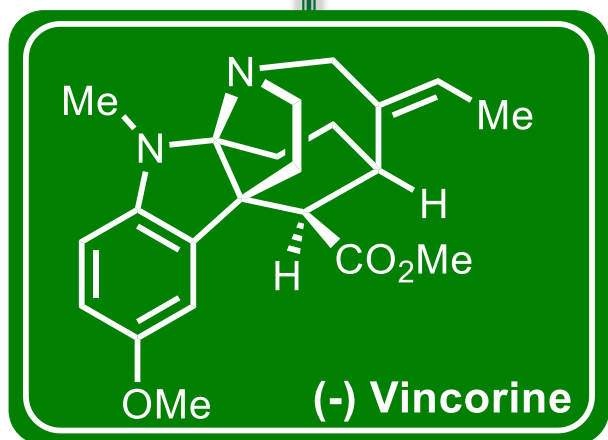


Total Synthesis of (-) Vincorine

Proposed by Gilles Galvani – Equipe CoSMIT, Postdoc Lermite



➤ **Vinca alkaloid natural products** exhibit diverse pharmacological properties which have been studied for the development of anticancer agents (vinblastine), vasodilators (vincamine), antipsychotics and anti-hypertensives (reserpine).

➤ **(-) Vincorine** is a compound of this family which presents a singular tetracyclic core constituted by a **strained 7 membered azepanyl ring fused with a pyrroloindole motif**. Potential anti-cancer activity of this molecule is under investigation.

➤ **3 Total Syntheses** of Vincorine have been realized :

* **Qin** et al. JACS 2009, *131*, 6013-6020

Racemic, 35 steps, 1 % overall yield

Key steps: Iminium cyclisation; Cu(I) cat. Cyclopropanation; Mukaiyama.

* **Ma** et al. JACS 2012, *134*, 9126-9129

18 steps, 5 % overall yield, 64 % ee

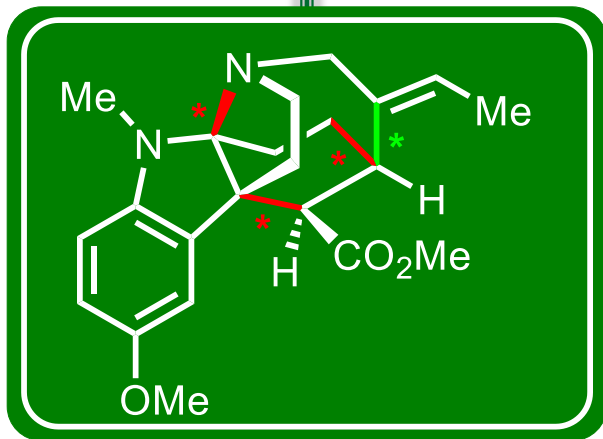
Key steps: Iminium cyclisation; Asymmetric Michael; Oxidative coupling.

➤ **The last one** is the purpose of the present Total Synthesis Problem. Based on an efficient organocatalytic key step, it prevails as the most valuable synthesis strategy.

* **MacMillan** et al. JACS 2013, *135*, 6442-6445

9 steps, 9 % overall yield, 95 % ee

Key steps: Catalytic cascade cyclisation, 9-membered azepanyl ring cyclisation

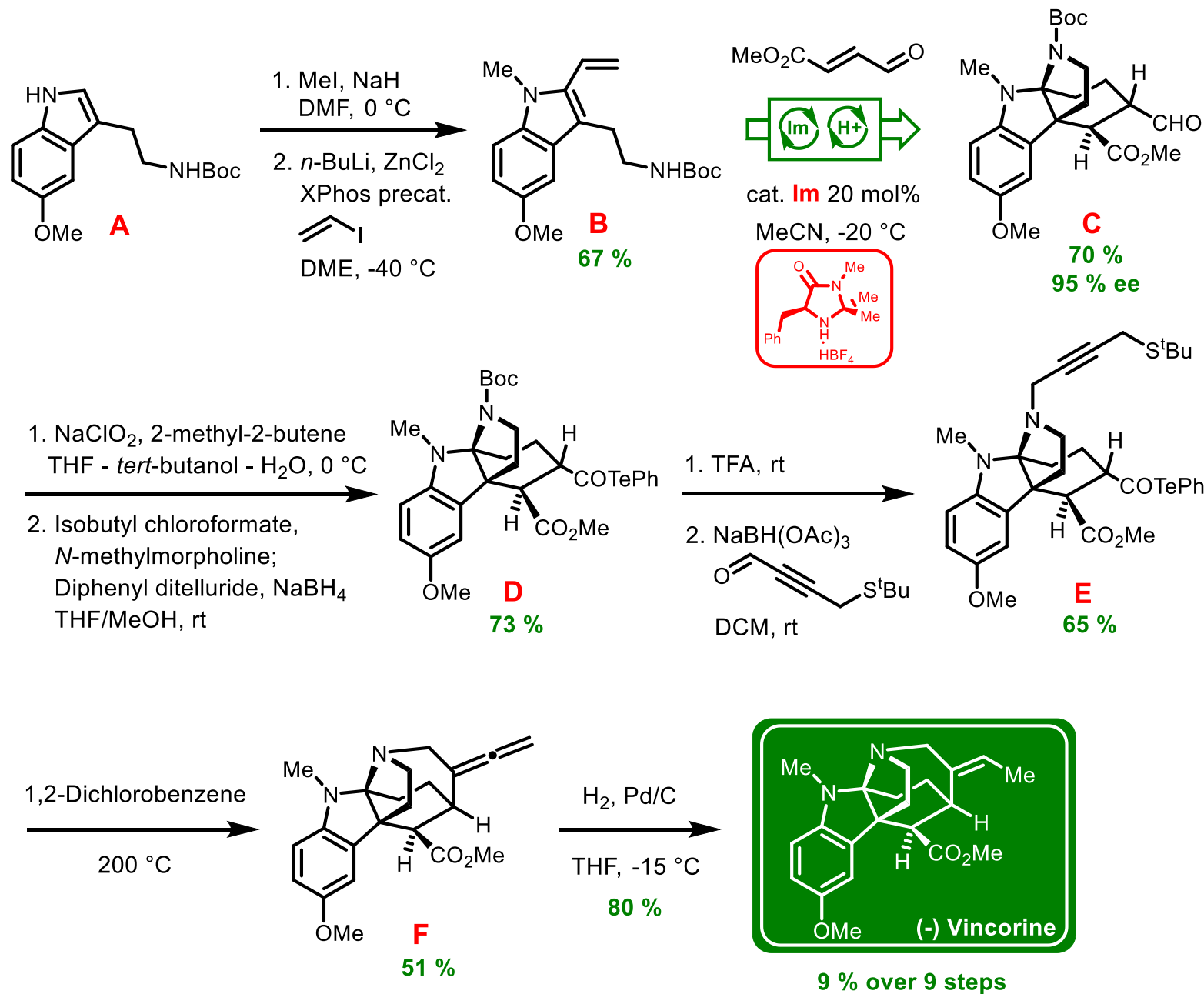


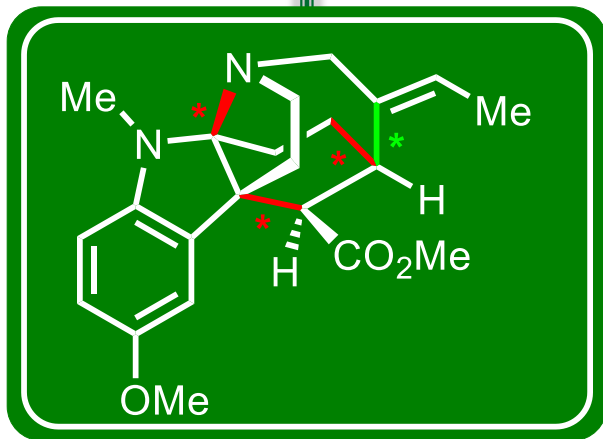
* Enantioselective
Organocatalytic Cascade

* Seven membered Azepanyl
formation

➤ Response :

✓ Structures of
B, C, D, E, & F



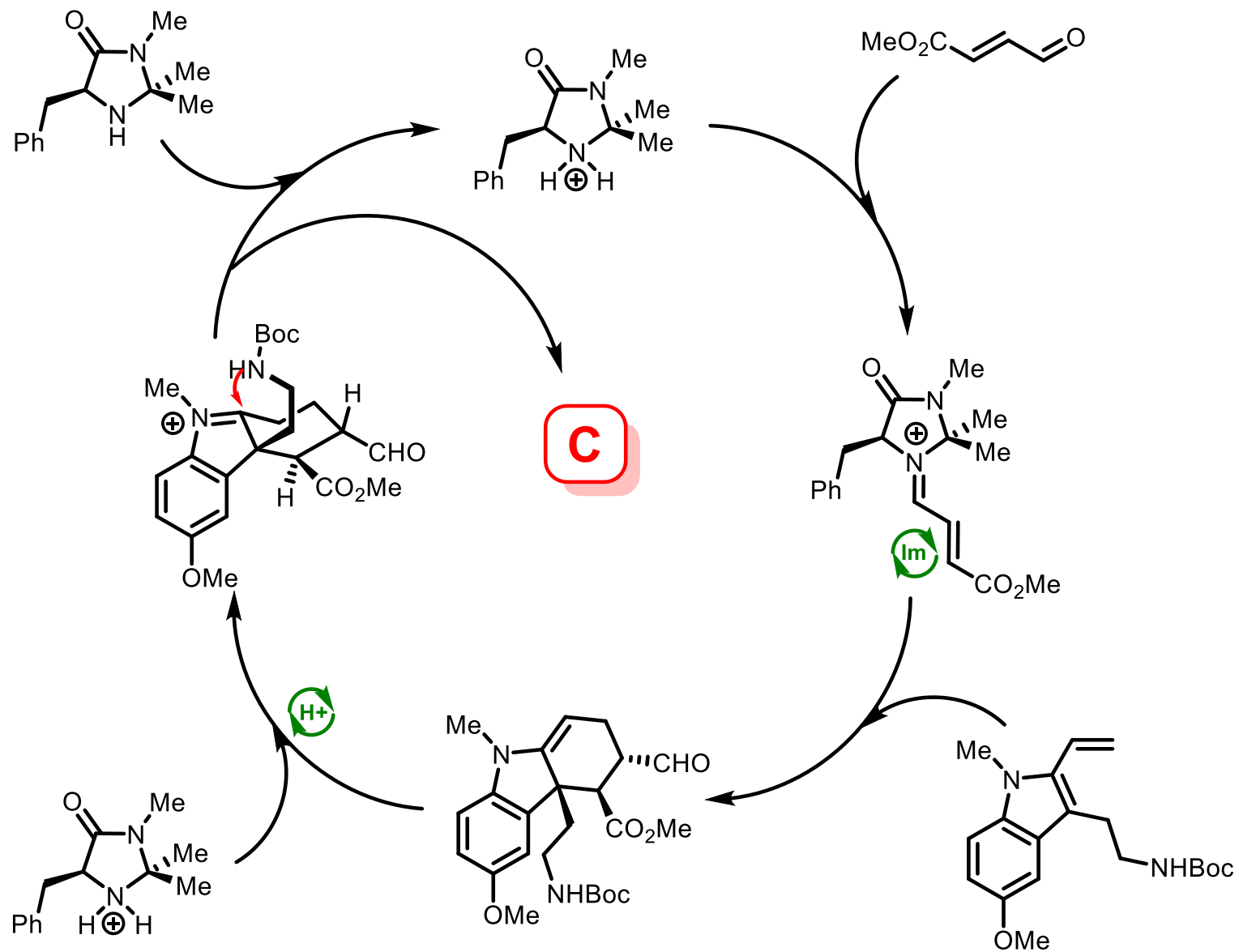


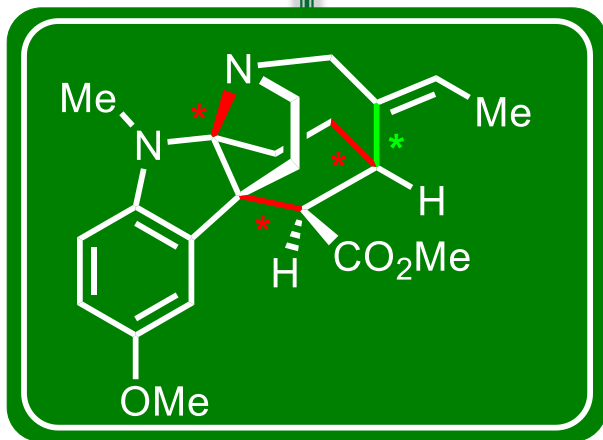
* Enantioselective
Organocatalytic Cascade

* Seven membered Azepanyl
formation

➤ Response :

✓ Proposed pathway
for **imidazolidinone**
catalytic event.





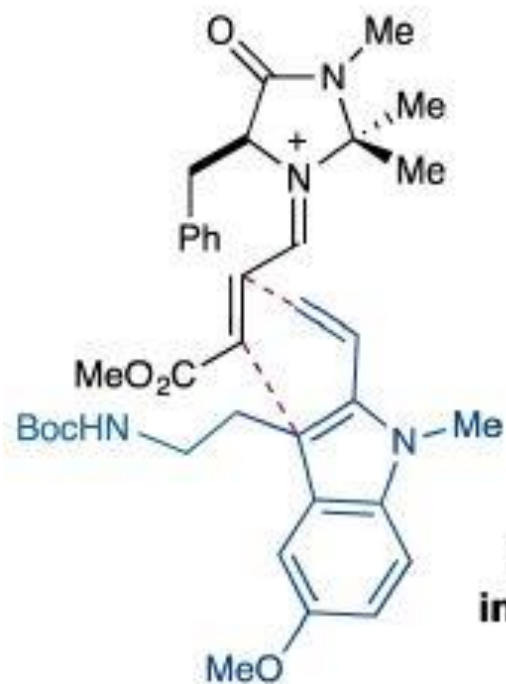
* Enantioselective
Organocatalytic Cascade

* Seven membered Azepanyl
formation

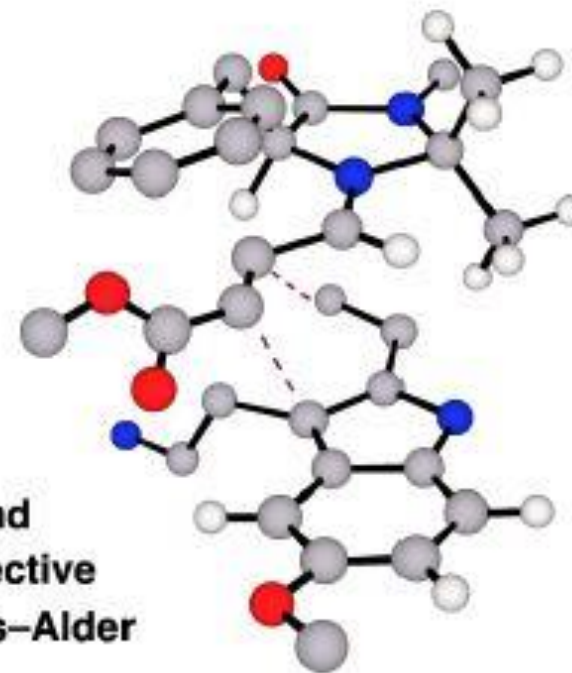
➤ Response :

✓ Proposed Asymmetric
Diels-Alder Transition
State.

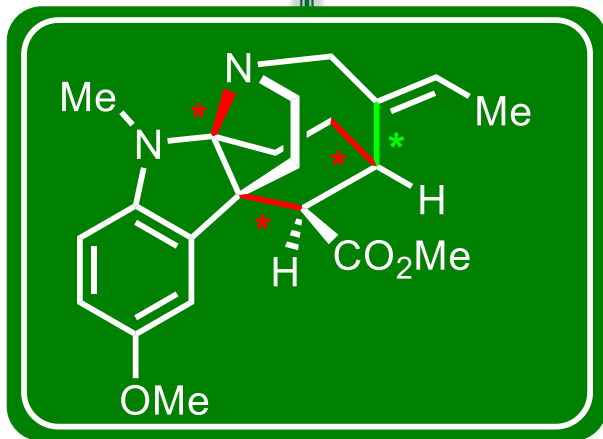
(TS-A) Proposed Asymmetric Diels–Alder Transition State



≡



endo- and
enantioselective
iminium Diels–Alder



* Enantioselective
Organocatalytic Cascade

* Seven membered Azepanyl
formation

➤ Response :

✓ Mechanism of
transformation from
E to F

