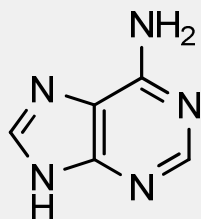


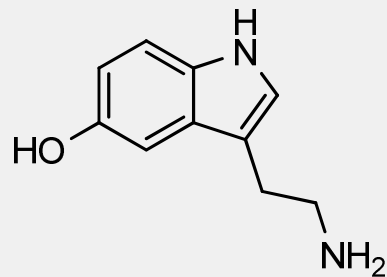
Csp³-H Amination Reactions: Different methods and Applications to Total Synthesis

Introduction

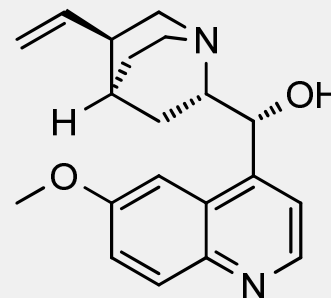
- Amines are ubiquitous in bioactive molecules



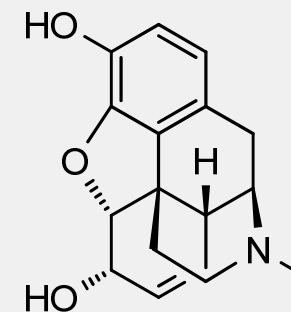
Adenine



Serotonin



Quinine

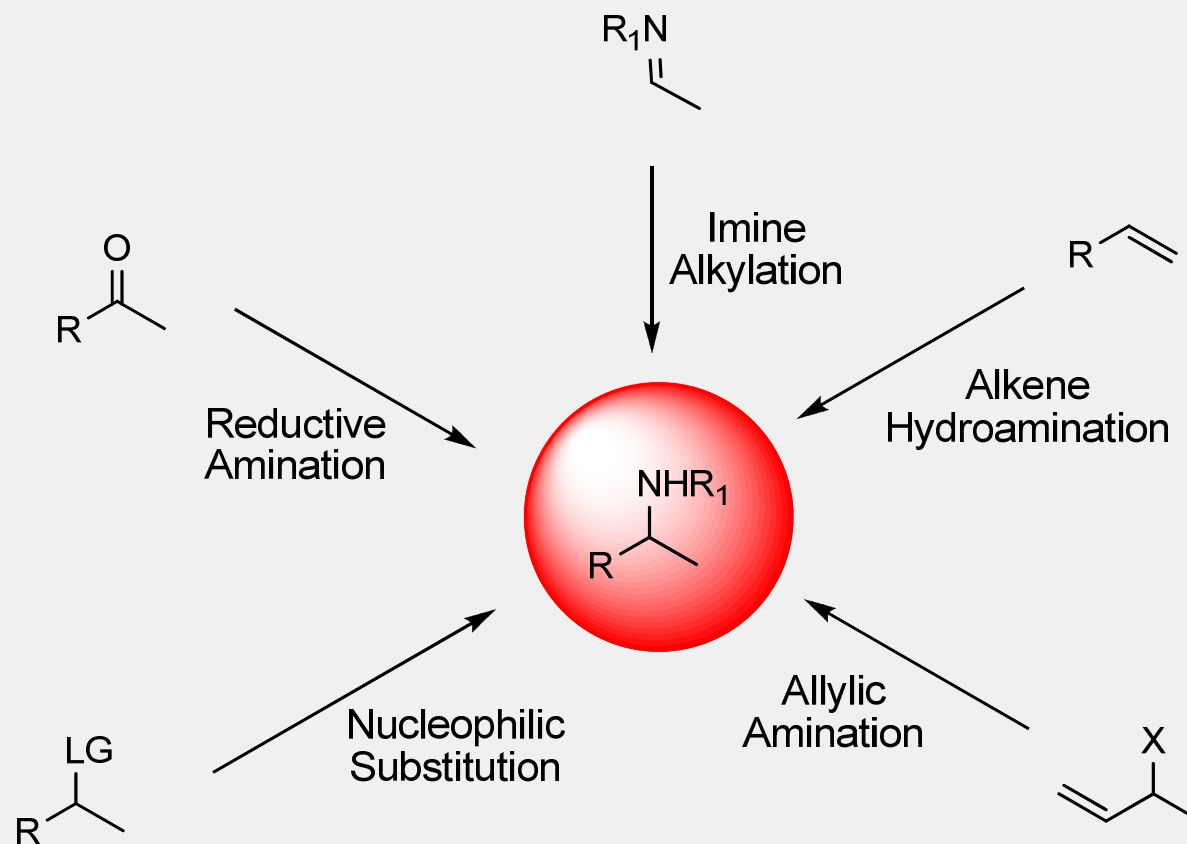


Morphine

- Constant development of new synthetic methods for the preparation of amines

Introduction

- Most widely employed approaches:

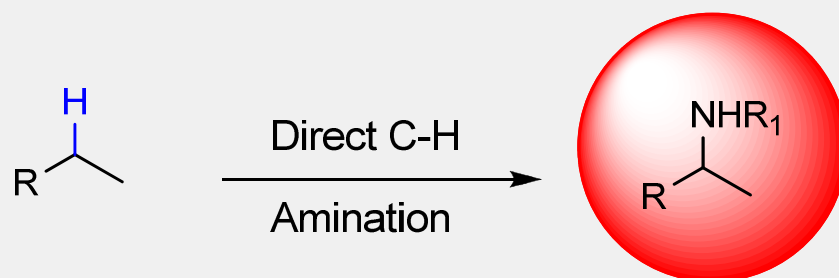


Transformation of pre-installed functional groups

Introduction

- Direct C-H Amination:

- Avoids installation of functional groups and their removal
- Complementary opportunities to usual aminations

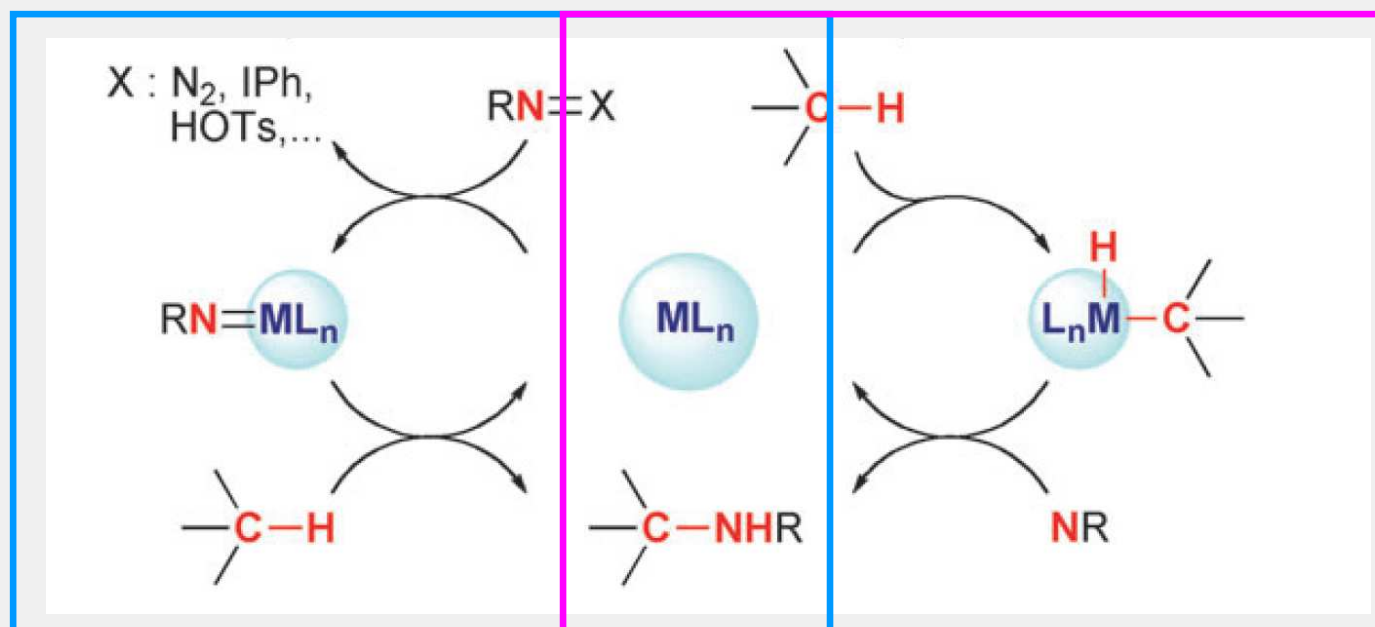


- Challenging problems such as C-H bond energy and selectivity
- Focus on Csp³-H aminations

Introduction

Different kinds of Csp³-H amination Reactions

- Metal-Catalyzed C-H amination reactions



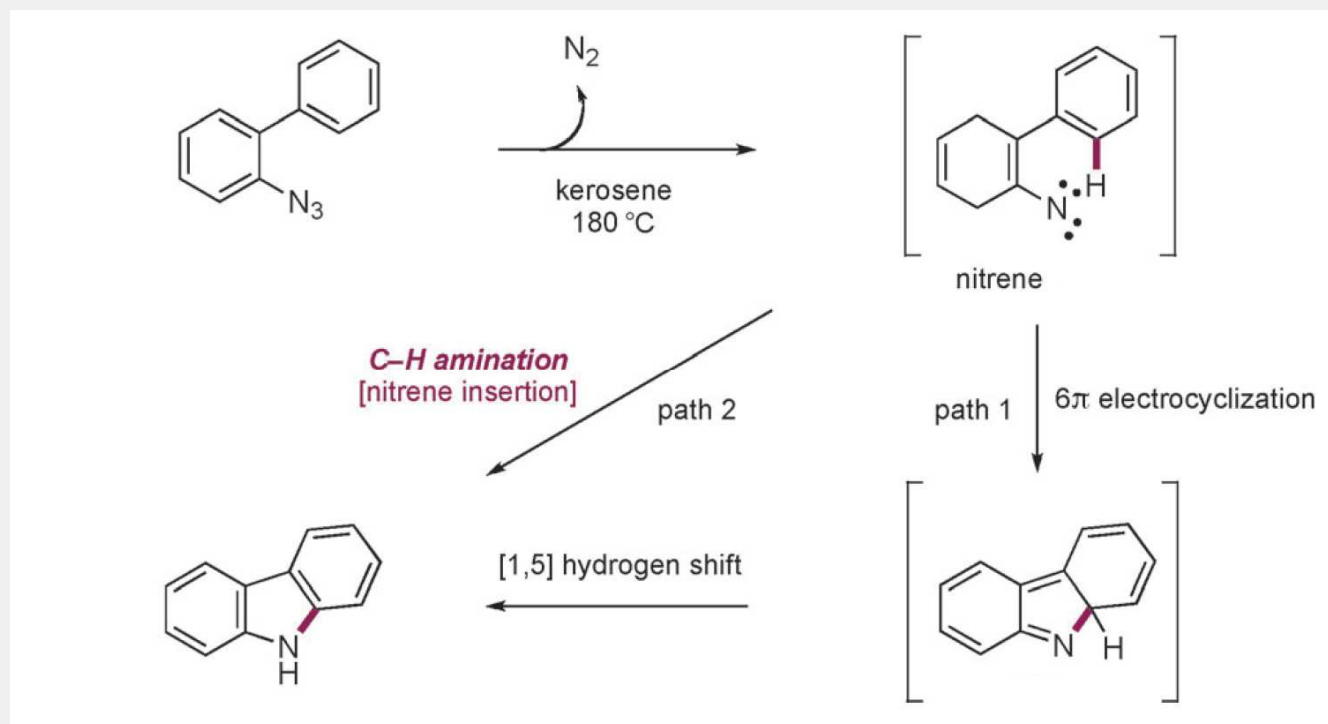
C-H Nitrene insertion Transition metal-Catalyzed C-H Activation

- Radical cyclizations: Hofmann-Löffler-Freytag Reaction
- Oxidation of C,N-Dianions

C-H Nitrene insertion

Reactivity of Nitrenes

- Nitrogen equivalent to carbenes
- Can be generated from azides by photolysis or thermolysis:

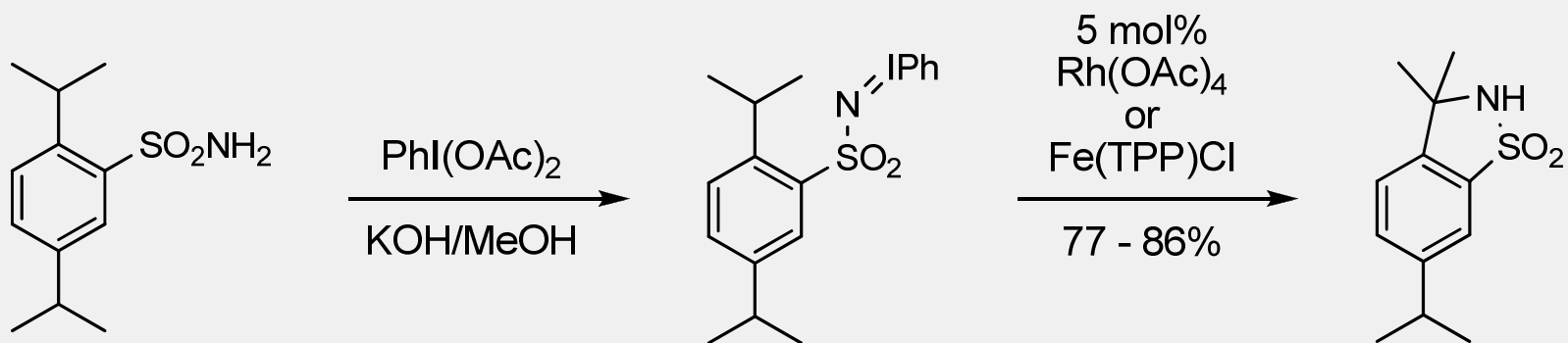


C-H Nitrene insertion

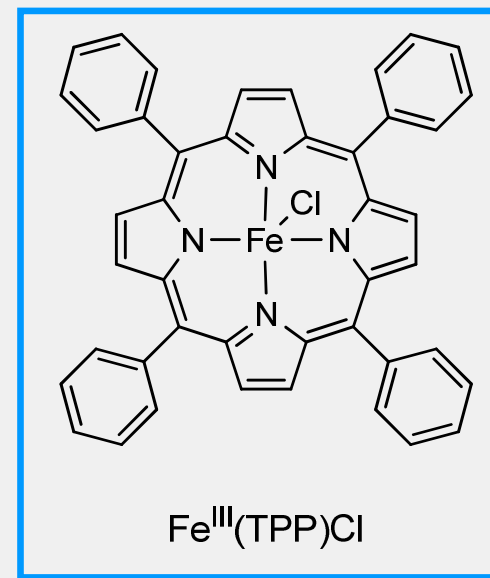
Metal-Catalyzed alternatives

- Control the reactivity of nitrenes:
 - Avoid competing processes
 - Site- and Stereo-selectivities
 - Mild reaction conditions

- Pioneering work from Breslow and Gellman:



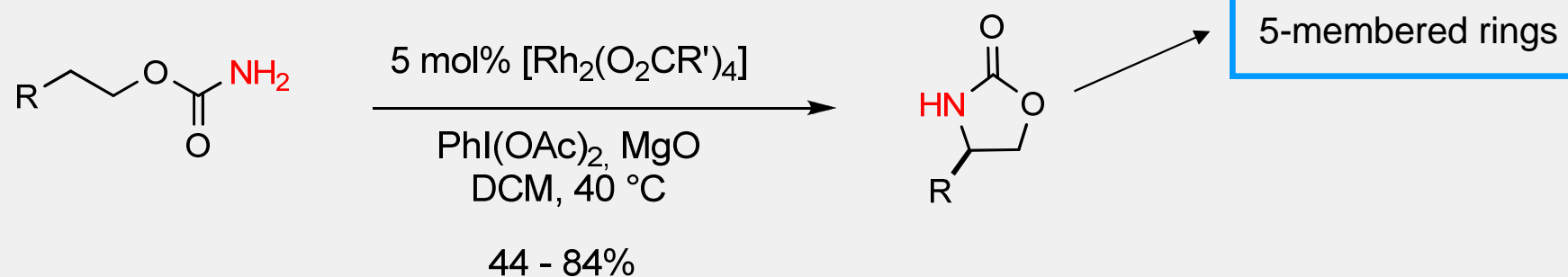
- Use of iminoiodanes: method of choice



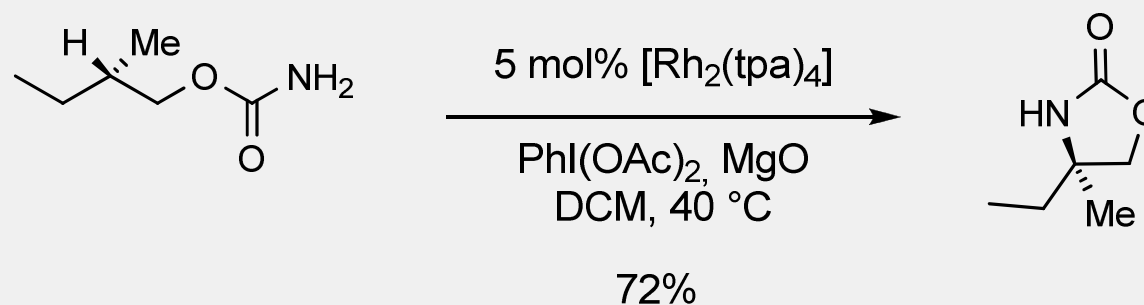
C-H Nitrene insertion

Intramolecular C-H insertions: Du Bois

- In-situ* formation of the iminoiodanes



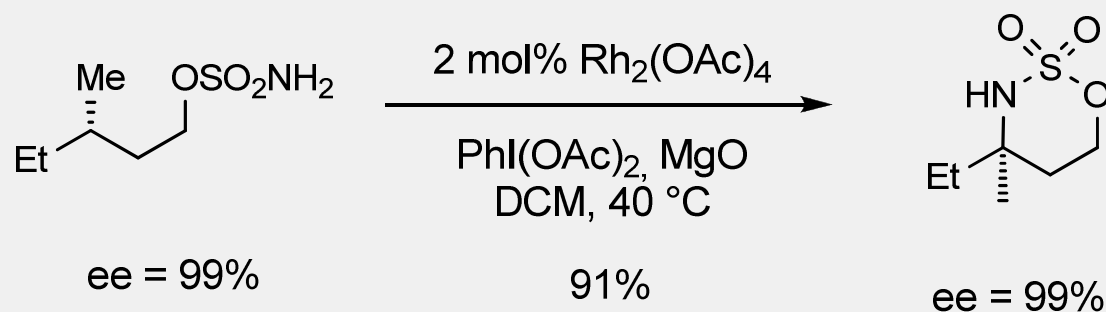
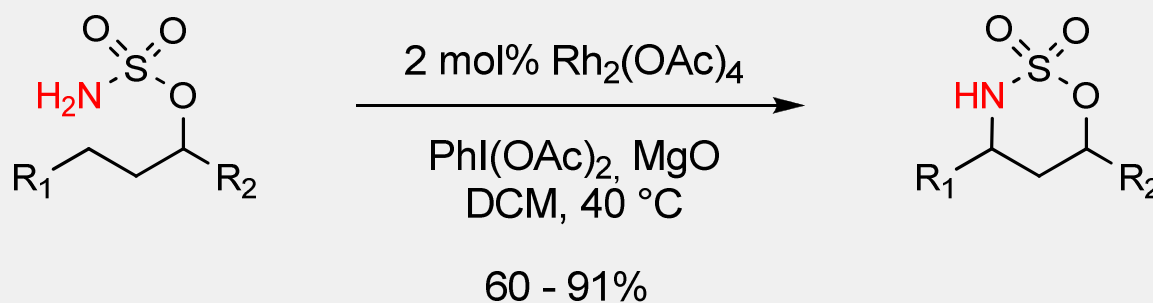
- Dirhodium catalysts: $\text{Rh}_2(\text{OAc})_4$ or $\text{Rh}_2(\text{tpa})_4$ (tpa = triphenylacetate)
- Reaction proceeds with retention of configuration:



C-H Nitrene insertion

Intramolecular C-H insertions: Du Bois

- Same observation from sulfamate esters

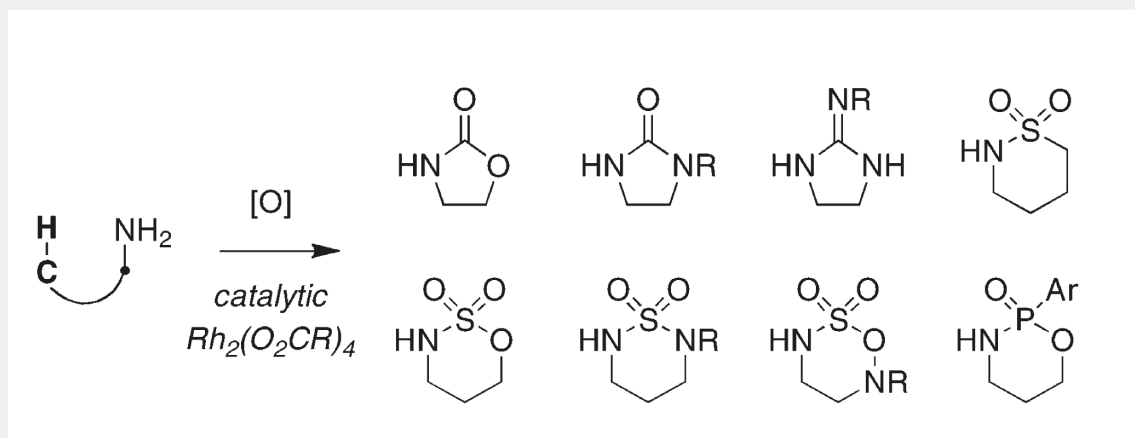


Formation of 6-membered rings

C-H Nitrene insertion

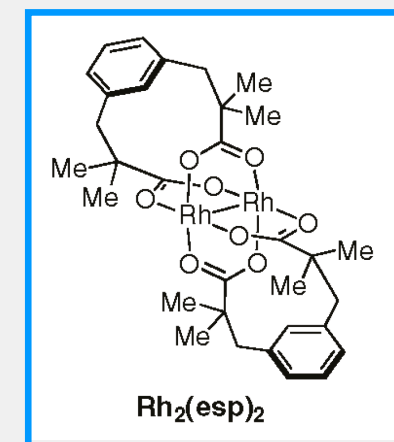
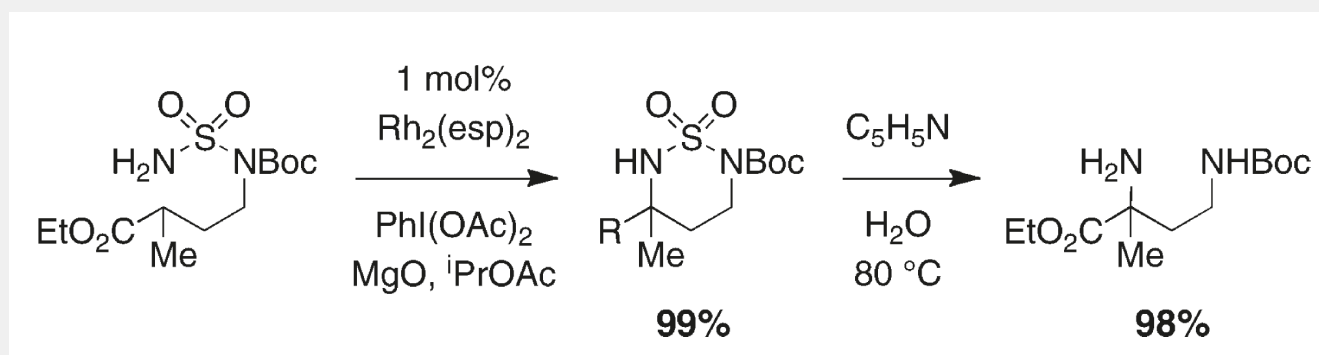
Intramolecular C-H insertions: Du Bois

- Synthesis from several N-containing starting materials



Presence of an EWG on the nitrogen

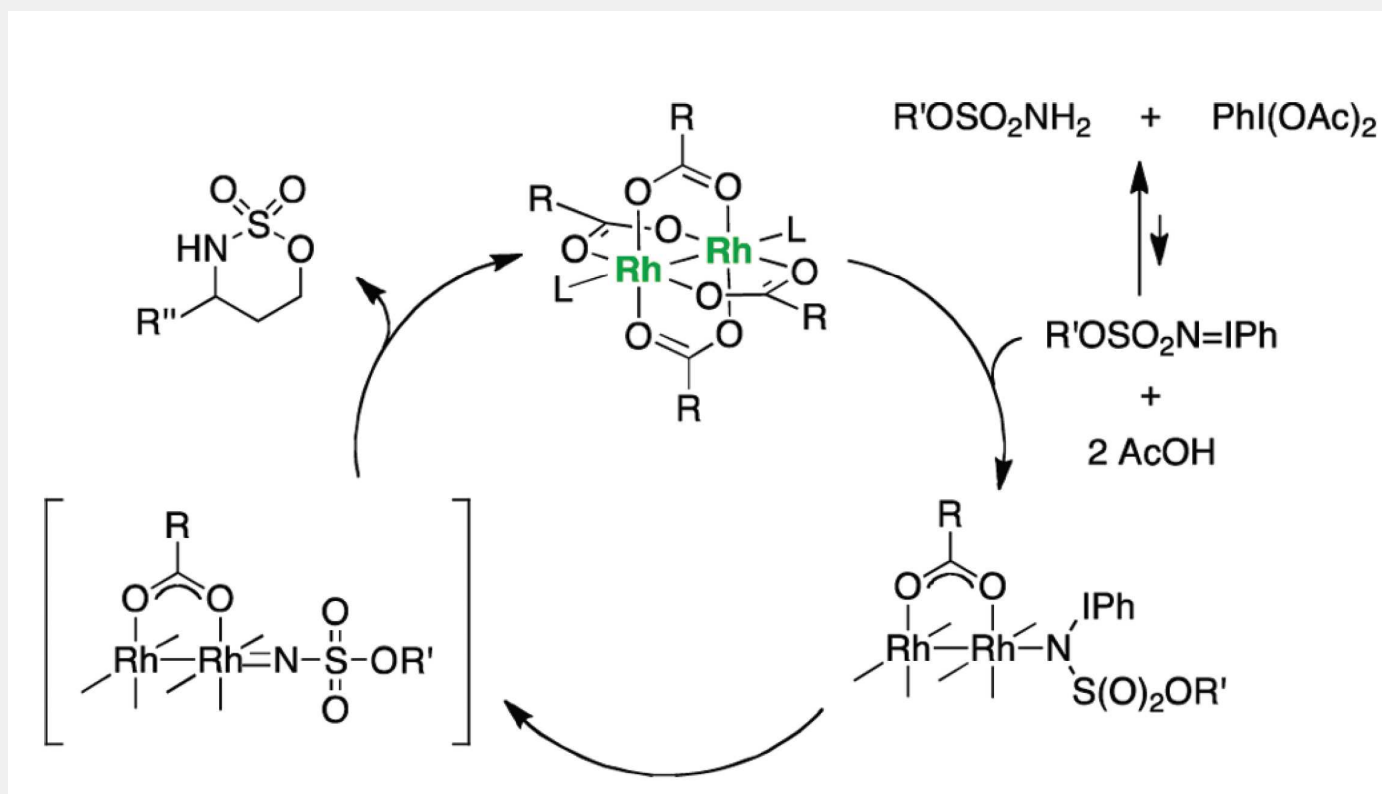
- $Rh_2(esp)_2$ catalyst: low loadings



C-H Nitrene insertion

Intramolecular C-H insertions: Du Bois

- Proposed mechanism:



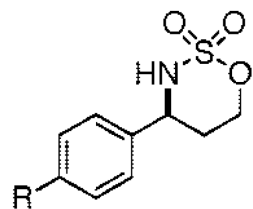
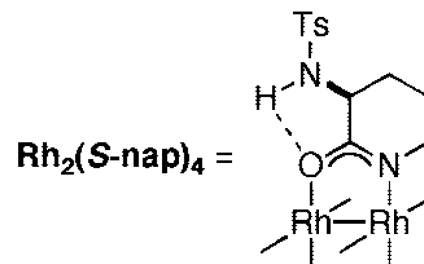
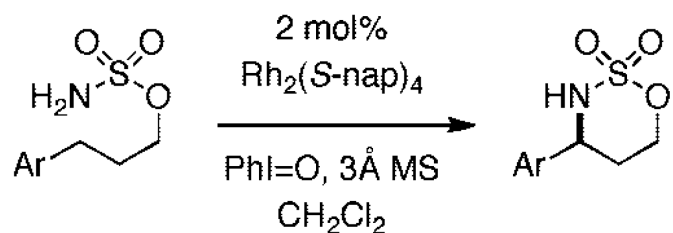
- Reactivity of C-H bonds:

Tertiary > ethereal ~ benzylic > Secondary >> Primary

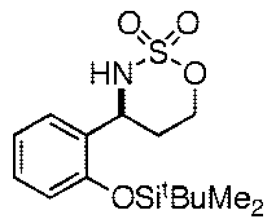
C-H Nitrene insertion

Intramolecular C-H insertions: Du Bois

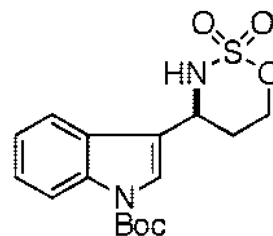
Enantioselective version



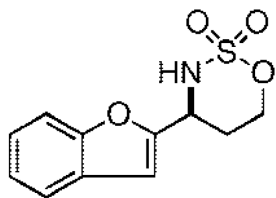
1. R = H 85%, **92% ee**
2. R = OMe 89%, **83% ee**
3. R = CF₃ 50%, **56% ee**



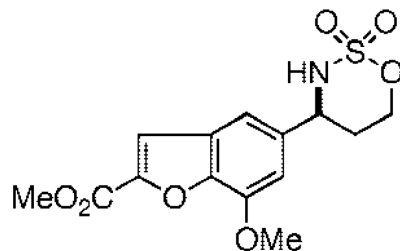
4. 45%, **85% ee**



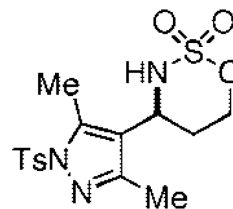
5. 98%, **92% ee**



6. 72%, **63% ee**



7. 87%, **99% ee**



8. 55%, **94% ee**

➤ Dirhodium carboxamidate complex

➤ Only benzylic and allylic C-H bonds

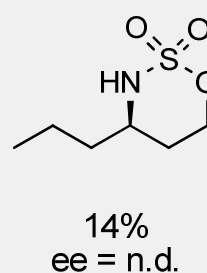
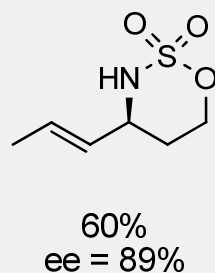
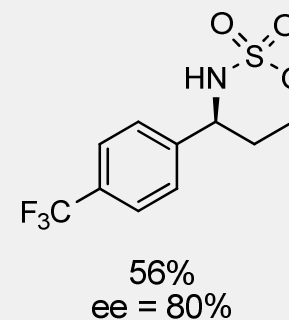
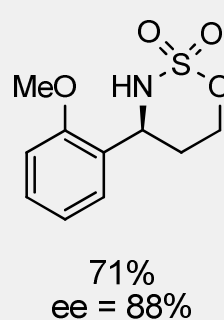
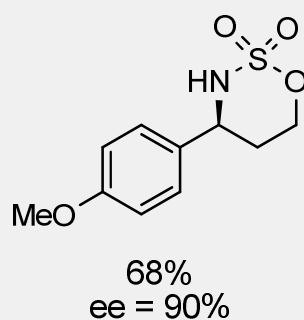
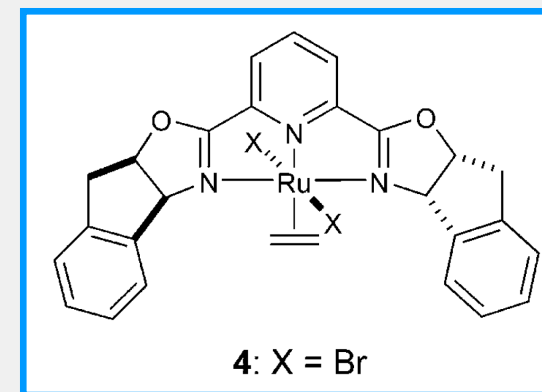
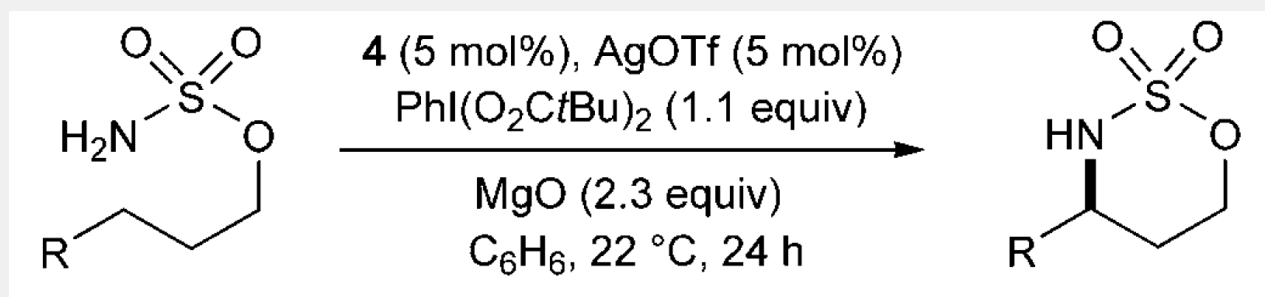
➤ Importance of the ligand-based H-bond

C-H Nitrene insertion

Intramolecular C-H insertions: Blakey

Enantioselective version

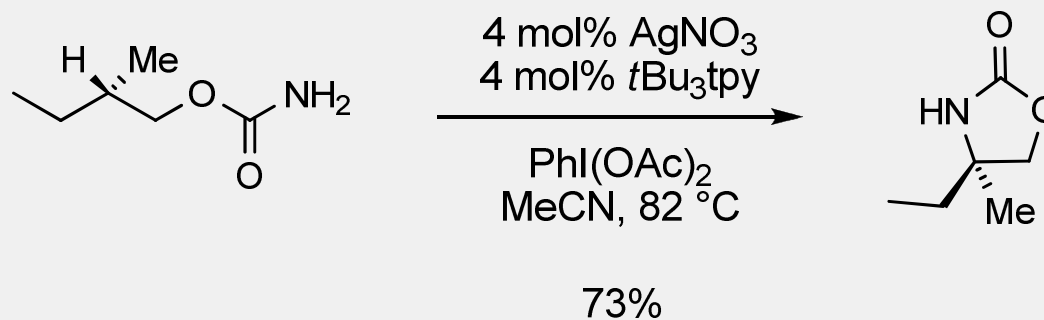
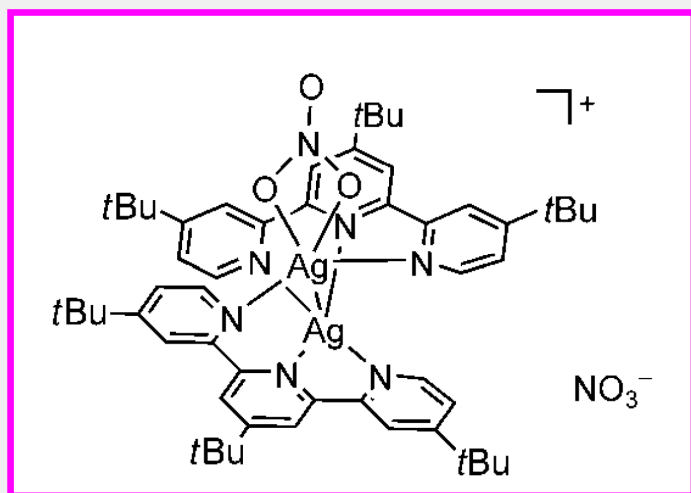
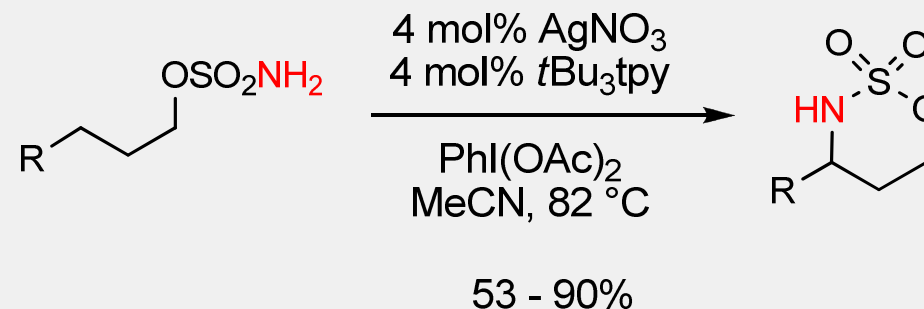
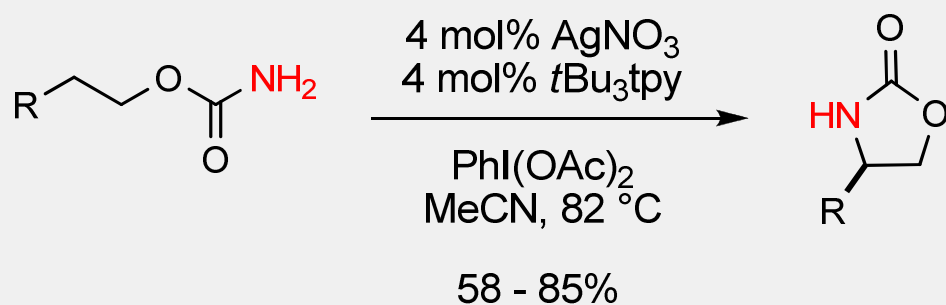
- Use of a Ru(pybox) catalyst



C-H Nitrene insertion

Intramolecular C-H insertions: He

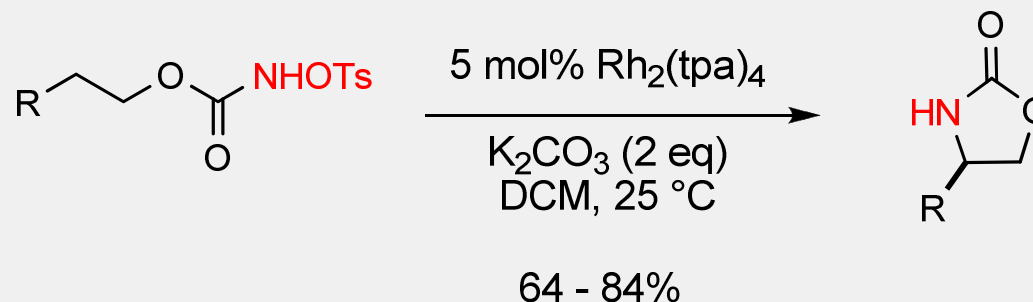
- Use of a Ag^I catalyst



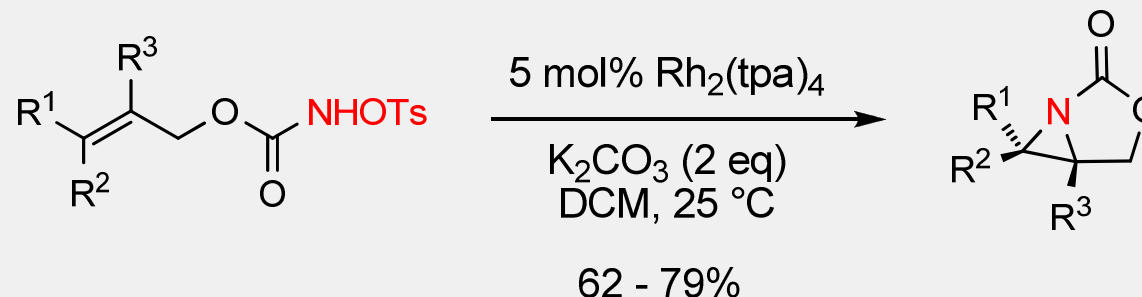
C-H Nitrene insertion

Intramolecular C-H insertions: Lebel

- Use of tosylates for the generation of nitrenoids

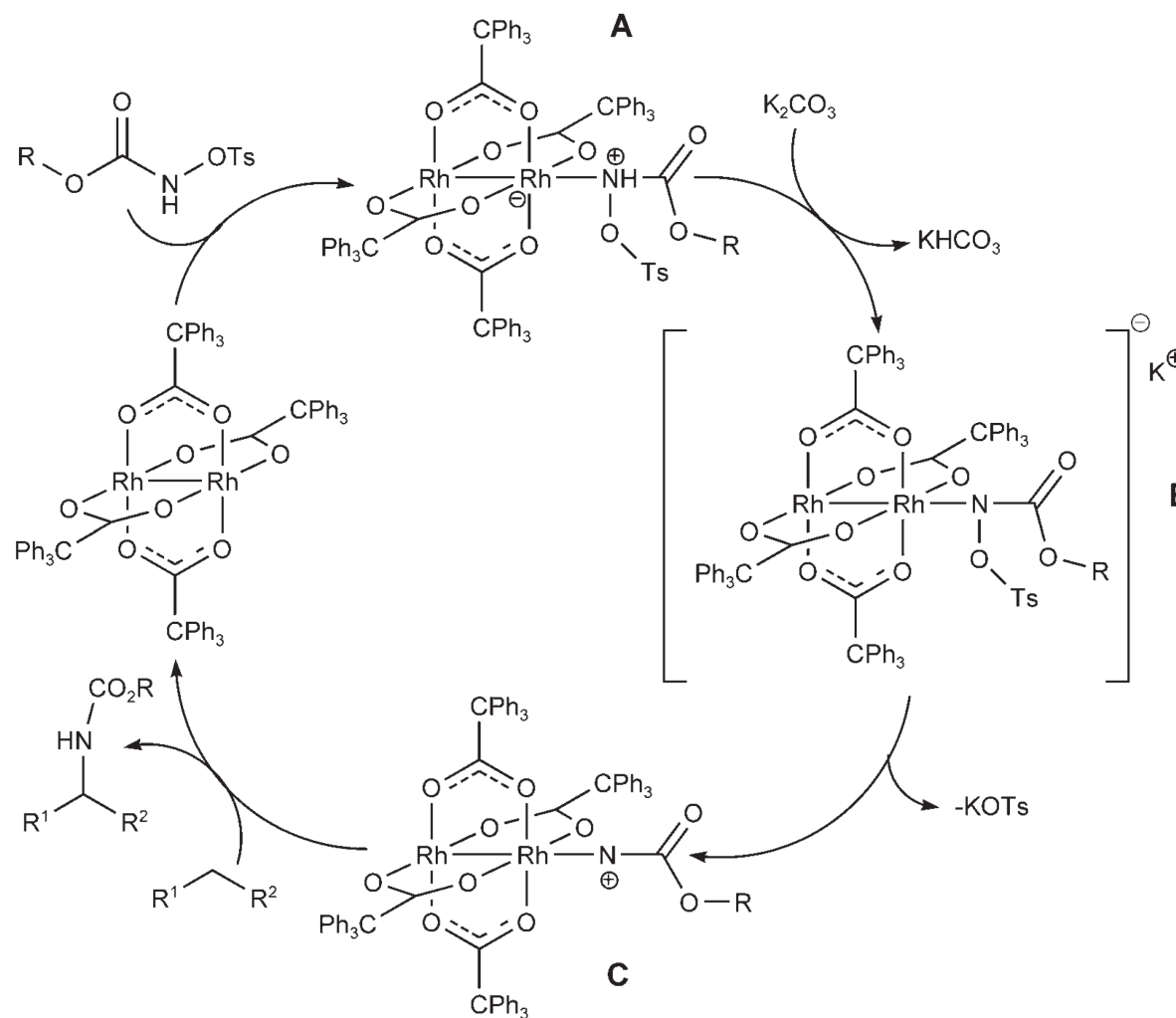


Same retention of configuration



C-H Nitrene insertion

Intramolecular C-H insertions: Lebel

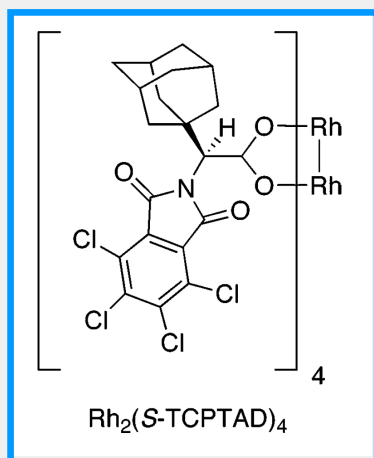
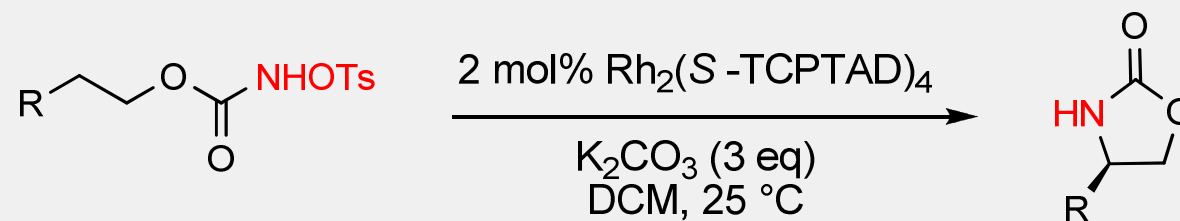


C-H Nitrene insertion

Intramolecular C-H insertions: Davies

Enantioselective version

- Use of tosylates for the generation of nitrenoids

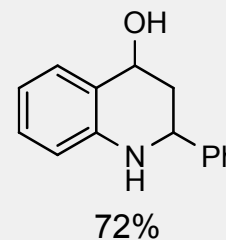
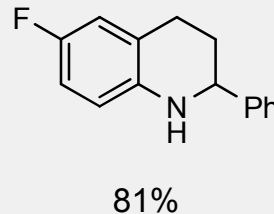
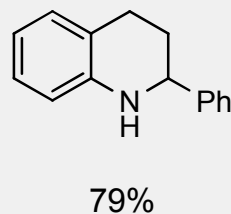
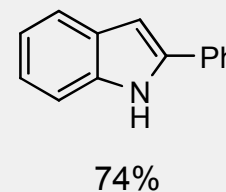
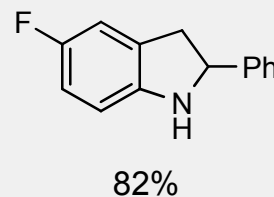
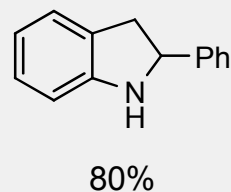
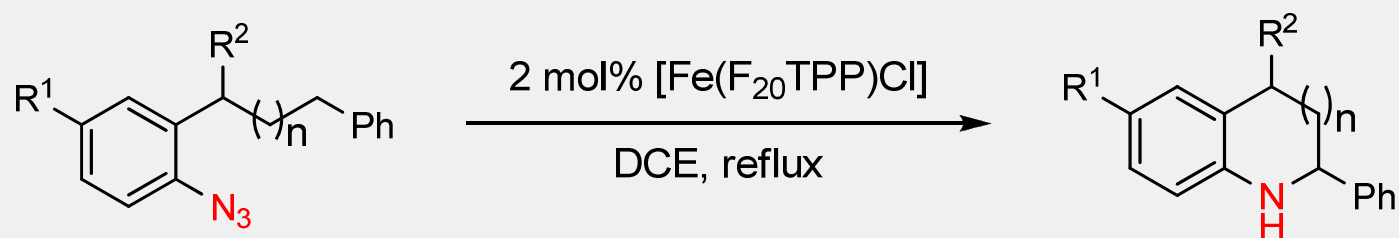


compound	product	yield, %	ee, %
a		72	82
b		75	78
c		62	79
d		69	43

C-H Nitrene insertion

Intramolecular C-H insertions: Che

- Use of aryl azides for the generation of nitrenoids

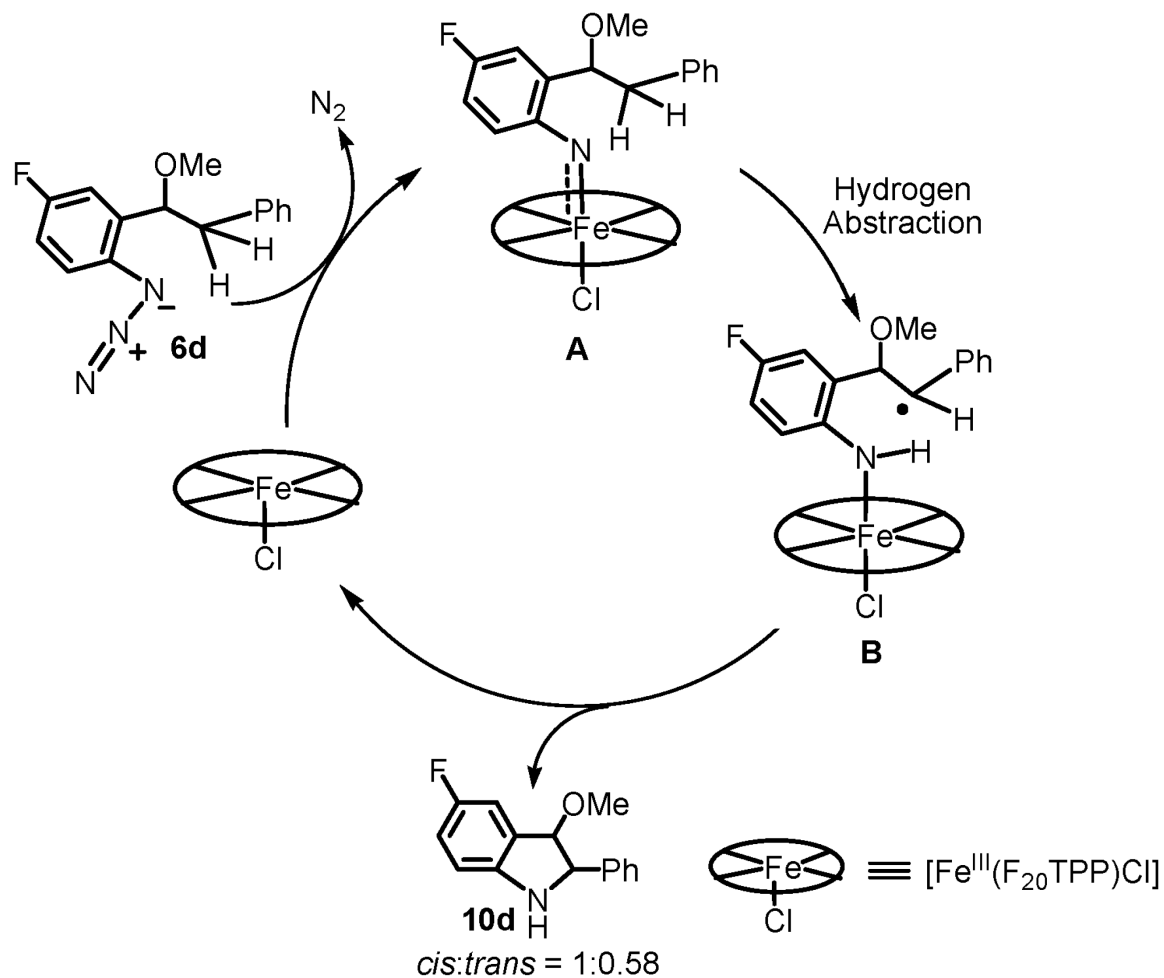
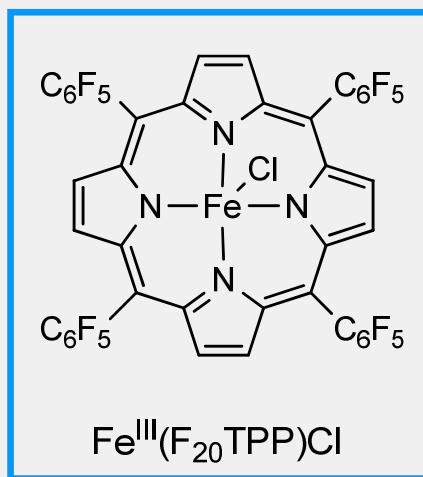


- Formation of Indolines and tetrahydroquinolines

C-H Nitrene insertion

Intramolecular C-H insertions: Che

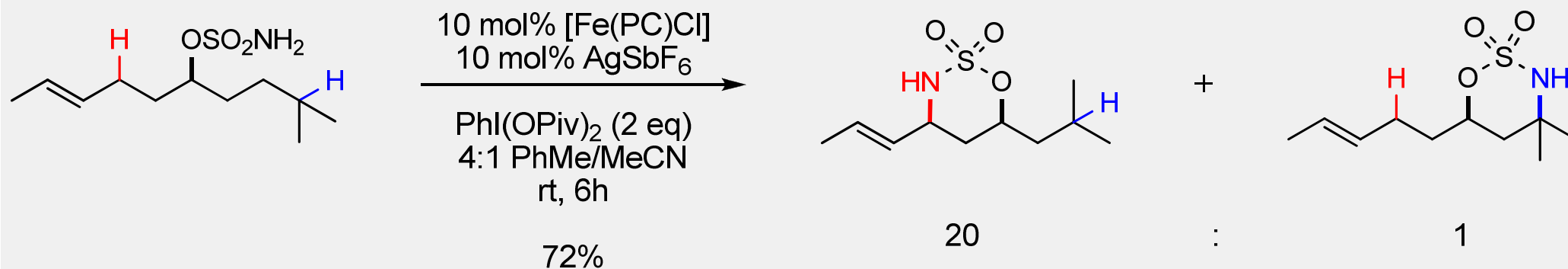
• Mechanism



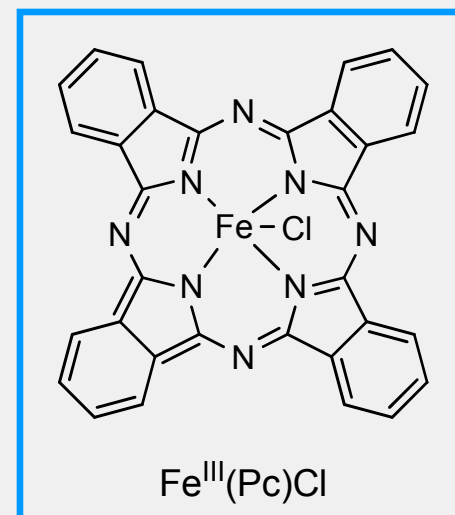
C-H Nitrene insertion

Intramolecular C-H insertions: White

- Use of a Fe-catalyst to produce allylic amination



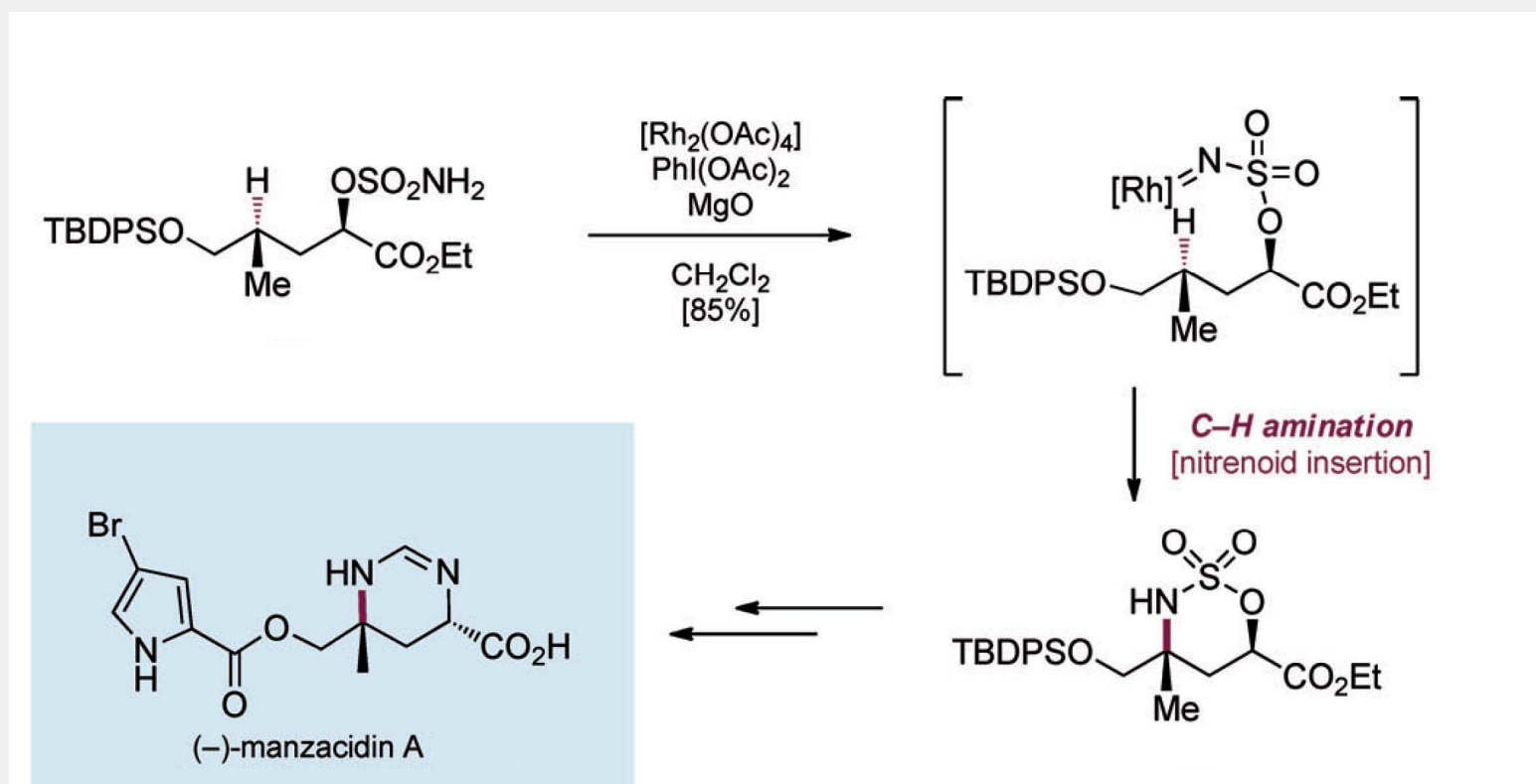
- Allylic position more reactive than tertiary!



C-H Nitrene insertion

Intramolecular C-H insertions: Synthesis of natural products

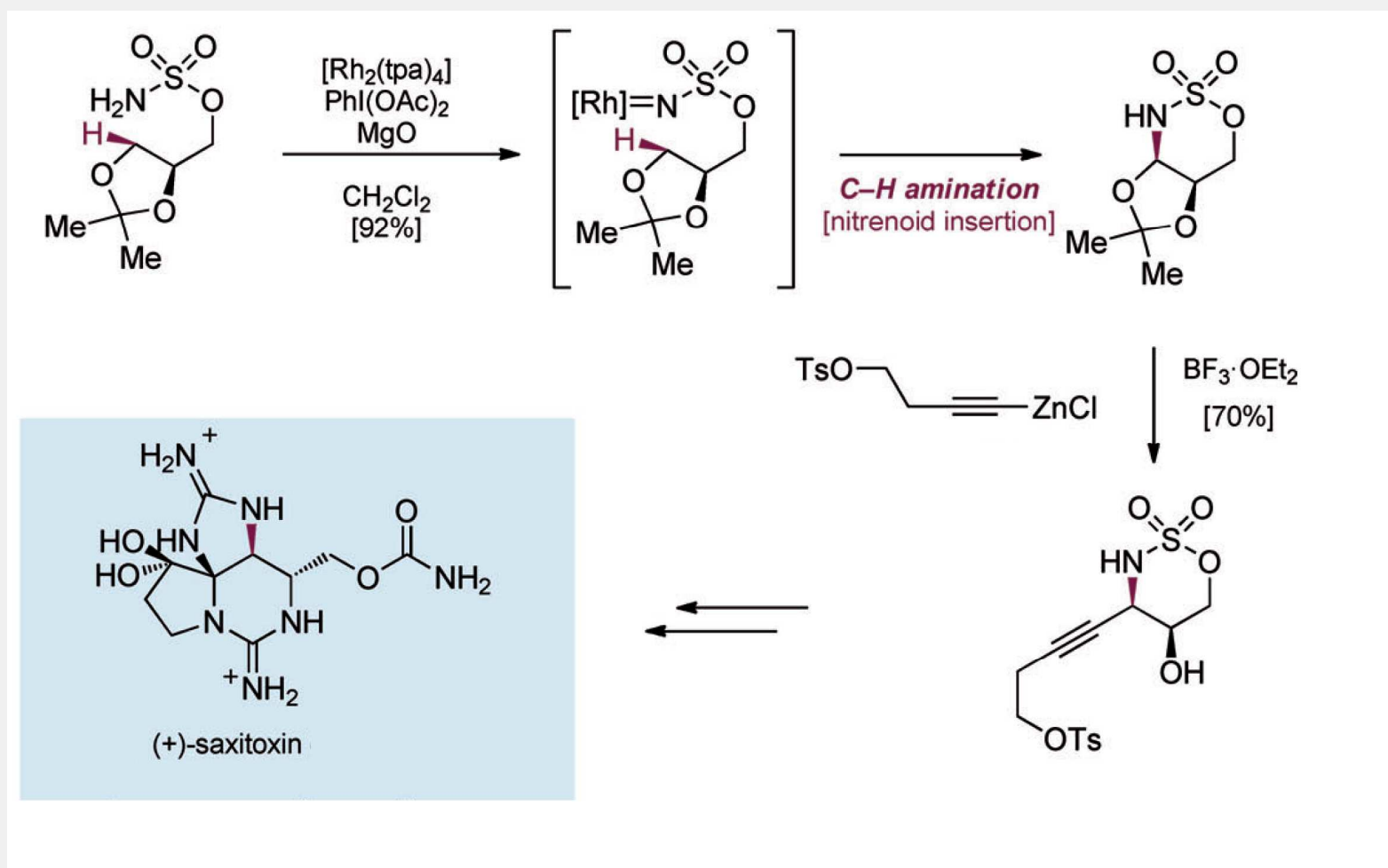
- Du Bois: Synthesis of (-)-manzacidin A



C-H Nitrene insertion

Intramolecular C-H insertions: Synthesis of natural products

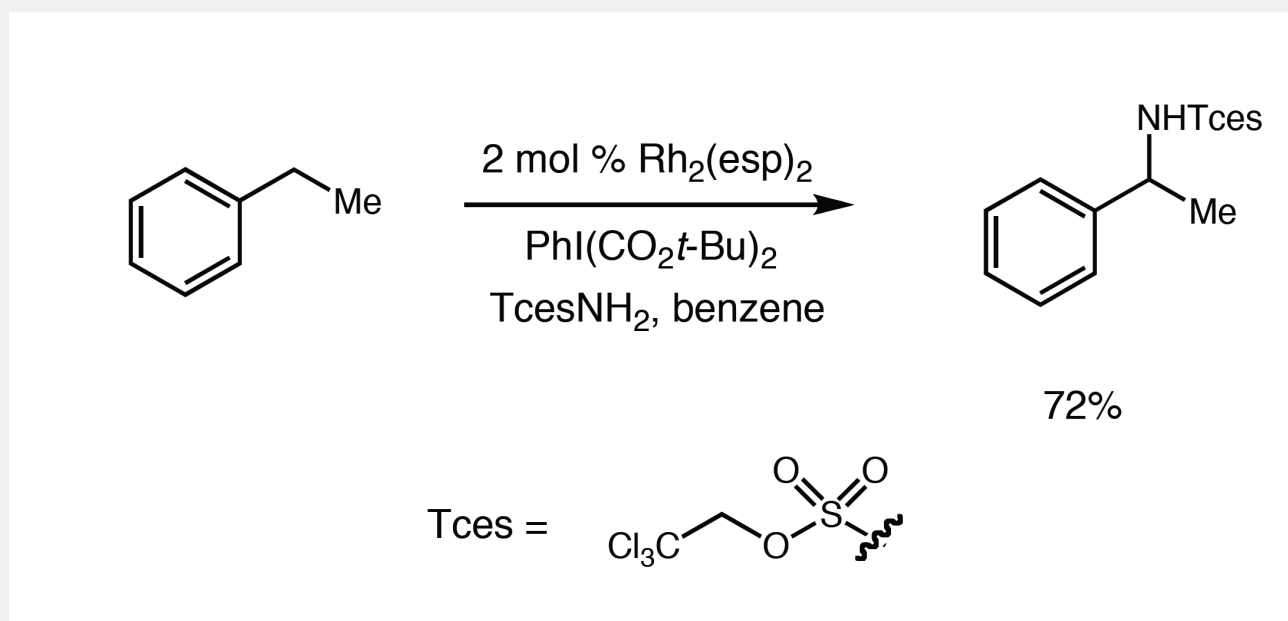
- Du Bois: Synthesis of (+)-saxitoxin



C-H Nitrene insertion

Intermolecular C-H insertions: Du Bois

- Depending on -R, 12 examples from 10 to 74% yield

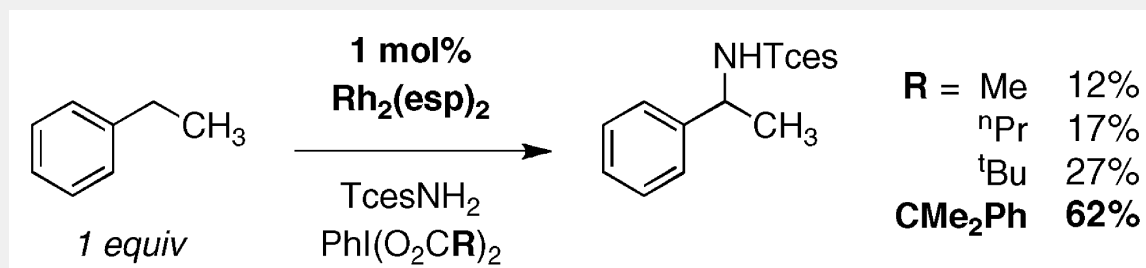
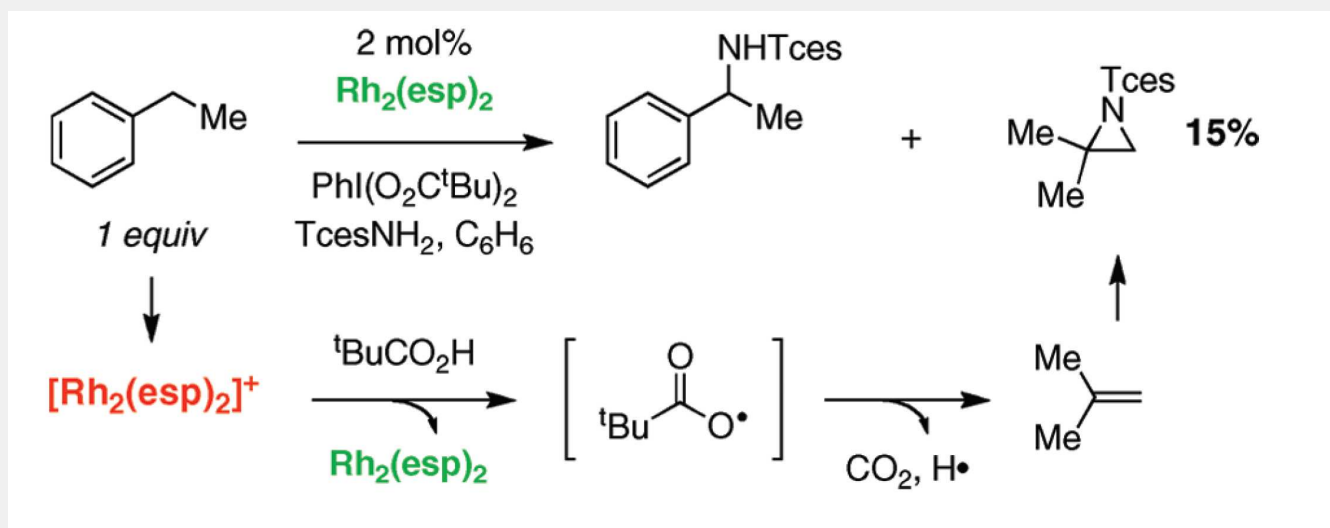


- Only benzylic C-H bonds

C-H Nitrene insertion

Intermolecular C-H insertions: Du Bois

- Search for an alternative hypervalent iodine oxidant



C-H Nitrene insertion

Intermolecular C-H insertions: Lebel

- Use of N-tosylates to generate the metallanitrene



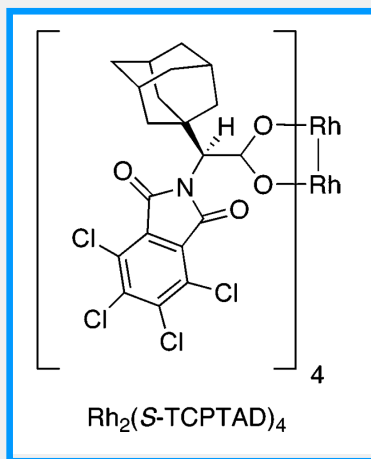
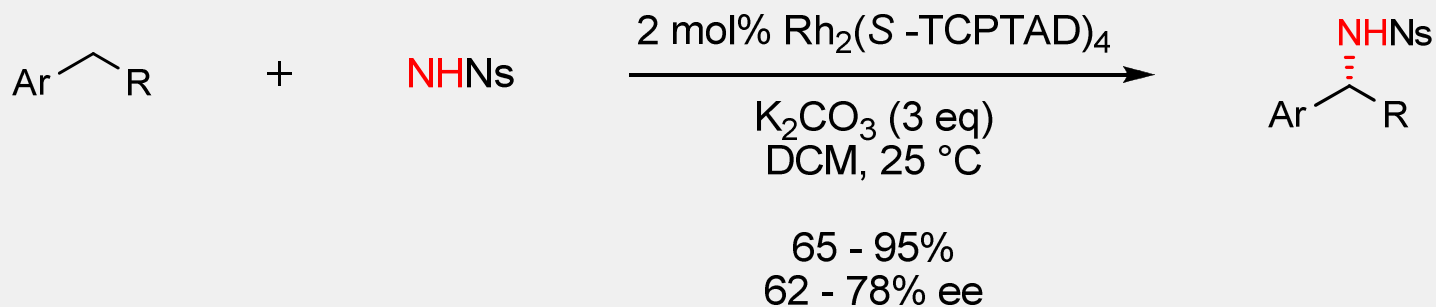
- Up to 15 equivalents of the alkane
- Only with benzylic C-H bonds

C-H Nitrene insertion

Intermolecular C-H insertions: Davies

Enantioselective version

- Same reagents as for the intramolecular reaction

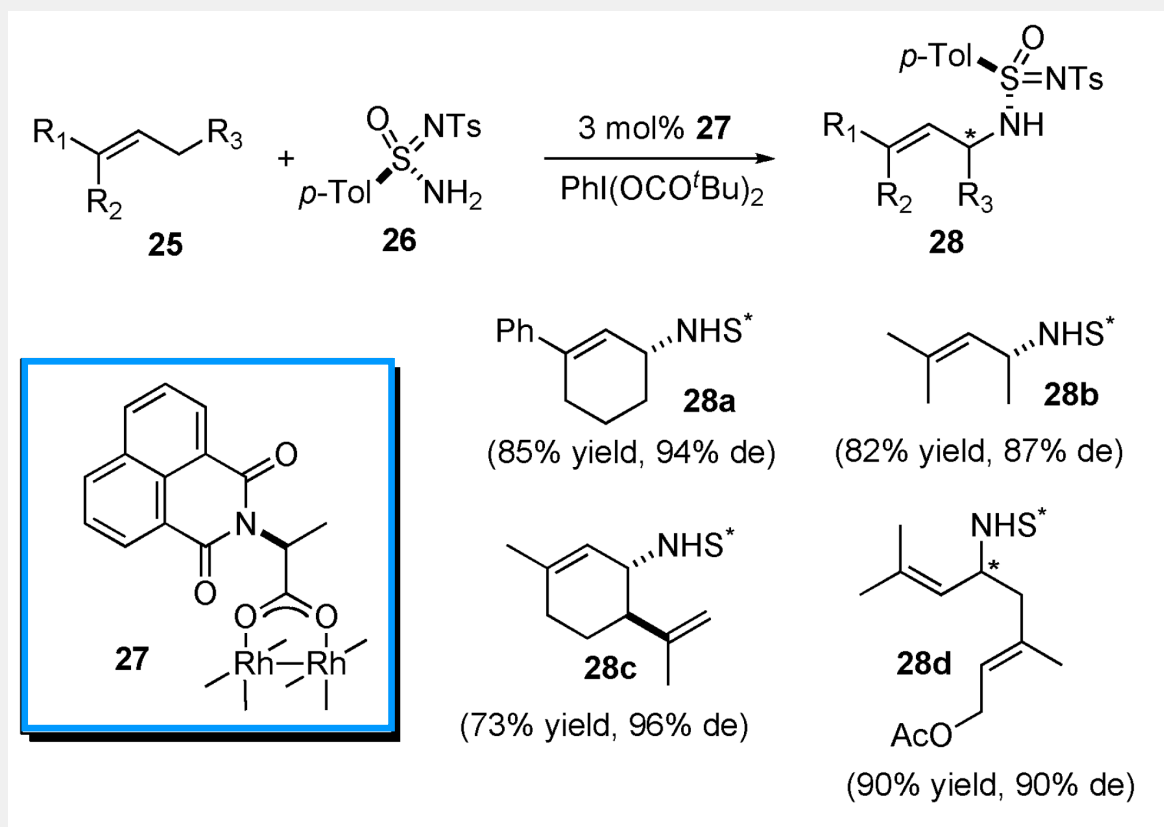


C-H Nitrene insertion

Intermolecular C-H insertions: Dauban

Diastereoselective version

- Use of a chiral sulfonimidamide

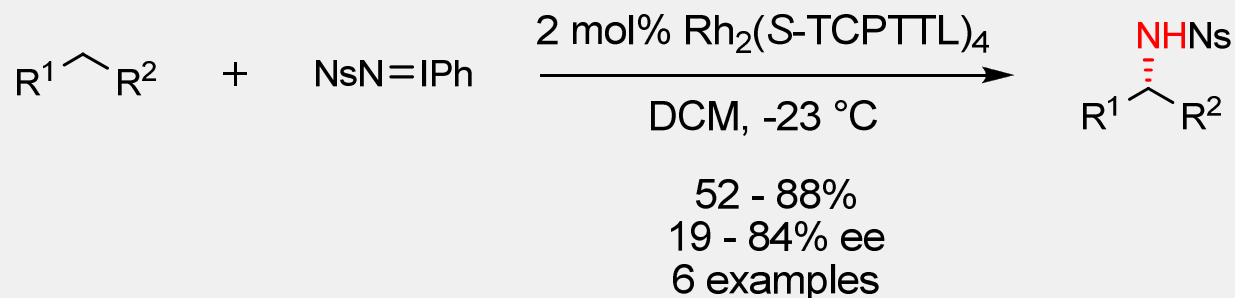
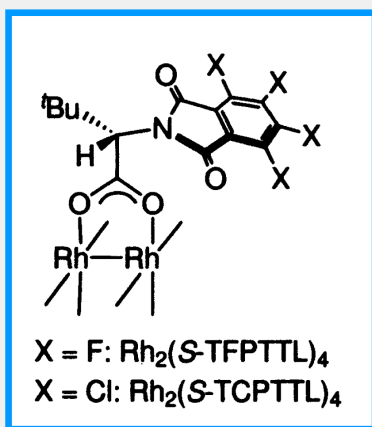


C-H Nitrene insertion

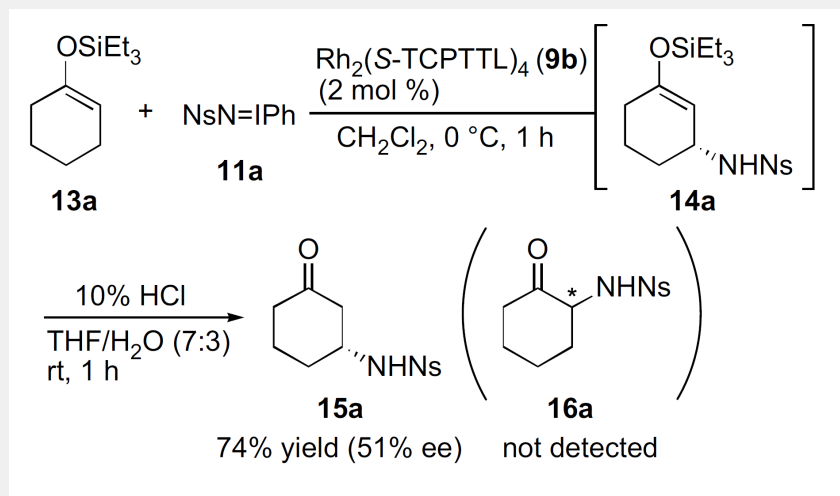
Intermolecular C-H insertions: Hashimoto

Enantioselective version

- Benzylic and allylic C-H bonds



- Use of TES enol ethers: Formal Synthesis of (-)-pancracine



C-H Nitrene insertion

Conclusion

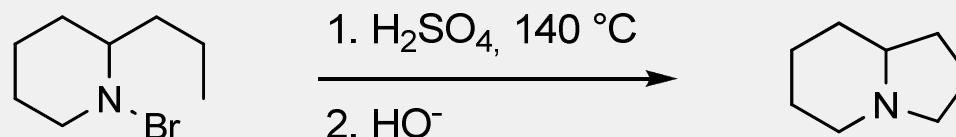
- Very efficient and selective stereospecific transformations
- Selective for tertiary and benzylic positions or allylic positions
- Applicable to the synthesis of natural products

- Need of a primary amine: nitrene can not be formed with a secondary one
- Requirement for transition-metal catalysts and hypervalent iodine reagents which can interact with many functions

Introduction

Hofmann-Löffler-Freytag Reaction

- Initial discovery by Hoffmann:

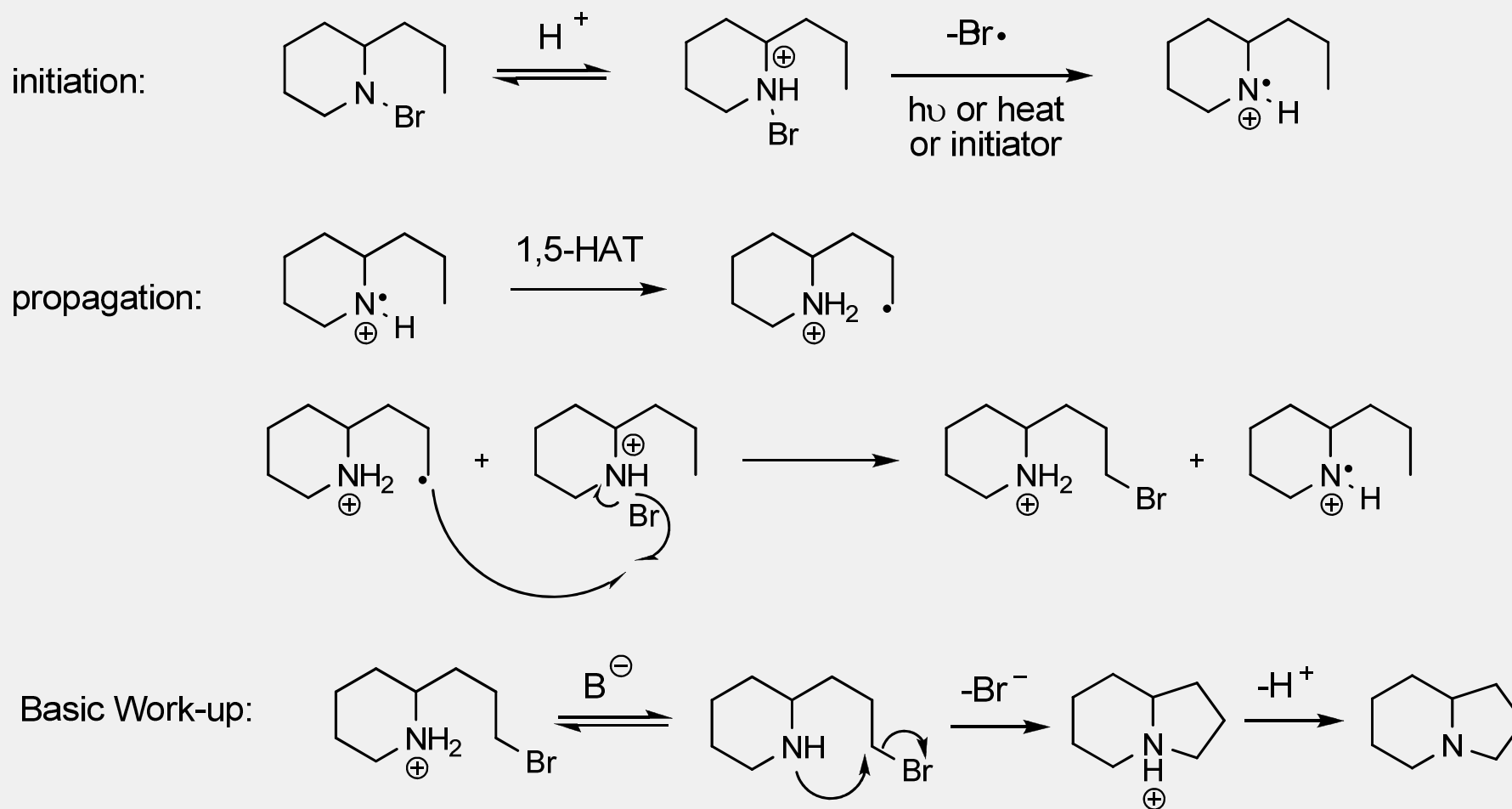


- Since: widely used method for the preparation of 5-membered tertiary amines
- The procedure requires strong acidic conditions

Introduction

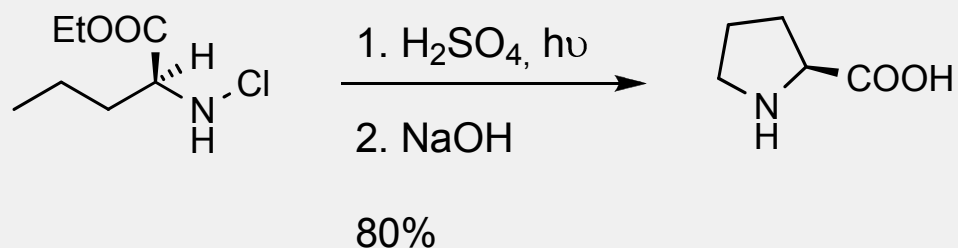
Hofmann-Löffler-Freytag Reaction

• Mechanism

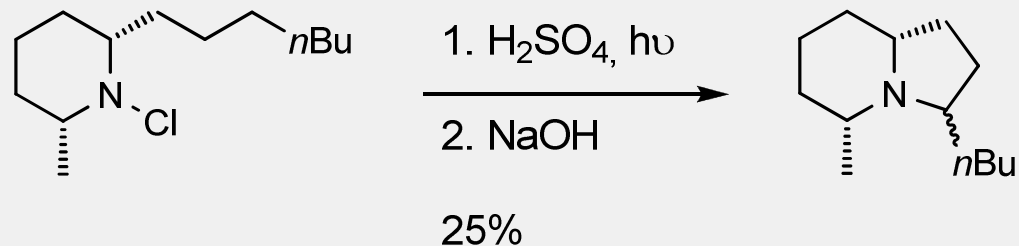


Application in the synthesis of natural products

- Lavergne: Synthesis of D-proline

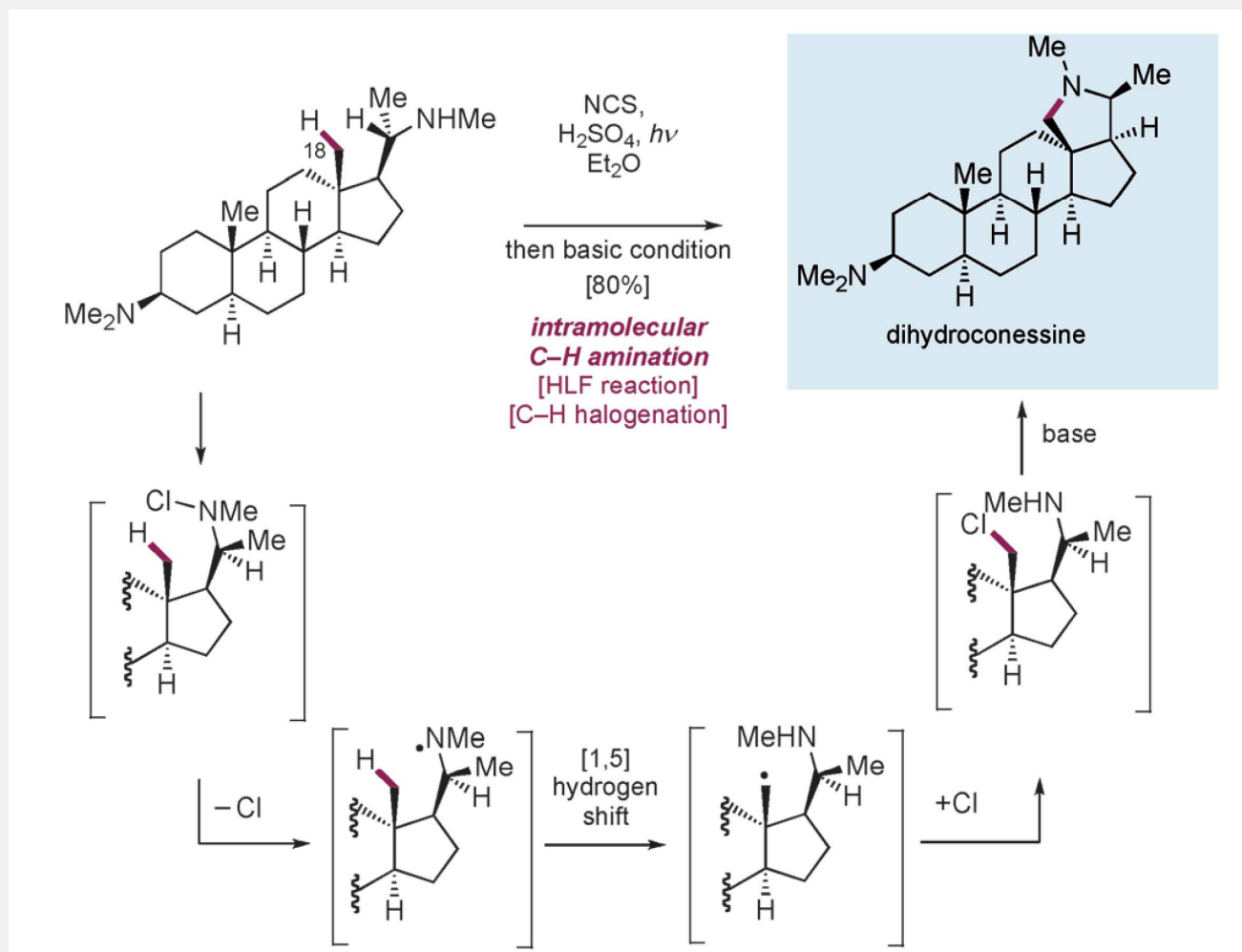


- Sonnet and Oliver: Synthesis of potential sex pheromone precursors



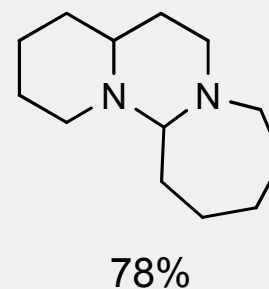
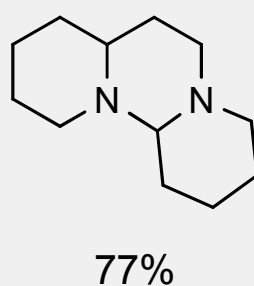
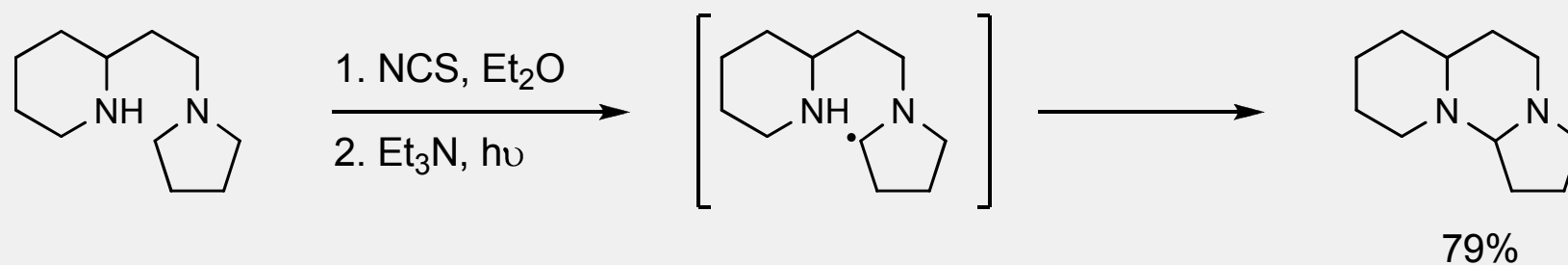
Application in the synthesis of natural products

- Corey: Synthesis of dihydroconessine



HLF Reaction under neutral or basic conditions

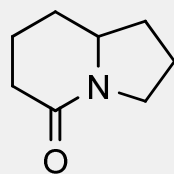
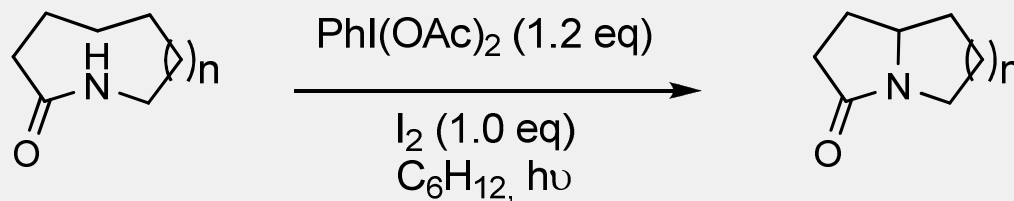
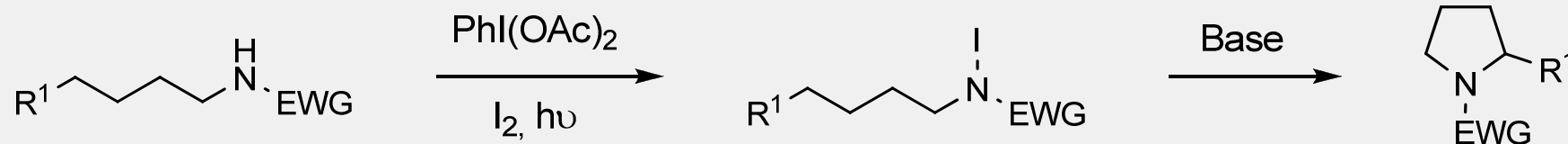
- N-stabilized radical



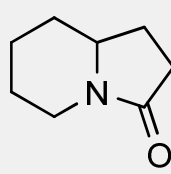
- Formation of 6-membered rings

Sùarez modification

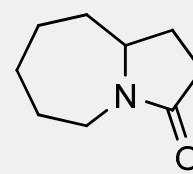
- Mild alternative
- Presence of an EWG on the nitrogen atom: $-\text{CN}$, $-\text{NO}_2$ or $-\text{P}(\text{O})(\text{OR})_2$



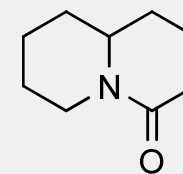
82%



14%



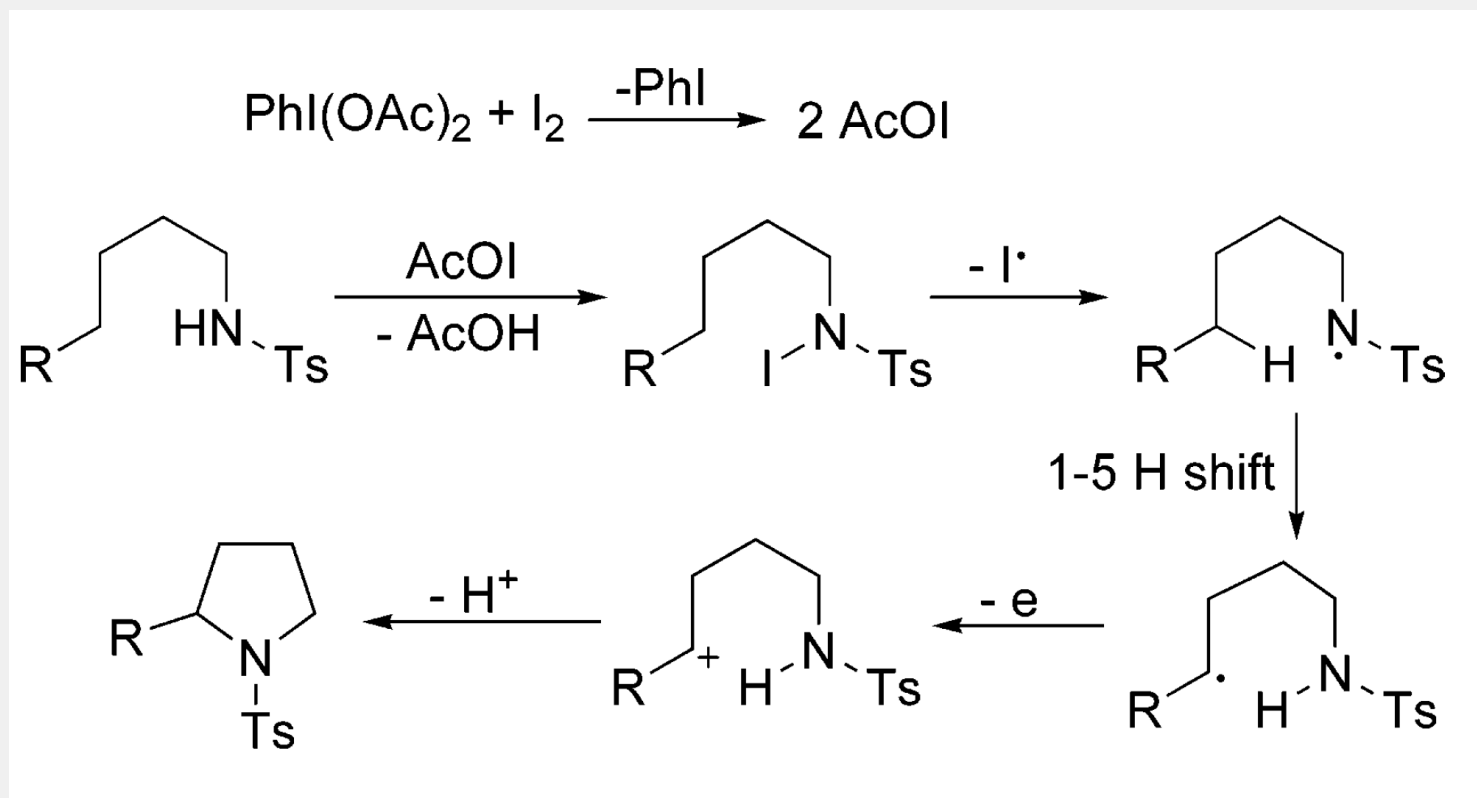
67%



13%

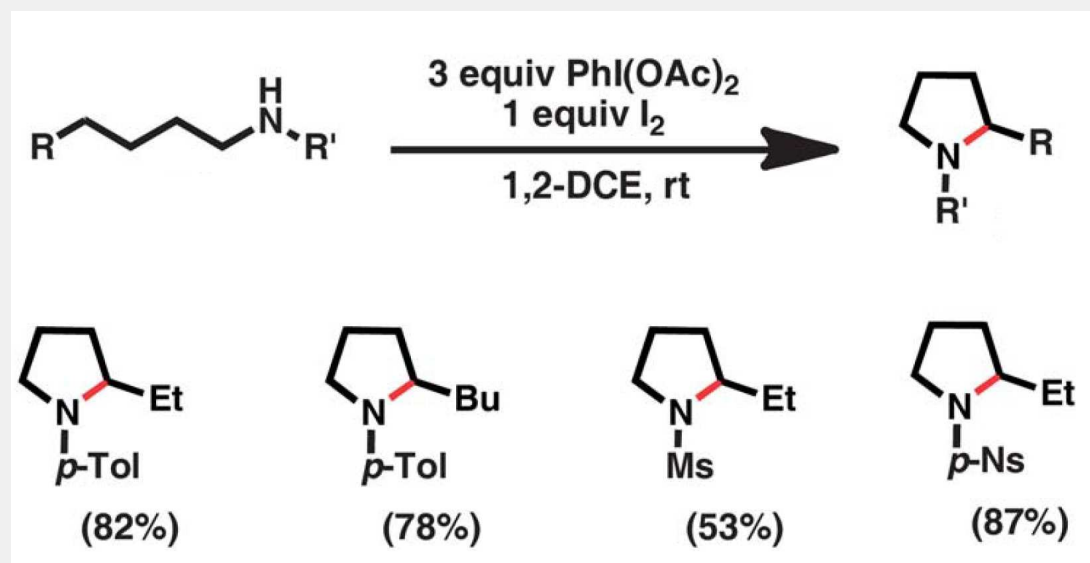
Sùarez modification

- Mechanism



Sùarez modification

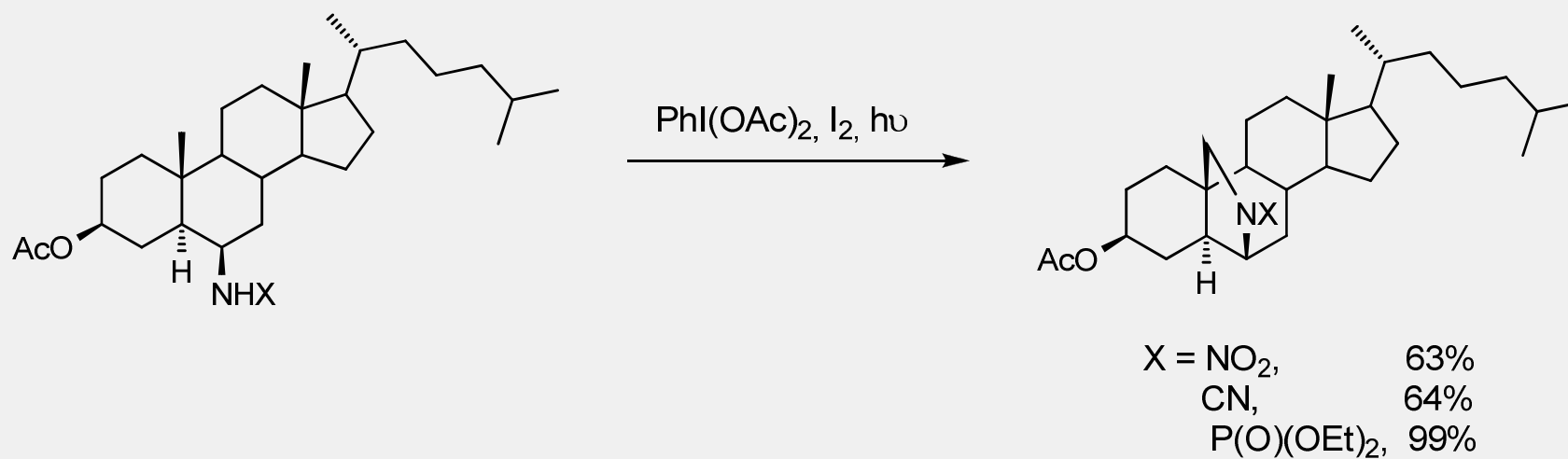
- Fan synthesis of pyrrolidines



- No irradiation

Sùarez modification: Natural product synthesis

- Synthesis of terpenoids



Metal-catalyzed C-H
Aminations

Hofmann-Löffler-Freytag
Reaction

via C,N-dianions

Conclusion

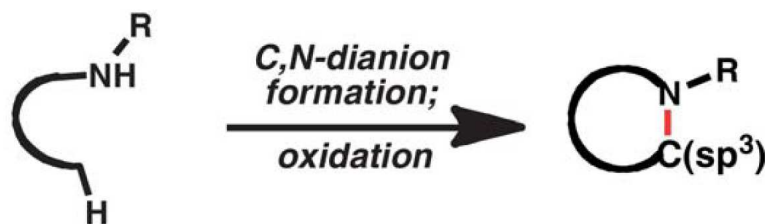
Hofmann-Löffler-Freytag Reaction

- Original conditions too harsh
- Powerful and selective

- Very specialized
- Only intramolecular

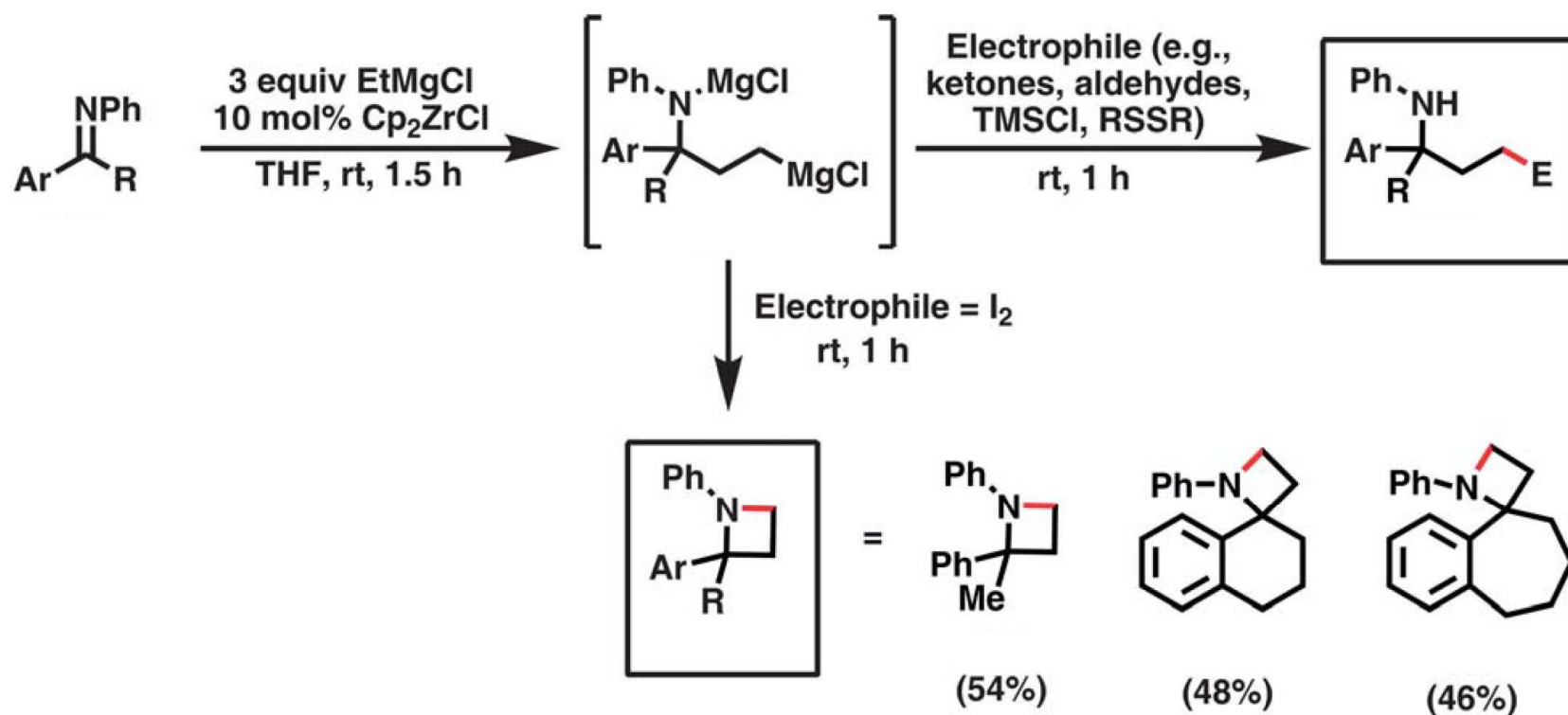
Reactivity of C-N dianions

- Complementary to aminyl and nitrene-based intermediates
- Generated by successive deprotonation of N-H and C-H groups
- Focus on intramolecular reactions



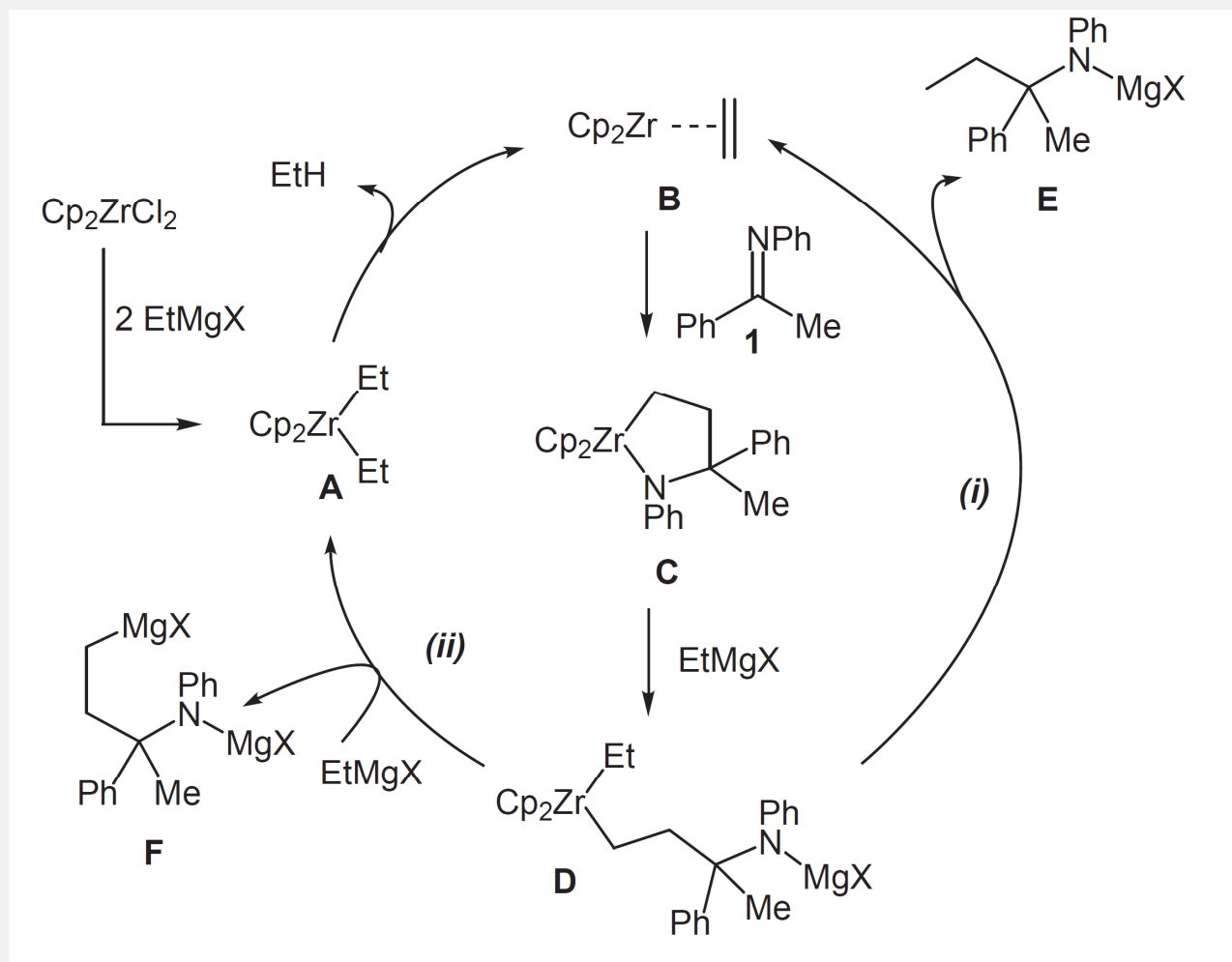
C-N dimagnesiated compounds: Szymoniak

- Zirconium-catalyzed reaction



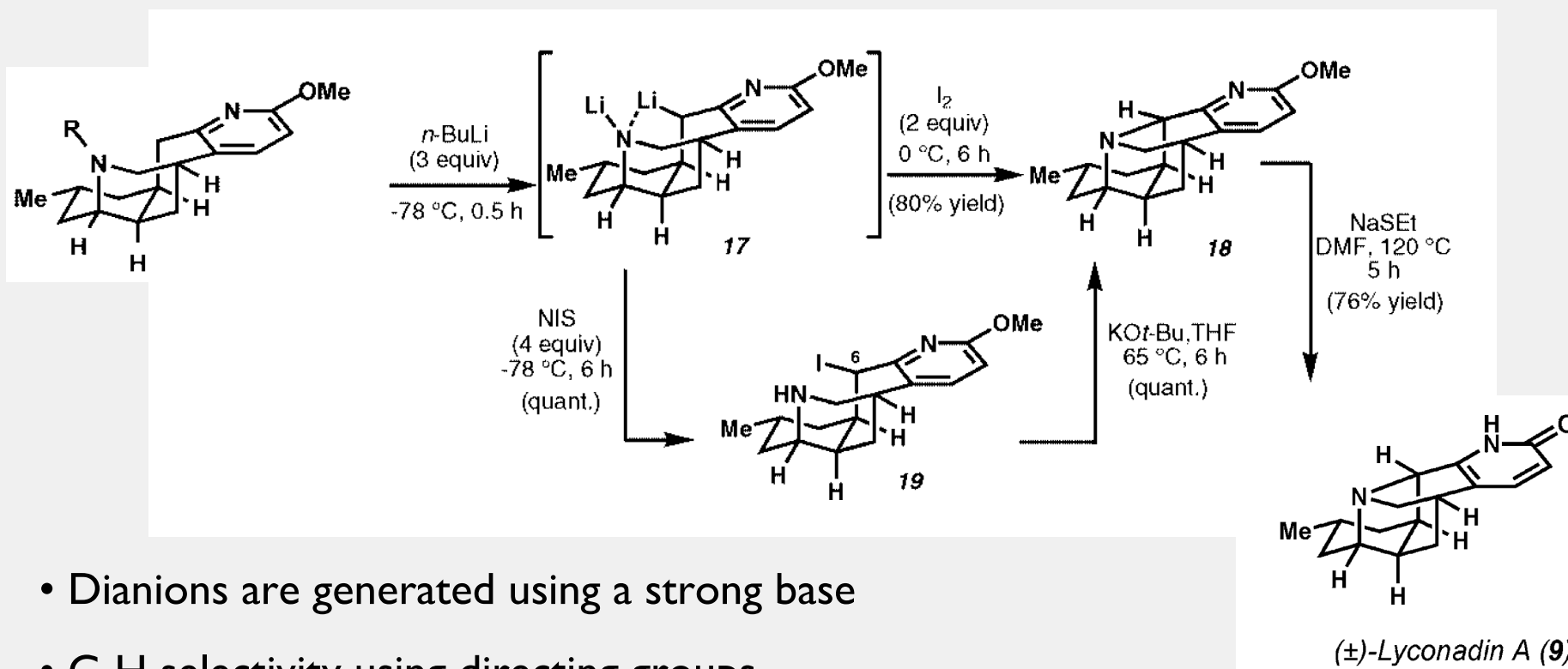
C-N dimagnesiated compounds: Szymoniak

- Proposed mechanism



C-N dianions: Sarpong, towards *Lycopodium* alkaloids

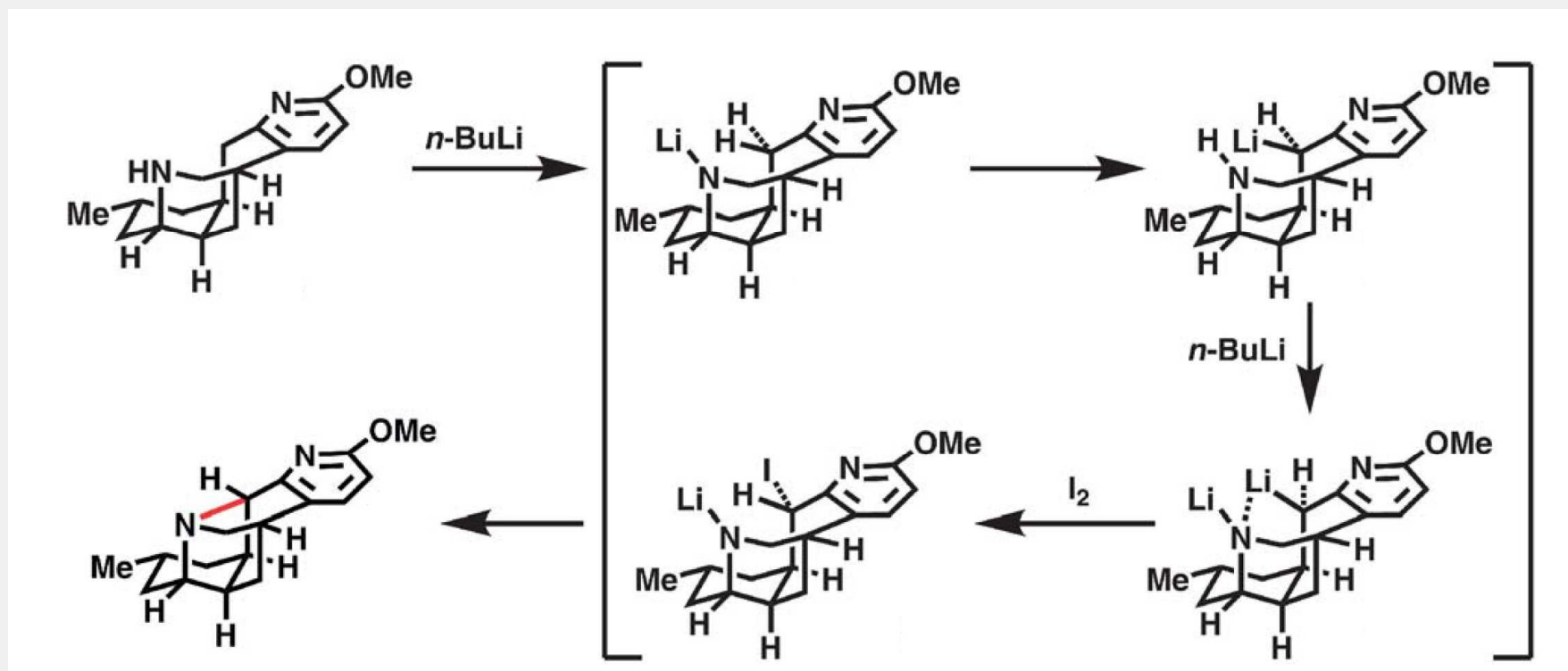
- Generated from N,N-dialkylamines and benzylic carbon groups



- Dianions are generated using a strong base
- C-H selectivity using directing groups
- Deprotonation of the N-H is crucial

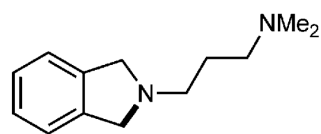
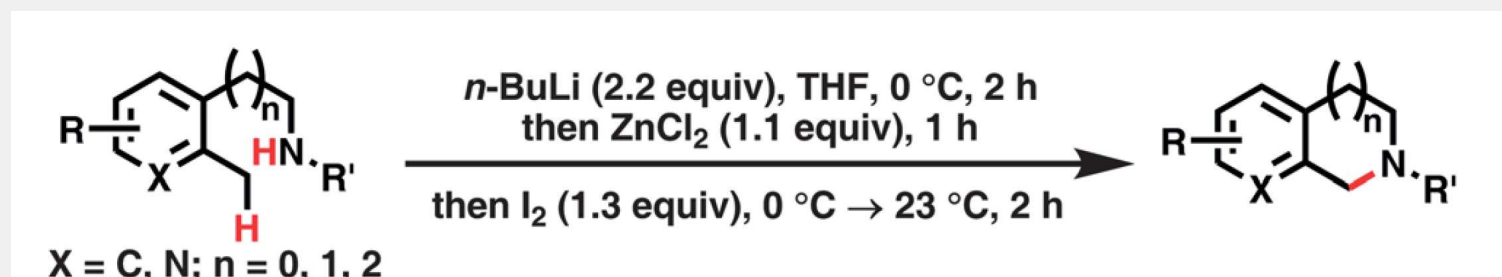
C-N dianions: Sarpong, towards *Lycopodium* alkaloids

- Mechanism of the transformation

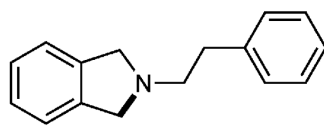


C-N dianions: Sarpong

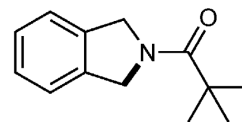
- Generalisation to other substrates



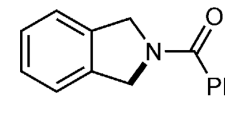
6 (53%)



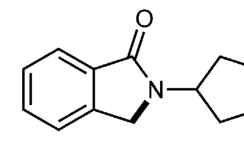
7 (51%)



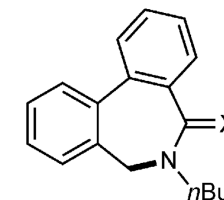
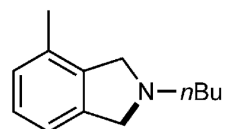
17 (67%)



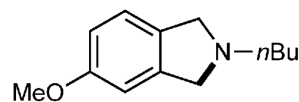
18 (57%)



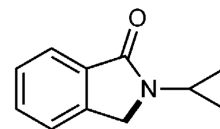
19 (71%)

25a (X = H₂) 51% yield25b (X = O) 46% yield^[a]

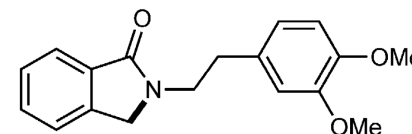
12 (57%)



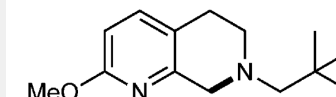
13 (52%)



20 (75%)



21 (58%)



27 64% yield

C-N dianions

- Efficient and Selective methods
- Complementary to other C-N bond formations such as HLF

- Not compatible with acidic protons in the molecule
- Sarpong's method needs to be generalised

Thanks for your attention!