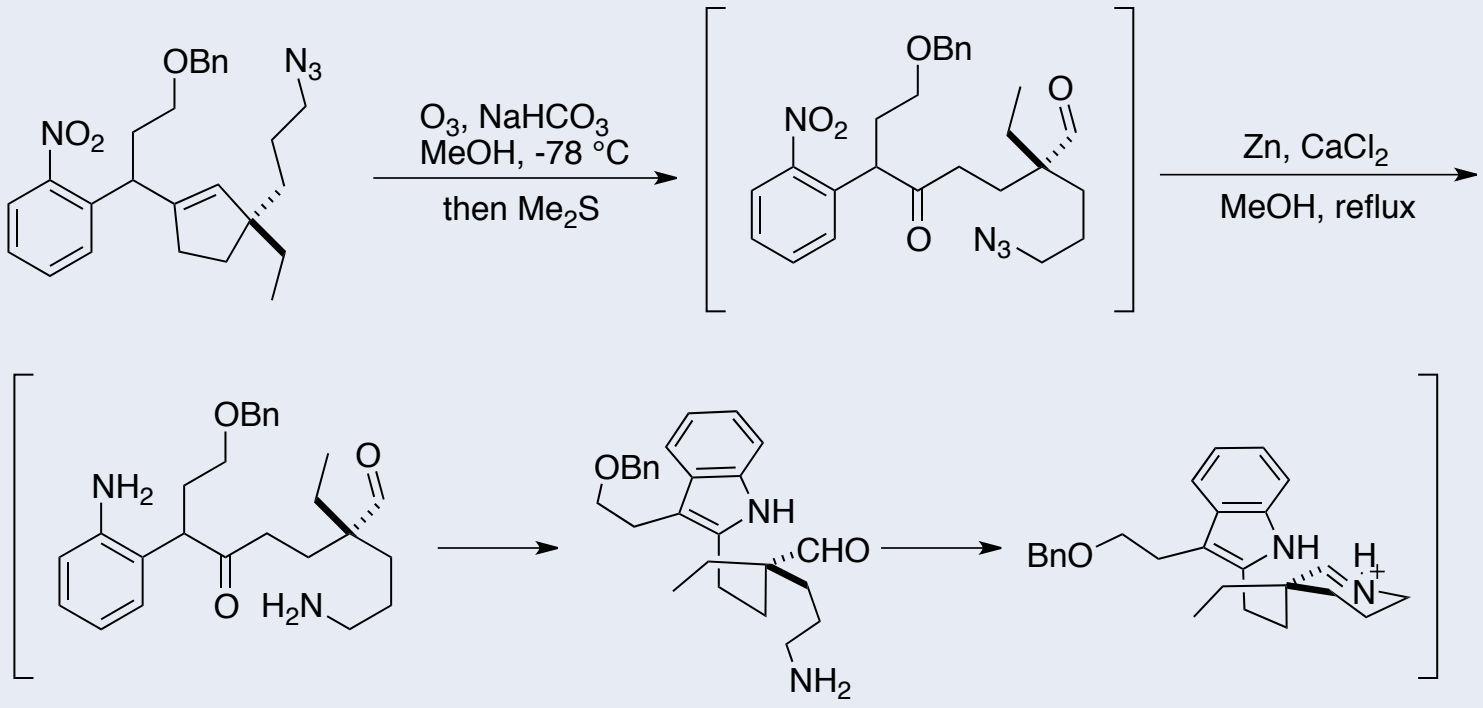


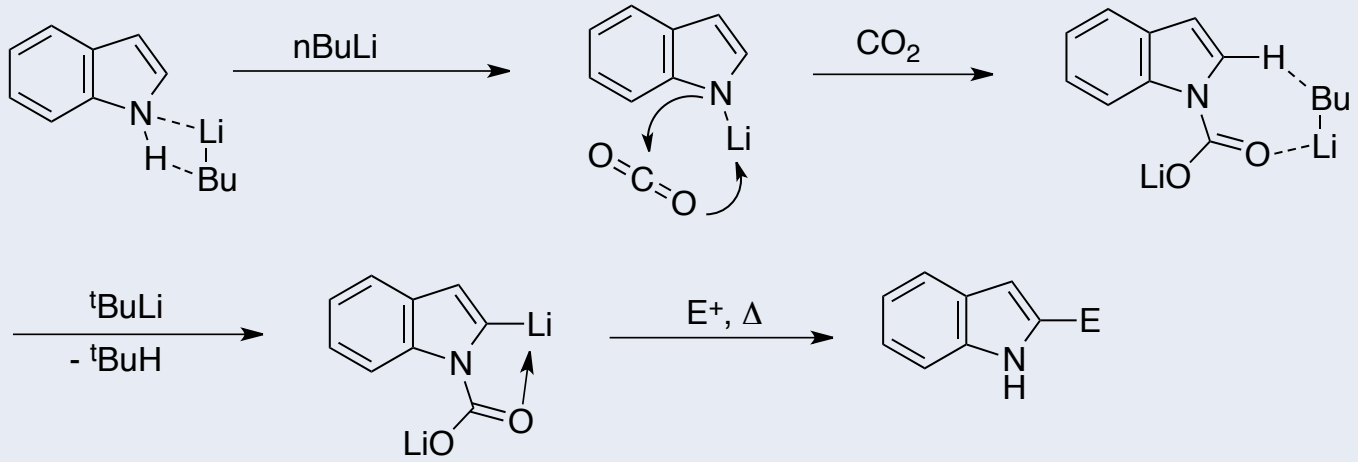
Conclusion

- **Seven linear steps** with two key steps:
  a. *Pd-catalyzed decarboxylative coupling reaction* between potassium nitrophenyl acetates and vinyl triflates
  b. *One-pot integrated oxidation/reduction/cyclization (IORC)* in a high regio-, chemo-, and diastereo-selective manner

- No rational/good explanation for some additives in some steps (*i.e.* azide/nitro reduction with $Zn/CaCl_2$/ MeOH) → *try and error*

- Racemic goniomitine is as cytotoxic as the natural occuring (−)-goniomitine (against cancer cells)

Carbon dioxide as protecting and directing group (Katritzky *et al. Tet. Lett.* **1985**, *26*, 5935-5938)



Proposed Biosynthesis starting from Vincadifformine