Université du Québec
à Trois-Rivières

Strategies for sustainable total syntheses of natural products

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Progrès en Développement Durable - Saguenay

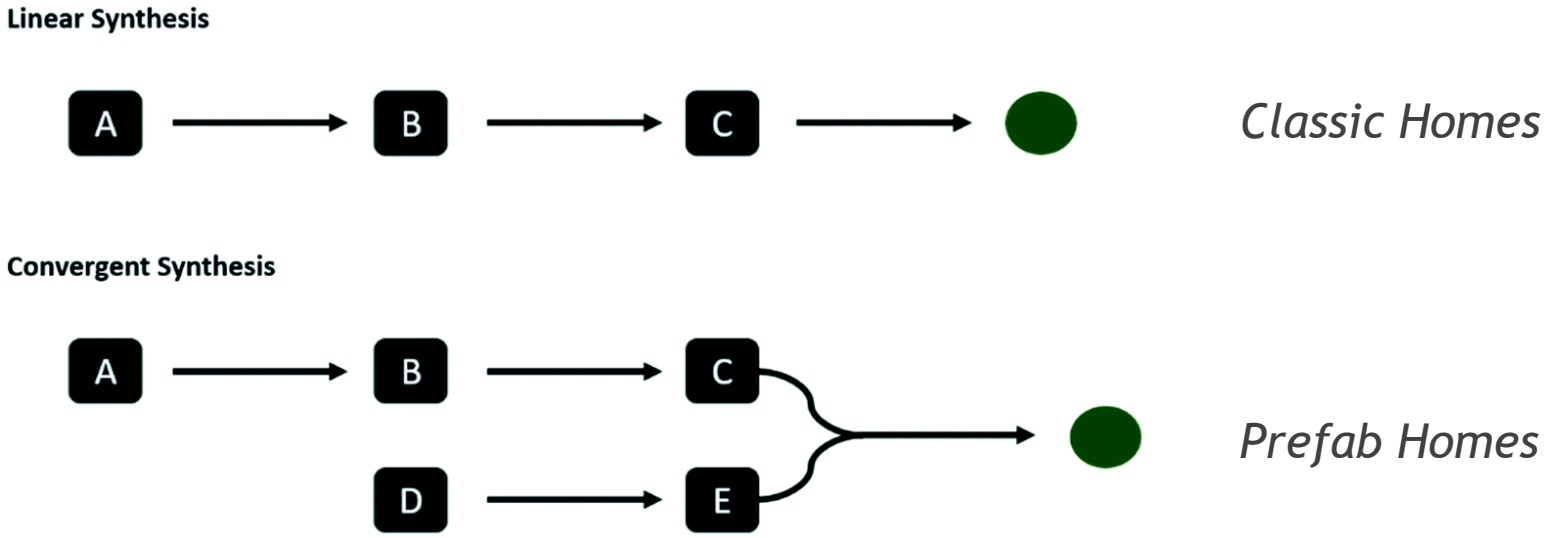
Total synthesis

- *What is total synthesis ?*
  - Chemical synthesis of a complex molecule, often a natural product, from simple, commercially-available precursors.

- *Why is total synthesis useful ?*
  - Extraction from natural sources inefficient or wasteful
  - Structure elucidation and access to derivatives

Total synthesis

- Two main approaches: linear or convergent.

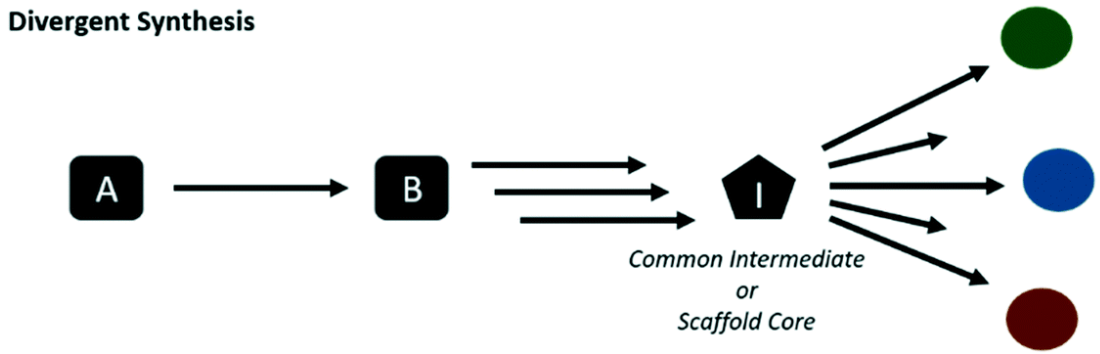


  - Many steps for a single target
  - Not always adapted to the synthesis of derivatives

Scheme adapted from: *React. Chem. Eng.*, **2021**, *6*, 27-51.

Total synthesis

- Alternative approach: divergent.



  - Allows access to many derivatives
  - Linear part might require wasteful steps

Scheme adapted from: *React. Chem. Eng.*, **2021**, *6*, 27-51.

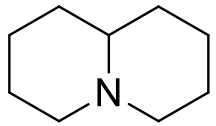
Objectives for sustainability

- In our opinion, to exploit total synthesis more sustainably, three objectives must always be put forward:

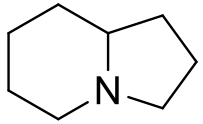
1) The synthetic pathway should give access to a family of compounds (*i.e.*, divergent approach).
2) Core construction should be performed early via catalytic and energy-efficient processes.
3) Use of protecting groups should be limited as much as possible to late-stage synthetic steps.

Izidine alkaloids

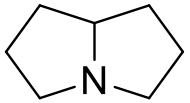
- Izidines are widespread structural motifs among alkaloid natural products.



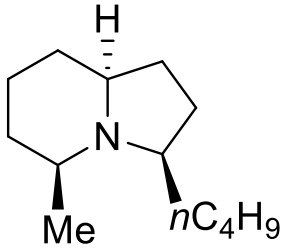
Quinolizidine core



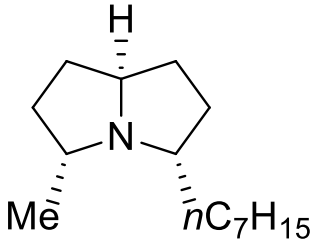
Indolizidine core



Pyrrolizidine core



Monomorine I



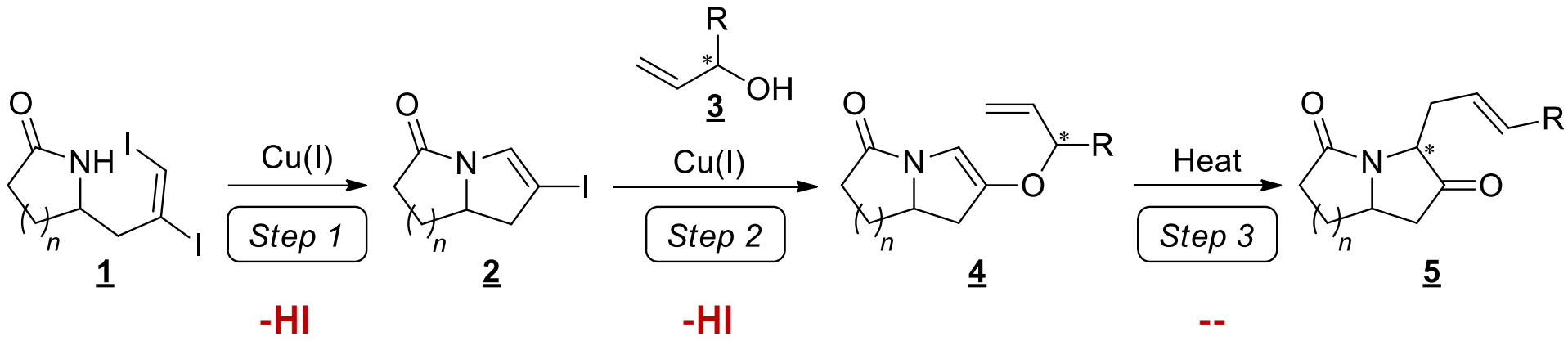
(+)-Xenovenine

Monomorium pharaonis
(Pharaoh ant)

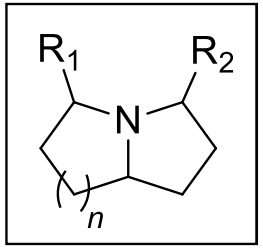
Phyllobates lugubris
(Lovely Poison Frog)

Izidine alkaloids

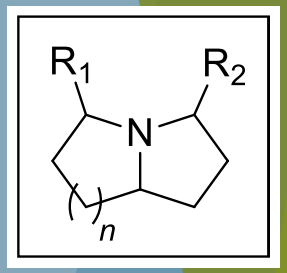
- Proposed 3-step sequence:



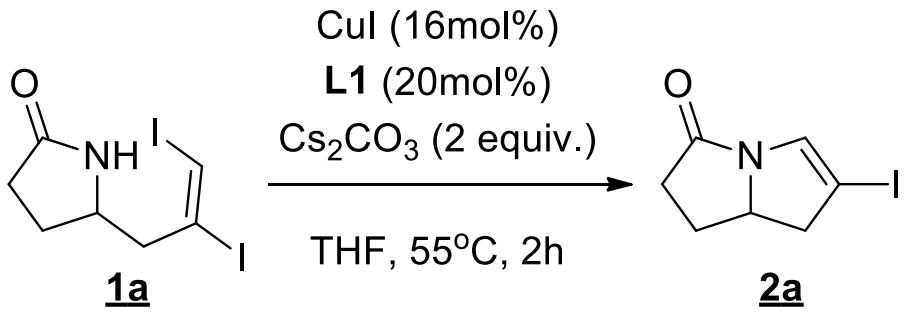
- Core synthesis with chemical handles
- Catalytic conditions and limited wastes
- No PGs required to access the bicyclic core

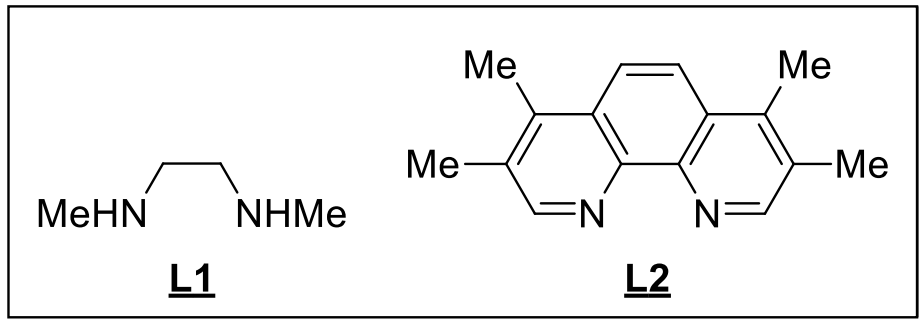


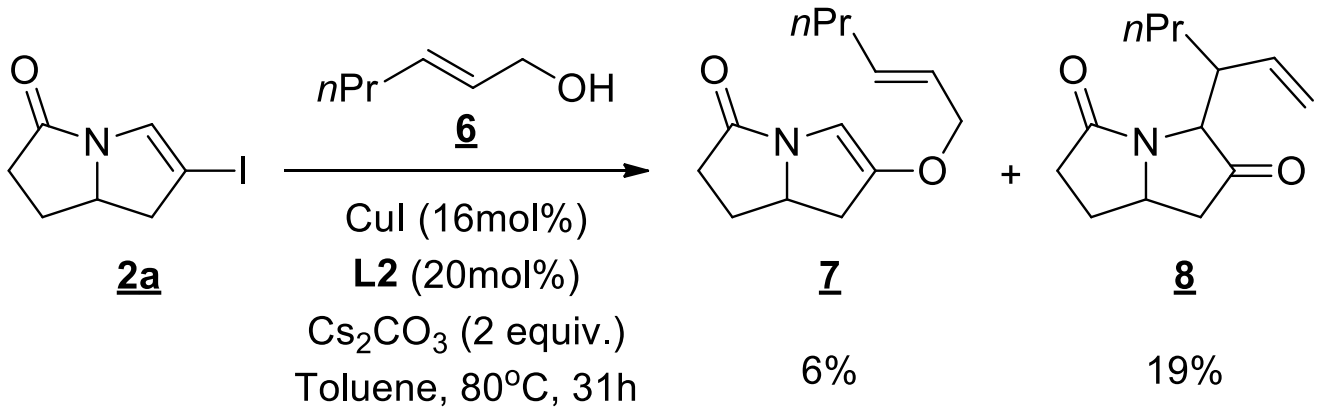
Izidine alkaloids – Pyrrolizidines



- Proof of concept with n=1

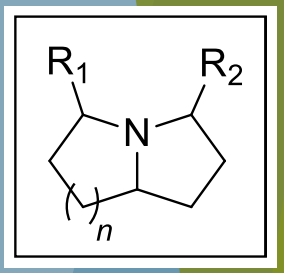




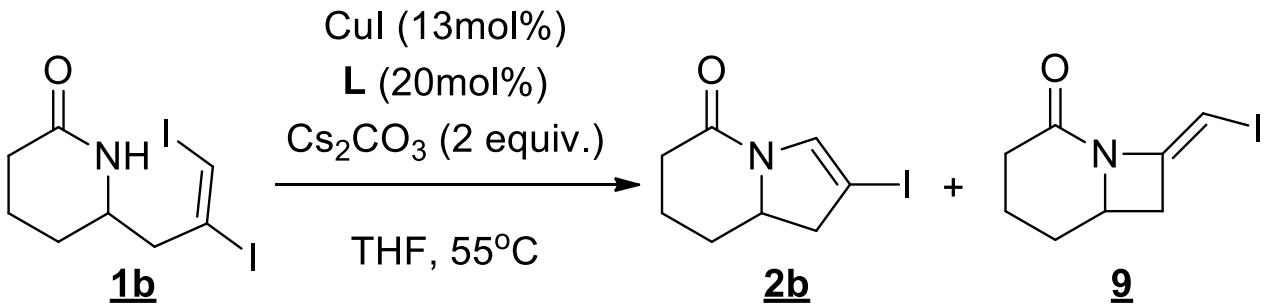


Eur. J. Org. Chem., **2020**, *17*, 2517.

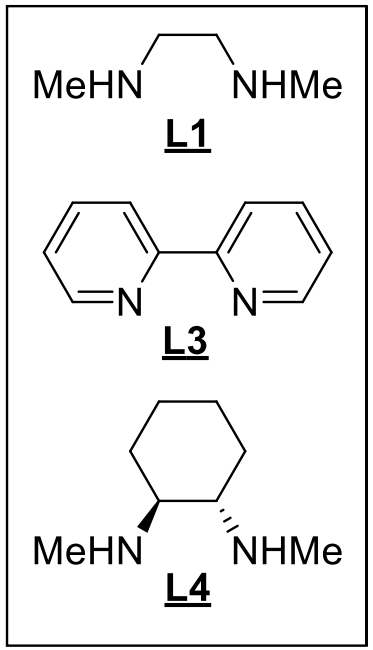
Izidine alkaloids – Indolizidines



- Surprise with n=2



Ligand	Reaction time	Global yield (**2b** + **9**)	Ratio **2b** : **9**
L1	3h	95%	1 : 5.4
L3	3h	88%	1 : 10.8
L4	24h	89%	1 : 2.0



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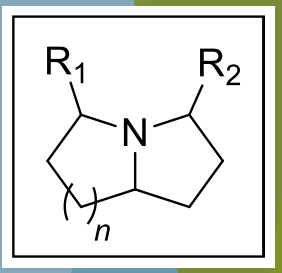
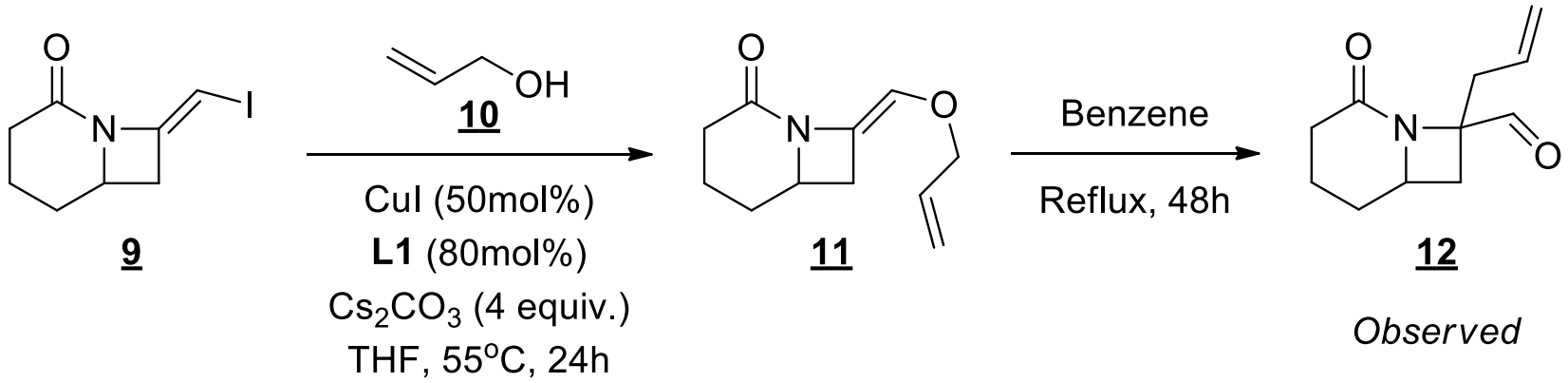
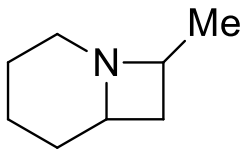
Izidine alkaloids – Indolizidines



- Proof of concept with peculiar bicyclic compound



- Interest ?
  - Synthesis of ε-coniceine derivatives



ε-Coniceine

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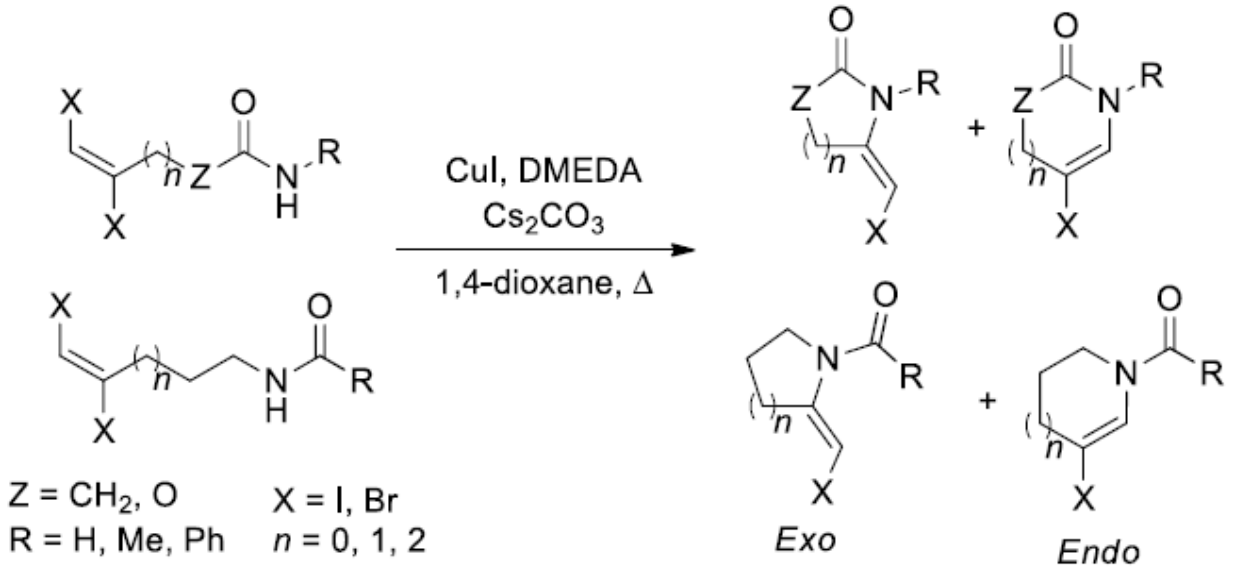
Cyclisation of other substrates

- Extension of our method to other substrates



  - We demonstrate that exo/endo selectivity is largely determined by ring strain, but that selectivity can also be modulated by varying reaction conditions.

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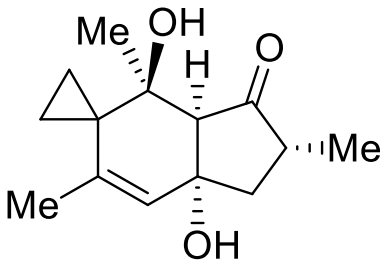
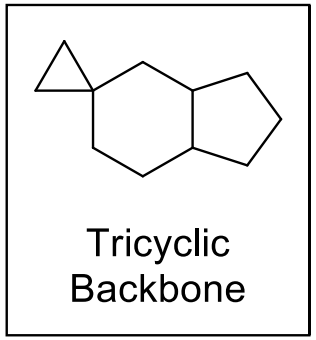
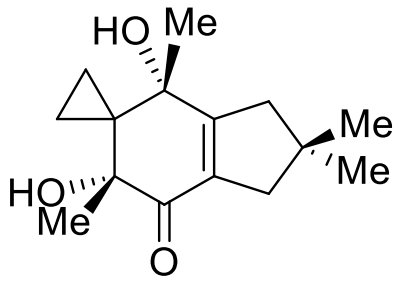
Illudane Sesquiterpenoids

- Illudane sesquiterpenoids are naturally occurring tricyclic bioactive compounds found in many plants and fungi.



Ptaquilosin



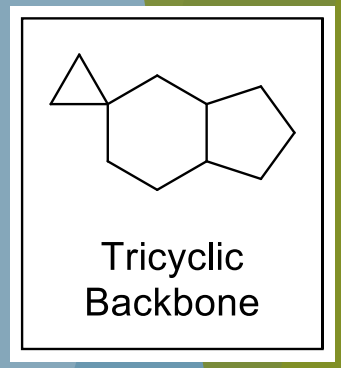


Illudin A

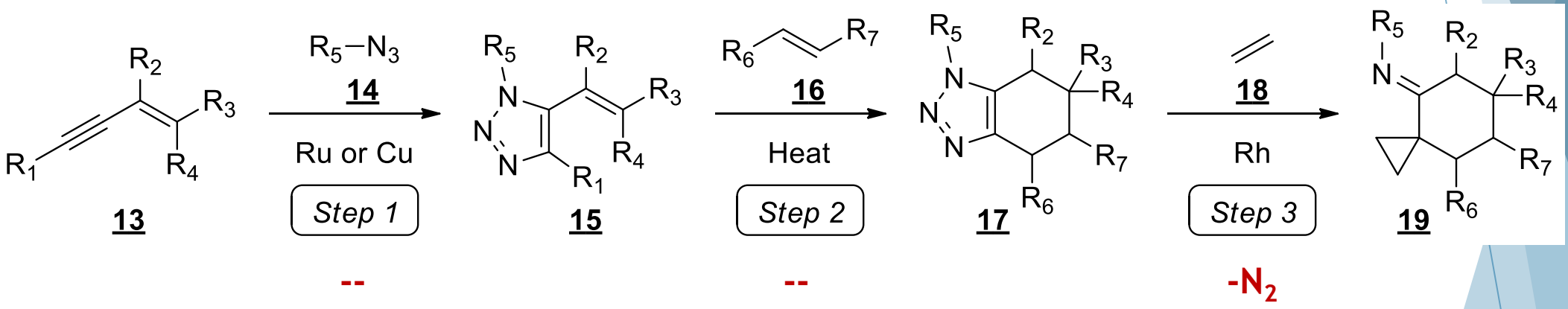
Pteridium aquilinum
(Bracken Fern)

Omphalotus illudens
(Eastern Jack-O'Lantern Mushroom)

Illudane Sesquiterpenoids



- Proposed 3-step sequence:



- Core synthesis with chemical handles
- Catalytic conditions and limited wastes
- Minimal PGs to access the tricyclic core

Conclusion

- Our 3 proposed objectives for sustainable total synthesis:
  1) Access to a family of compounds via a divergent approach
  2) Core construction performed early via catalytic and energy-efficient processes.
  3) Limited use of protecting groups

- Izidines Alkaloids
- Illudane Sesquiterpenoids

Acknowledgements

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UQTR
Université du Québec
à Trois-Rivières

GROUPE DE RECHERCHE
EN BIOLOGIE VÉGÉTALE (GRBV)

- Organizers of this conference

Questions ?