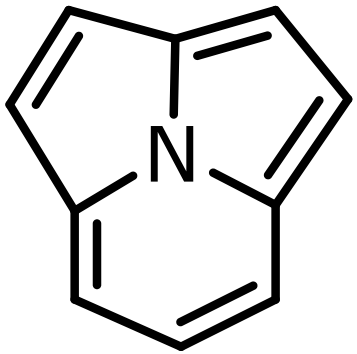
Cyclazines

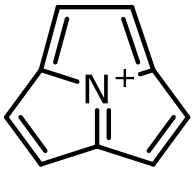
Nessa Carson | Denmark group meeting
27th May 2014

Introduction

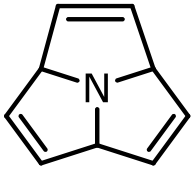
- (Conjugated) cyclic molecules with a central N atom
- Aromatic or antiaromatic
- Central N is planar and non-basic



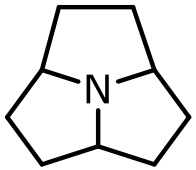
[2.2.3]cyclazine



[2.2.2]cyclazine

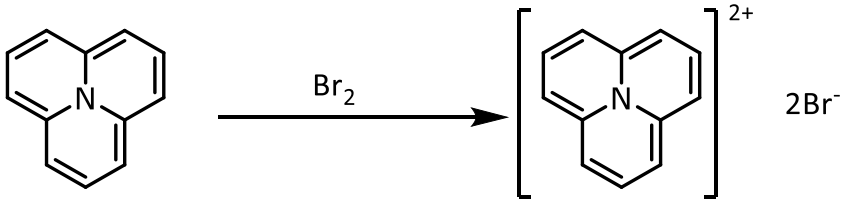


[2.2.2]cyclazine?



A cyclazine derivative?

Aromaticity of conjugated cyclazines



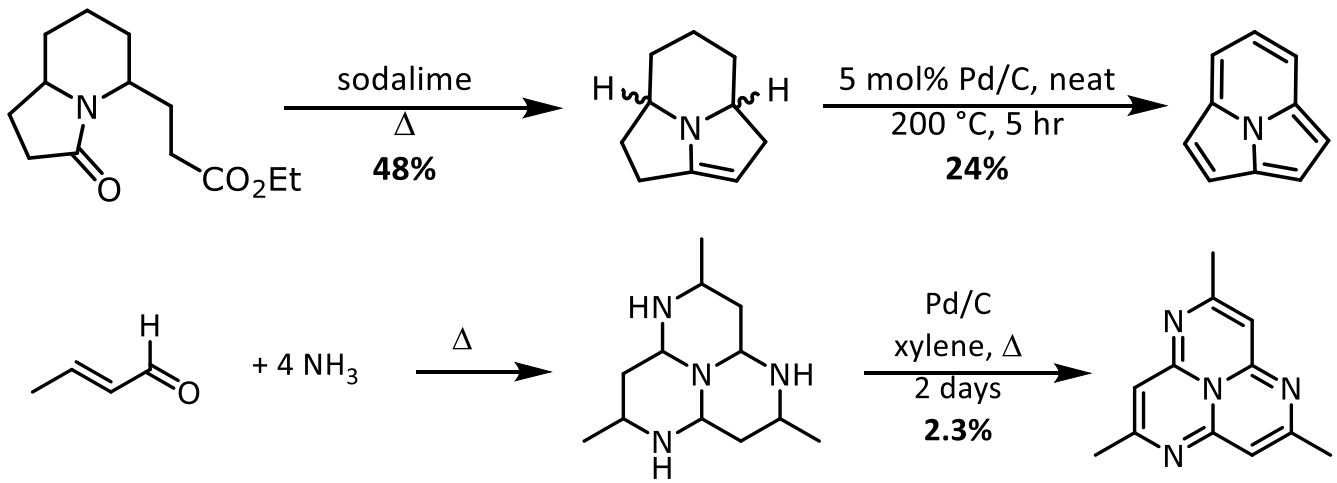
- Antiaromatic cyclazines are highly reactive with respect to oxidation and reduction
- Aromatic and antiaromatic cyclazines were originally synthesized to better understand the nature of aromaticity
- Antiaromatic cyclazines may be stabilized by heteroatoms on the periphery

Farquhar and Leaver – Chem. Commun. 1969, 24
Fallah-Bagher-Shaidaei et al. – Comp. Theor. Chem. 2011, 963, 525-532

Outline

- Methods of synthesis
- Uses and properties of cyclazines
- The perhydroazaphenalene natural products
  - Stevens's coccinelline synthesis
  - Stockman's hippodamine synthesis
  - Spring's myrrhine synthesis
- Summary

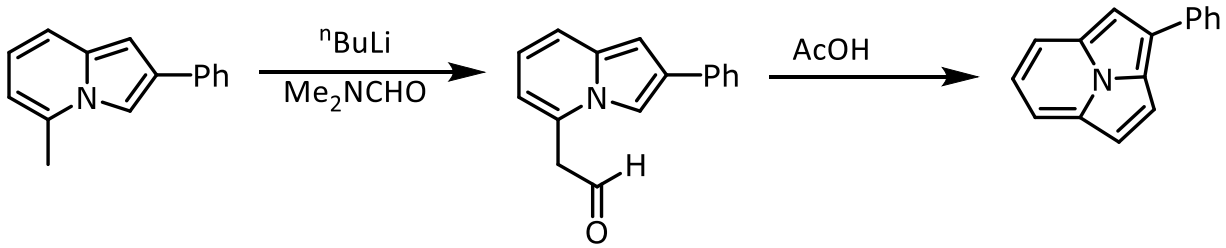
From partially unsaturated heterocycles



- These early syntheses are plagued by low yields

Murakoshi and coworkers – Chem. Pharm. Bull. 1976, 24, 2265-2266
Wirz and coworkers – J. Am. Chem. Soc. 1986, 108 (1), 17-22

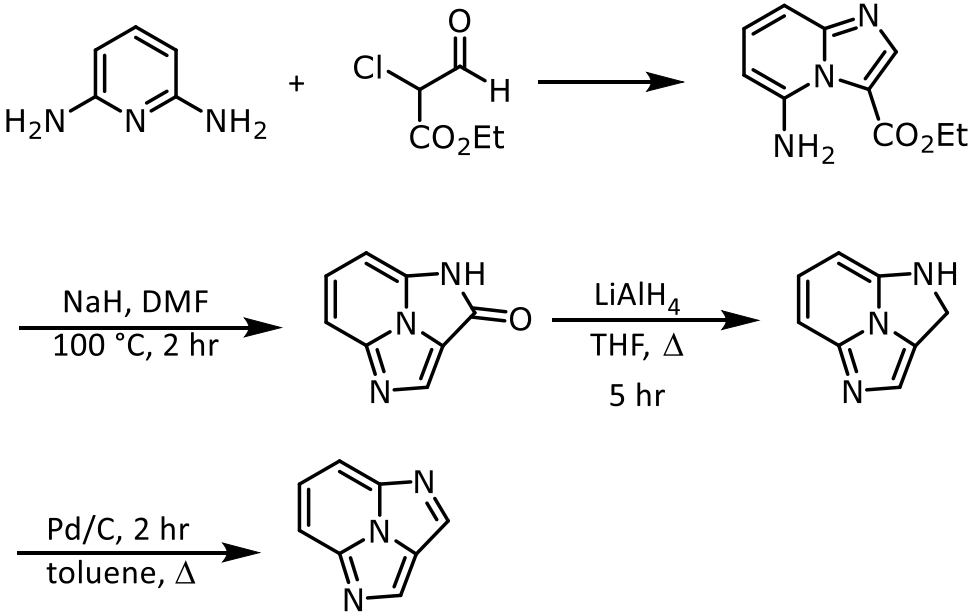
Synthesis by condensation reaction



- Condensation reactions from nucleophilic C-3 position of indolizine
- Rearomatization is fast due to large increase in stability

Boekelheide and coworkers – J. Am. Chem. Soc. 1959, 81, 1459-1465

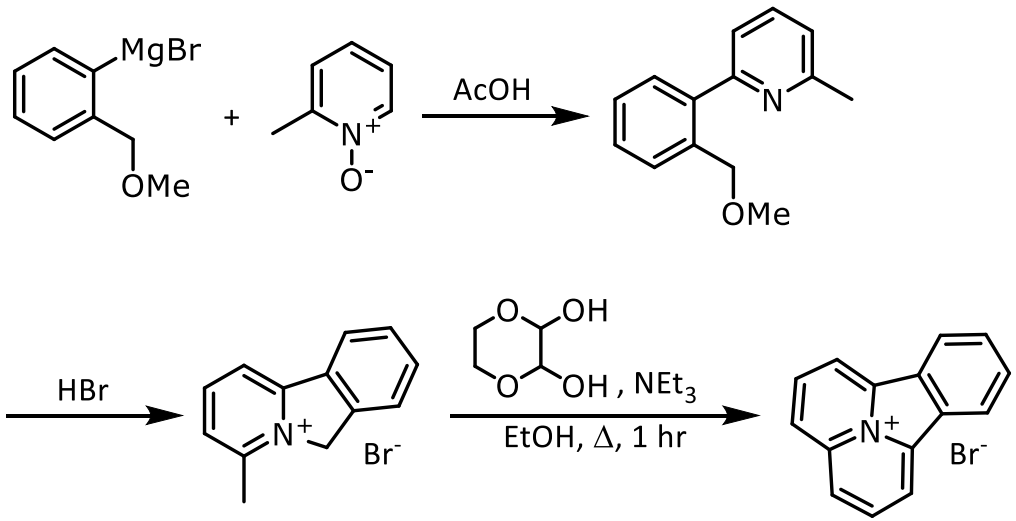
Synthesis by condensation reaction



- Condensation reaction then oxidation to aromatic cyclazine
- Formation of two C–N bonds in one step

Park and coworkers – J. Heterocycl. Chem. 1972, 9 (1), 81-85

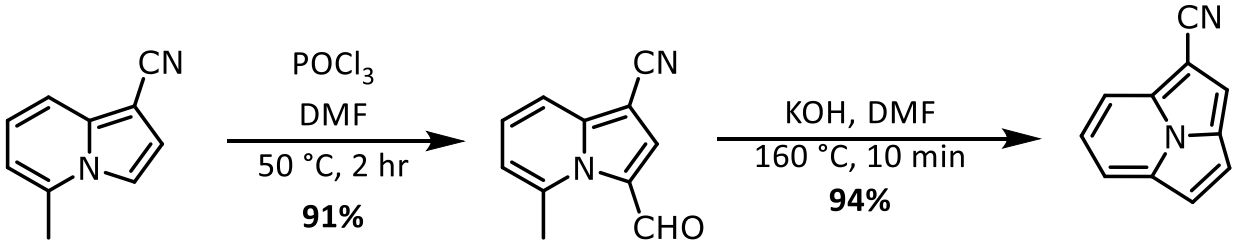
Synthesis by condensation reaction



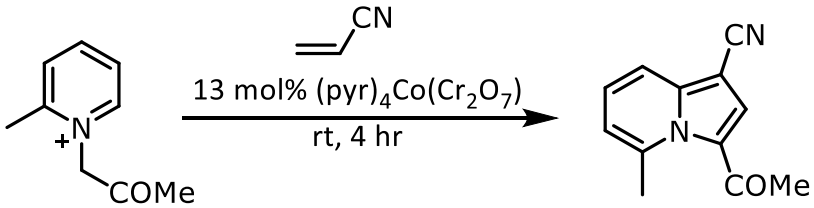
- Benzo-fusion decreases aromaticity of cyclazine structure
- Aromatization occurs *in situ*

Bechgaard and coworkers – Angew. Chem. Int. Ed. 1989, 28 (5), 588-590

Synthesis *via* indolizine formylation

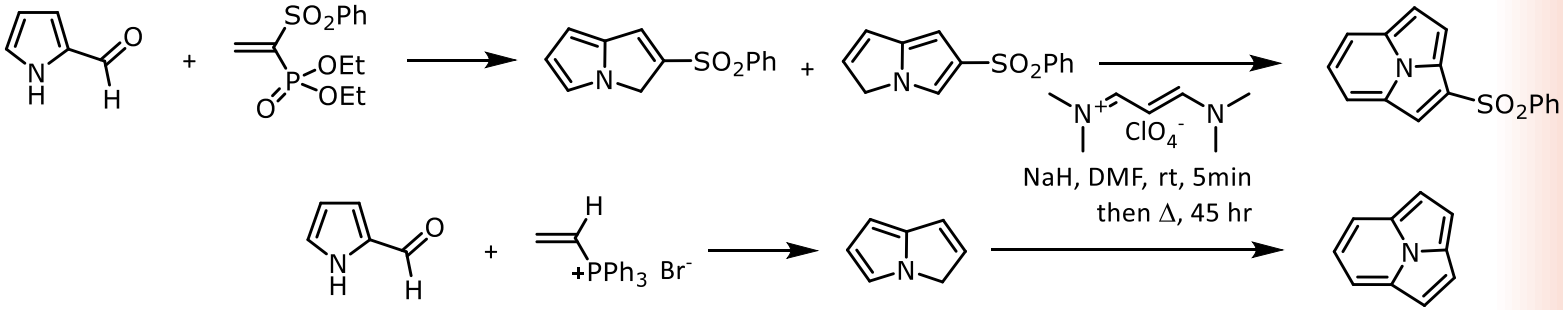


- Aromatic system acidifies methyl group and allows fast aromatization of new ring
- Yield falls sharply with Ph substitution at C-2
- Indolizinyl ketones can be synthesized from pyridines



Hu and coworkers – J. Heterocycl. Chem. 2001, 38 (4), 853-857

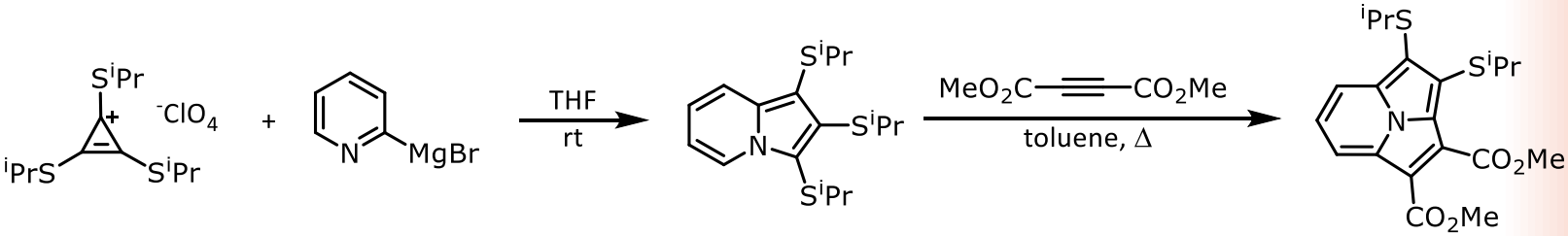
Synthesis by cycloaddition



- Substitution at C-2, C-6 and C-7 is tolerated
- Presence of electron-withdrawing groups is favorable for rate

Skinner and coworkers – Chem. Ber. 1984, 117 (5), 1649-1658

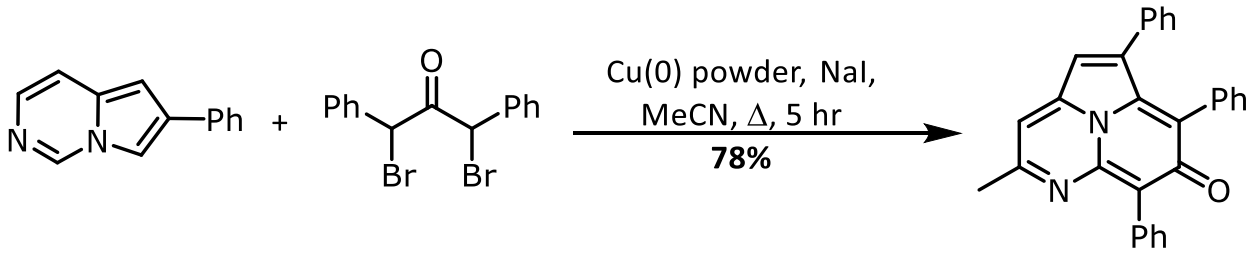
Synthesis by cycloaddition



- Cyclization to indolizine proposed to go *via* vinyl carbene intermediate
- An apparent [8+2]-cycloaddition

Inoue and coworkers – J. Heterocycl. Chem. 1991, 28, 2059-2060

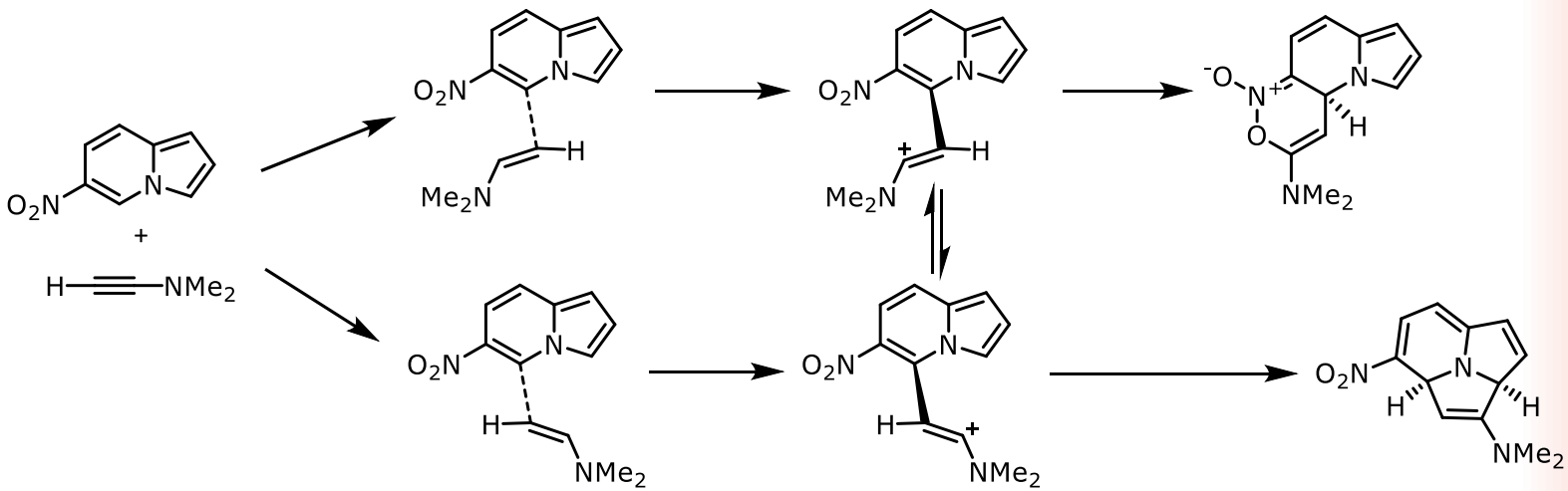
Synthesis by cycloaddition



- Regiochemistry from high nucleophilicity of azaindolizine C-3 position
- Proposed two-step mechanism: enamine-type addition followed by addition to imine-type electrophile
- Lower yields (max. 39%) from indolizines

Gotou and coworkers – Yakugaku Zasshi 1986, 106 (12), 1098-1107

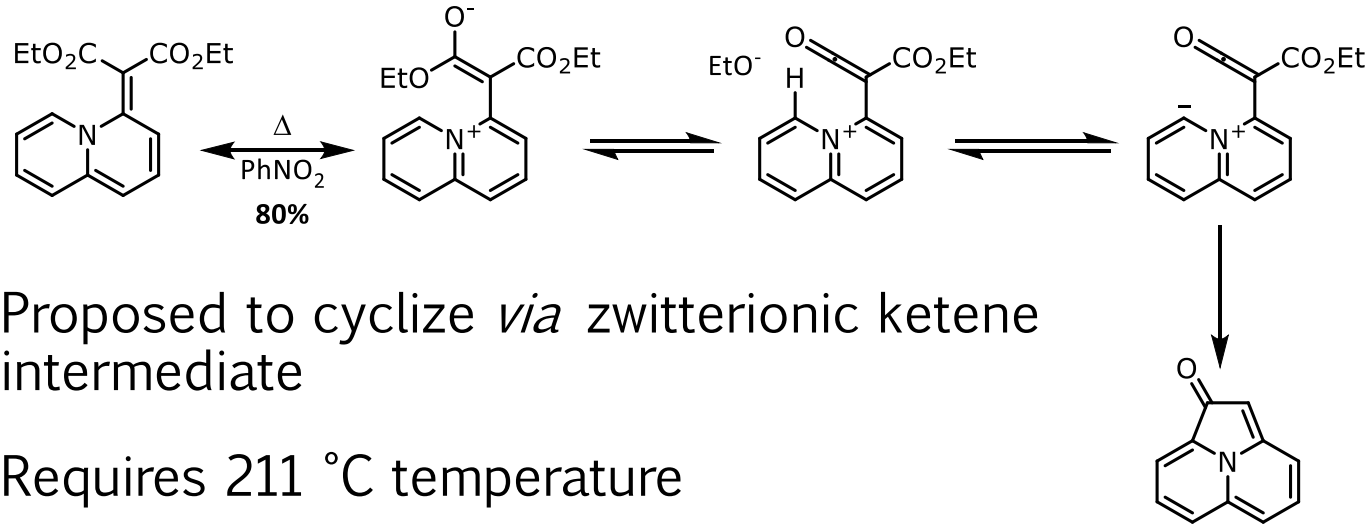
Stepwise cycloaddition



- Substitution with a nitro group allowed the authors to probe the mechanism of cycloaddition

Babaev et al. – J. Org. Chem. 1999, 64 (25), 9057-9062

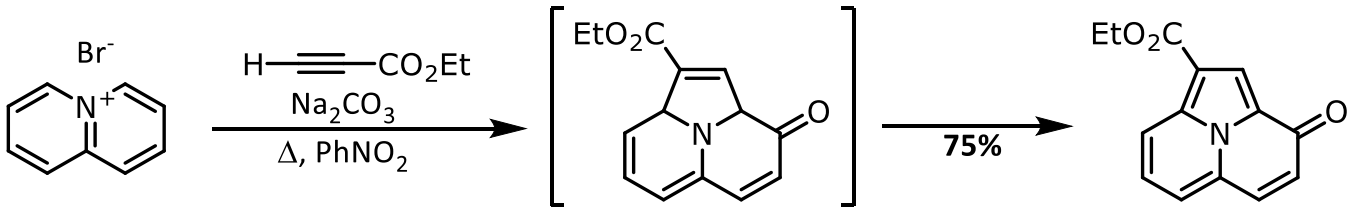
One-pot synthesis



- Proposed to cyclize *via* zwitterionic ketene intermediate
- Requires 211 °C temperature

Farquhar et al – J. Chem. Soc. Perkin Trans. 1 1984, 2553

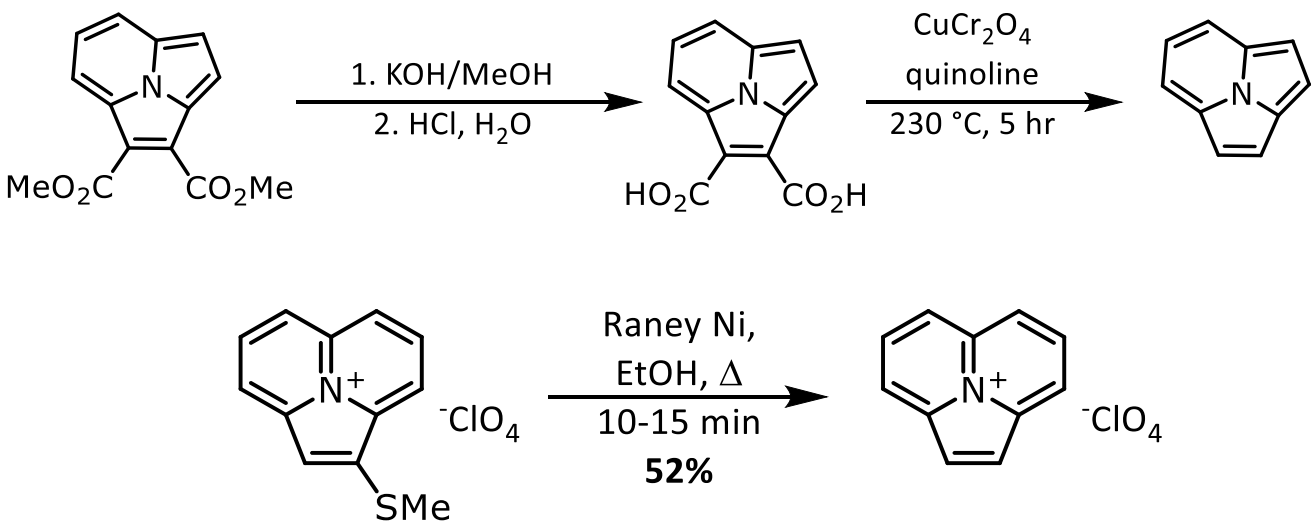
One-pot synthesis



- Nitrobenzene solvent oxidizes substrate to the 10π aromatic cyclazinone in one pot

Farquhar et al – J. Chem. Soc. Perkin Trans. 1 1984, 2553

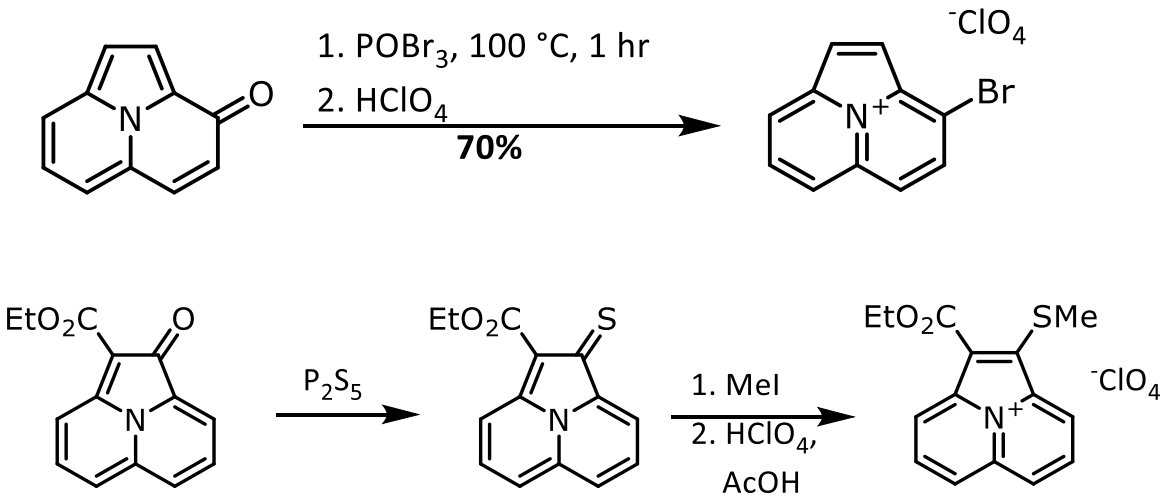
Modification of substituents



- Many of these syntheses start from ester- or sulfide-substituted starting materials – these can be removed

Boekelheide and coworkers - J. Am. Chem. Soc. 1961, 83 (2), 453-458
Farquhar et al – J. Chem. Soc. Perkin Trans. 1 1984, 2553

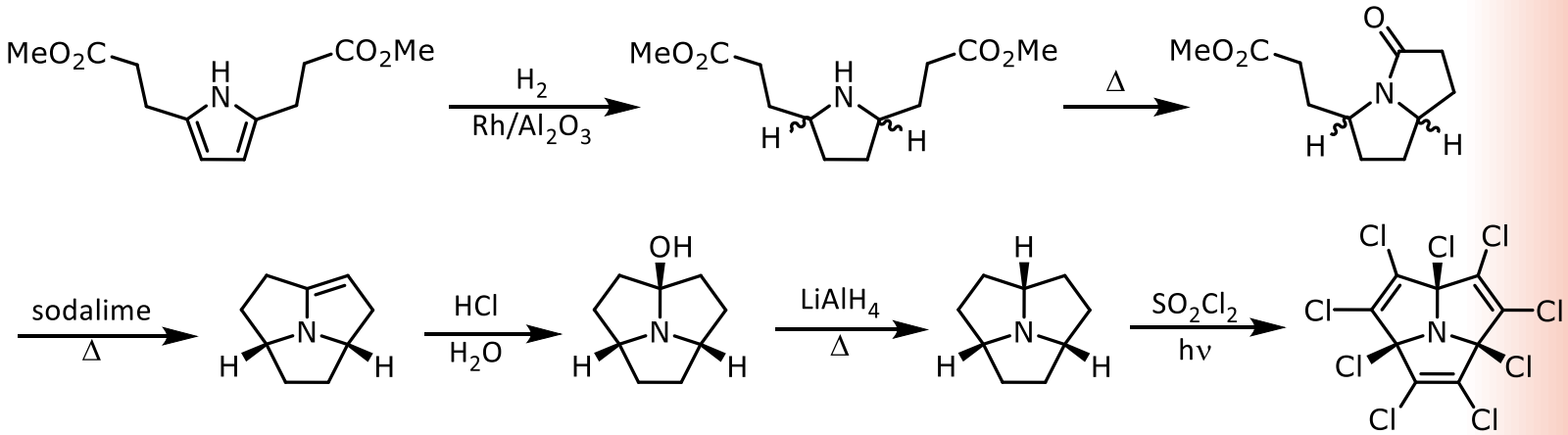
Modification of substituents



- Could provide functional handles for further derivatization – little of this has been explored

Boekelheide and coworkers – J. Chem. Soc. Perkin Trans. 1 1984, 2553

The first '[2.2.2]cyclazine'



- Formation of the strained tricyclic structure by photochemical oxidation

Mascal and coworkers – J. Org. Chem. 1998, 63, 6016-6020

Outline

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- Uses and properties of cyclazines
- The perhydroazaphenalene natural products
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  - Spring's myrrhine synthesis
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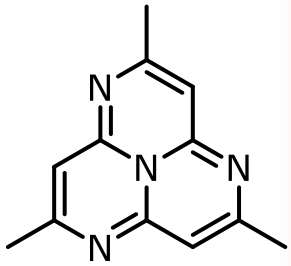
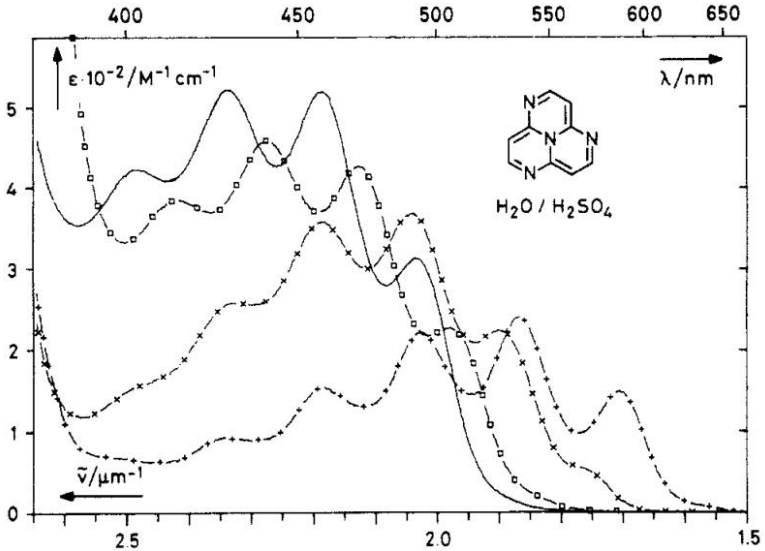
Optical properties

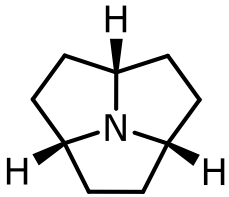
- Dark purple crystals
- In aqueous H_2SO_4, turns orange-red, then yellow-orange, then yellow with successive protonations
- Also exhibits fluorescence with pulsed laser excitation

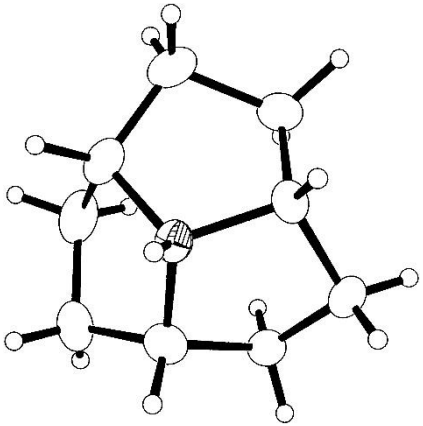




Wirz and coworkers – J. Am. Chem. Soc. 1986, 108, 17-22

Superbasic nitrogen

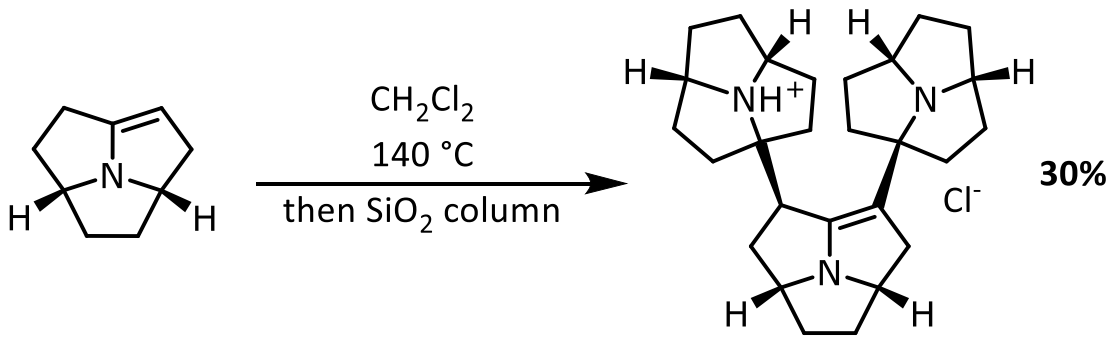


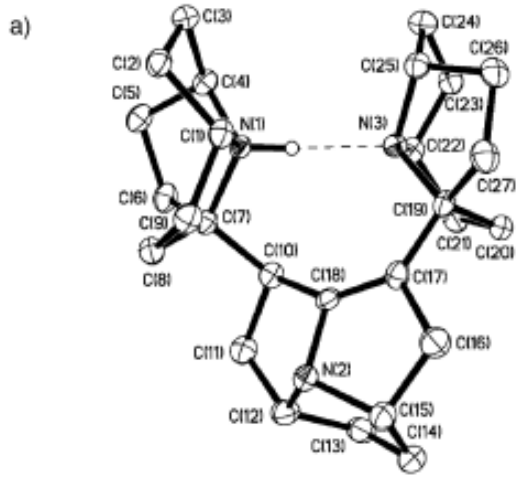


- Most basic trialkylamine known: $pK_aH \sim 11$ (H_2O)
- "Acutely pyramidalized" nitrogen

Mascal and coworkers – J. Org. Chem. 1998, 63, 6016-6020

Superbasic nitrogen

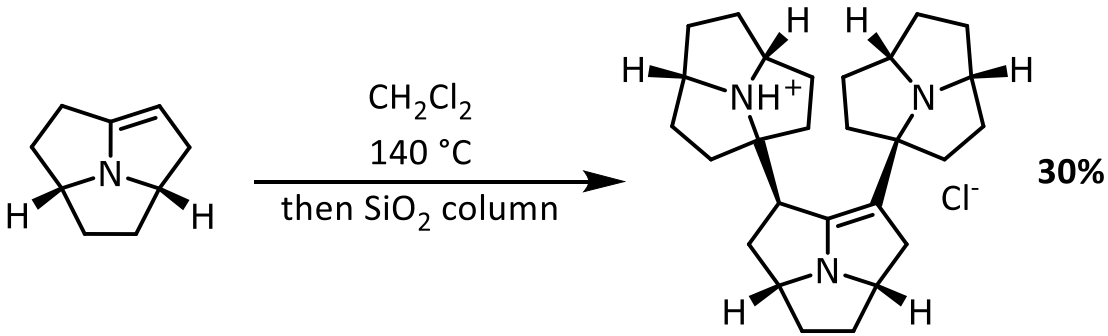




- Chelates protons between the saturated ring systems
- Chiral superbase
- Potential uses in cryptands

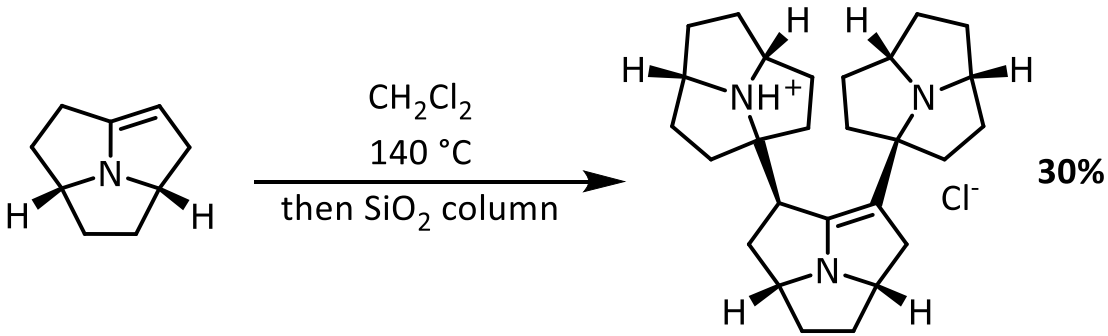
Mascal et al. – Angew. Chem. 2001, 113 (19), 3809-3811

Group problem



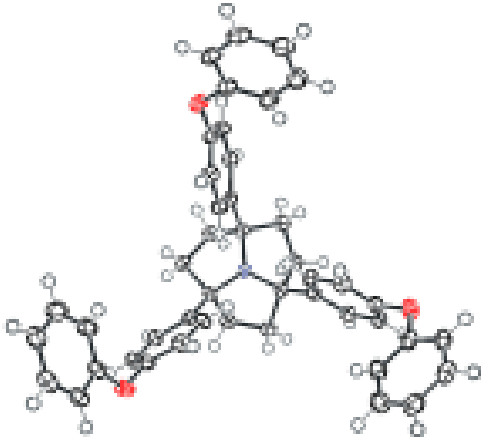
- What is the mechanism of this transformation? (Justify stereochemistry.)

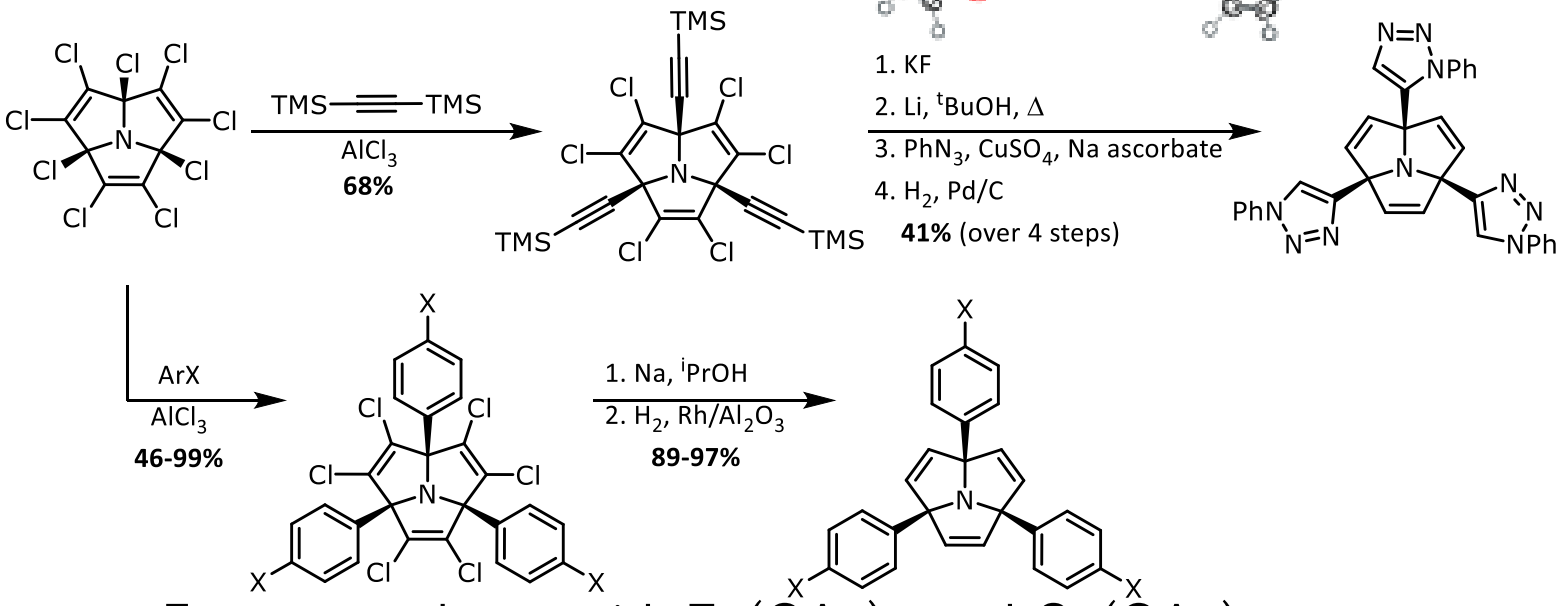
Group problem - solution



- Sufficiently basic to form a carbene from CH_2Cl_2
- The azatriquinenamine acts firstly as an enamine nucleophile, then tautomerizes and acts again as a nucleophile

Tripodal ligands





- Form complexes with $Zn(OAc)_2$ and $Co(OAc)_2$
- Comparison with tren – high degree of preorganization

Mascal and coworkers – Angew. Chem. 2011, 123 (3), 743-745

Outline

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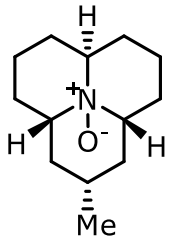
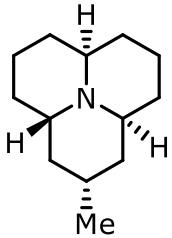
Perhydroazaphenalene natural products

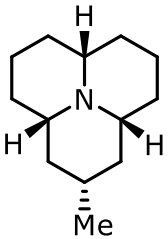
- Isolated from ladybug defense secretions



coccinelline



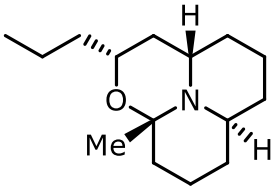
hippodamine



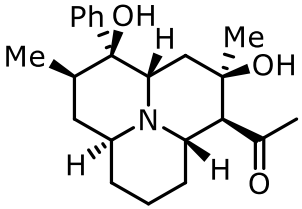
myrrhine


Hippodamia convergens

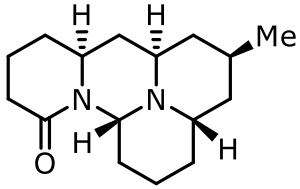
- Others from orchids, mosses



porantheridine



crepidine

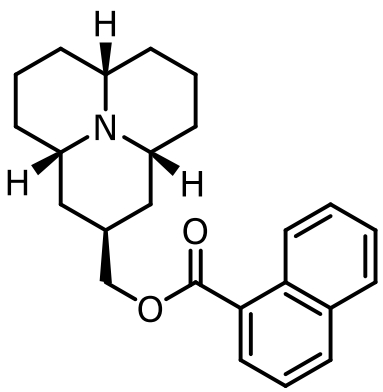


cernuine


Dendrobium crepidatum

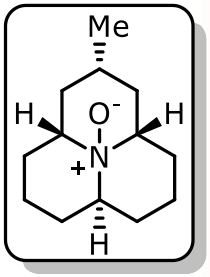
Uses of coccinellid derivatives

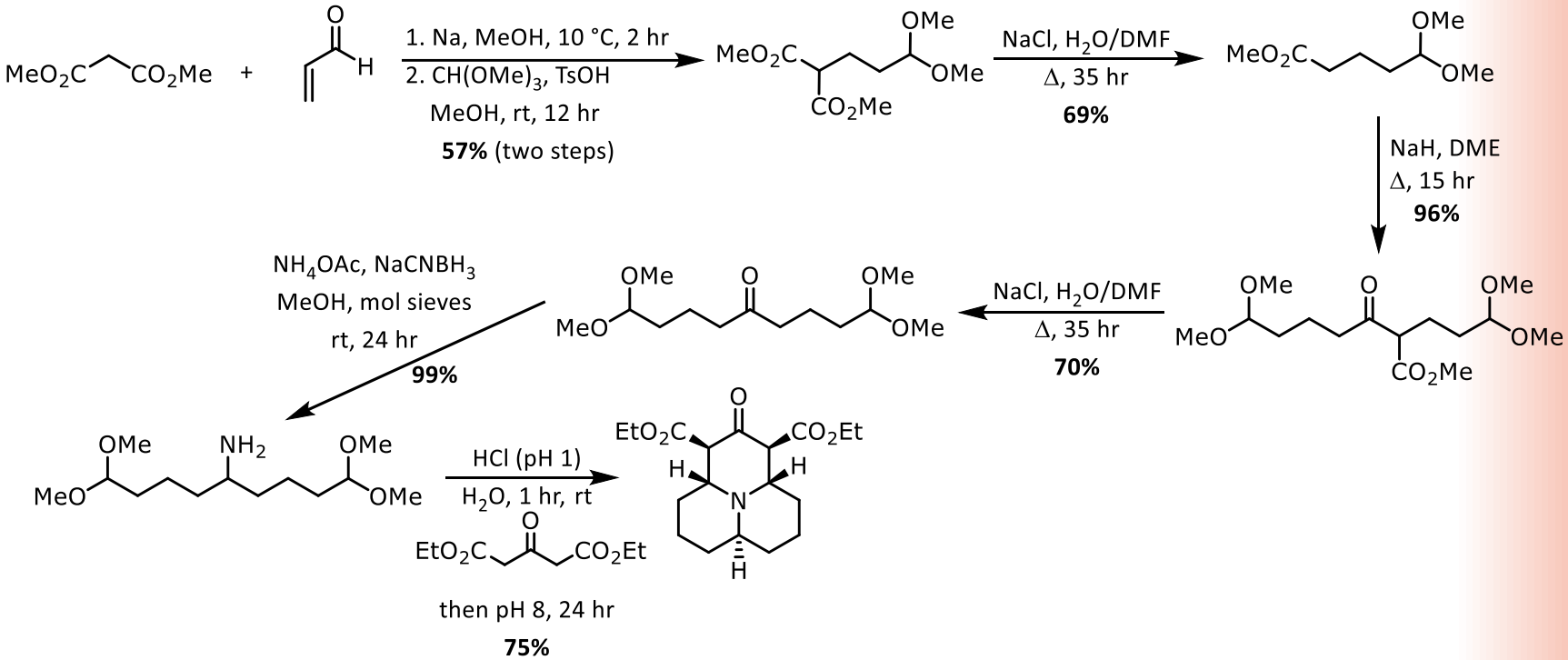
- Ladybug parasites are attracted to coccinellid alkaloids
- As well as their bitter taste, coccinellids interfere with vertebrate nervous systems
- Naphthalenoyl myrrhine displays affinity for rat 5-HT_3 receptors



Woodcock and coworkers – J. Chem. Ecol. 2001, 27 (1), 33-43
Langlois and coworkers – Eur. J. Med. Chem. 1993, 28, 369-880

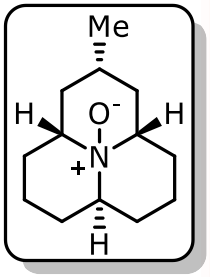
Coccinelline synthesis

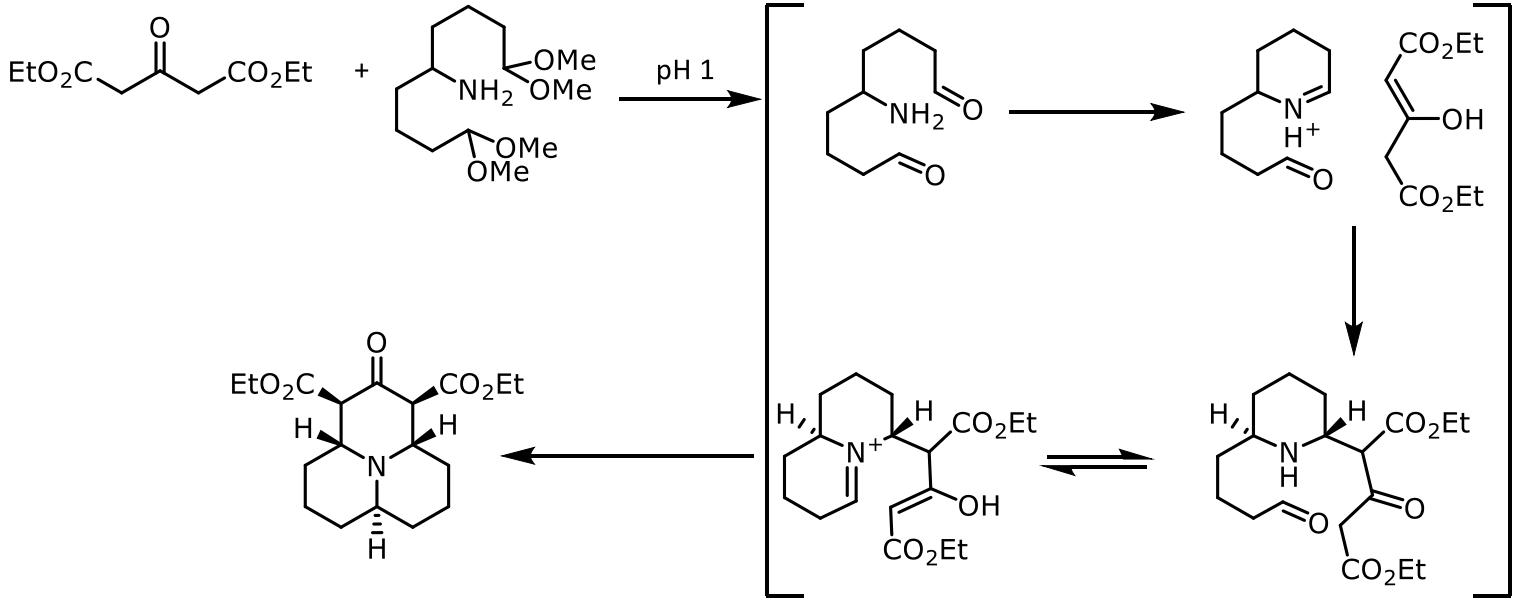




Stevens and coworkers – J. Am. Chem. Soc. 1979, 101 (23), 7032

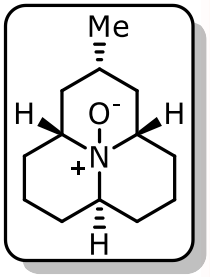
Cyclization step

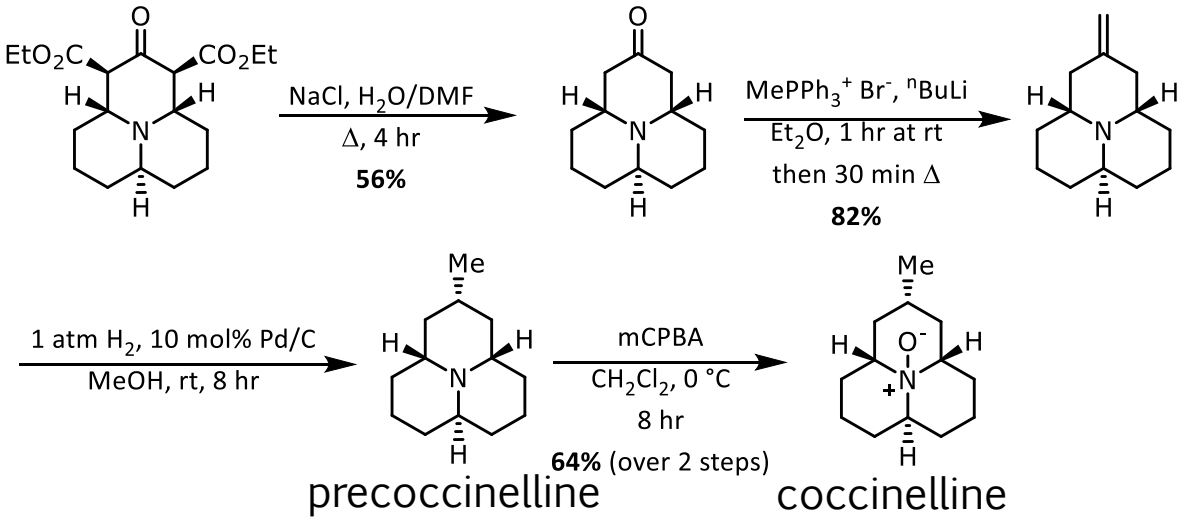




Stevens and coworkers – J. Am. Chem. Soc. 1979, 101 (23), 7032

Final steps

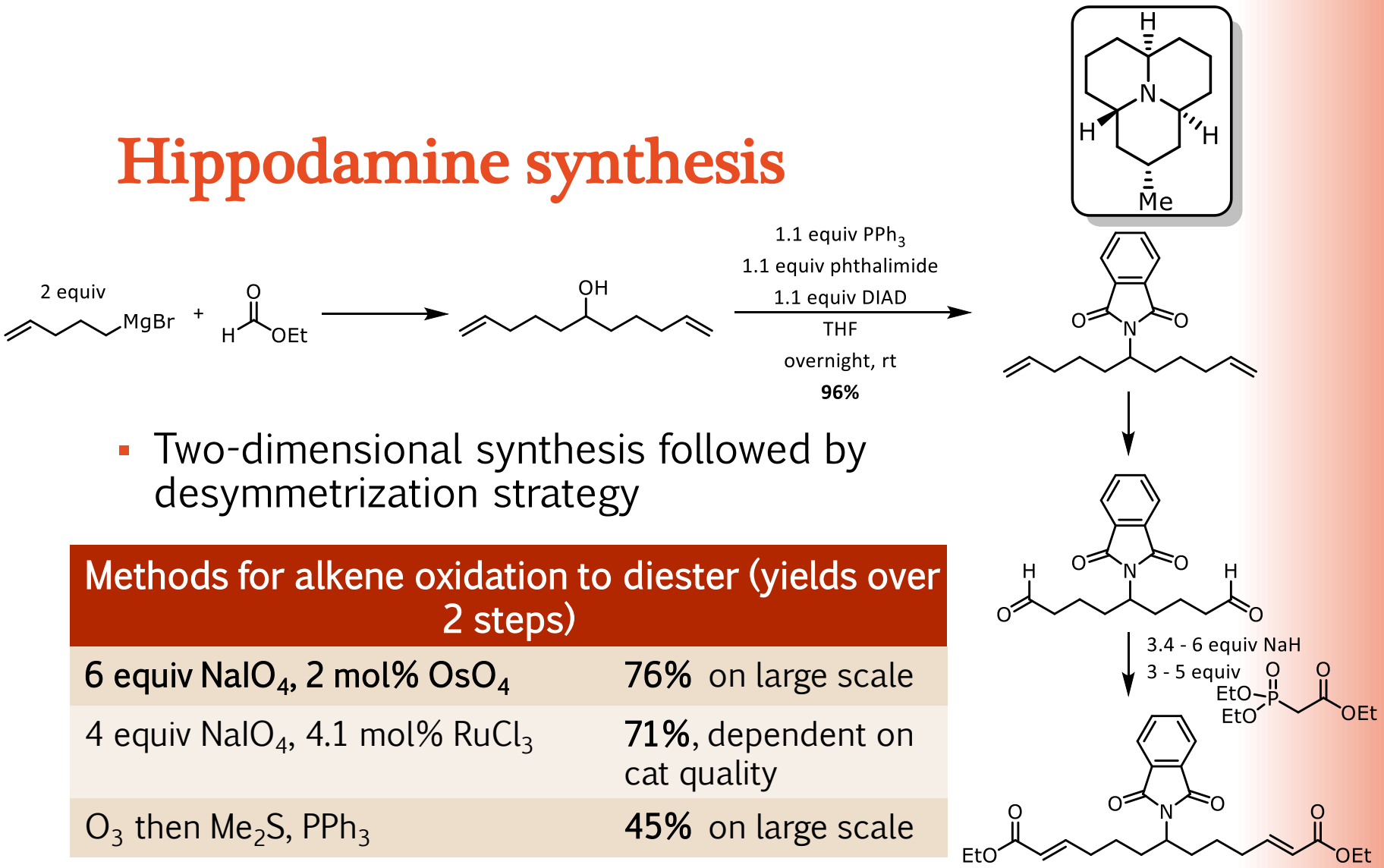




- Coccinelline in **5.8%** overall yield over 11 steps

Stevens and coworkers – J. Am. Chem. Soc. 1979, 101 (23), 7032

Hippodamine synthesis

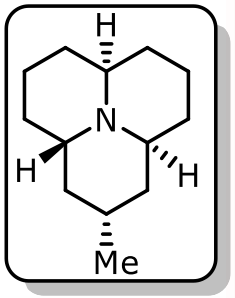


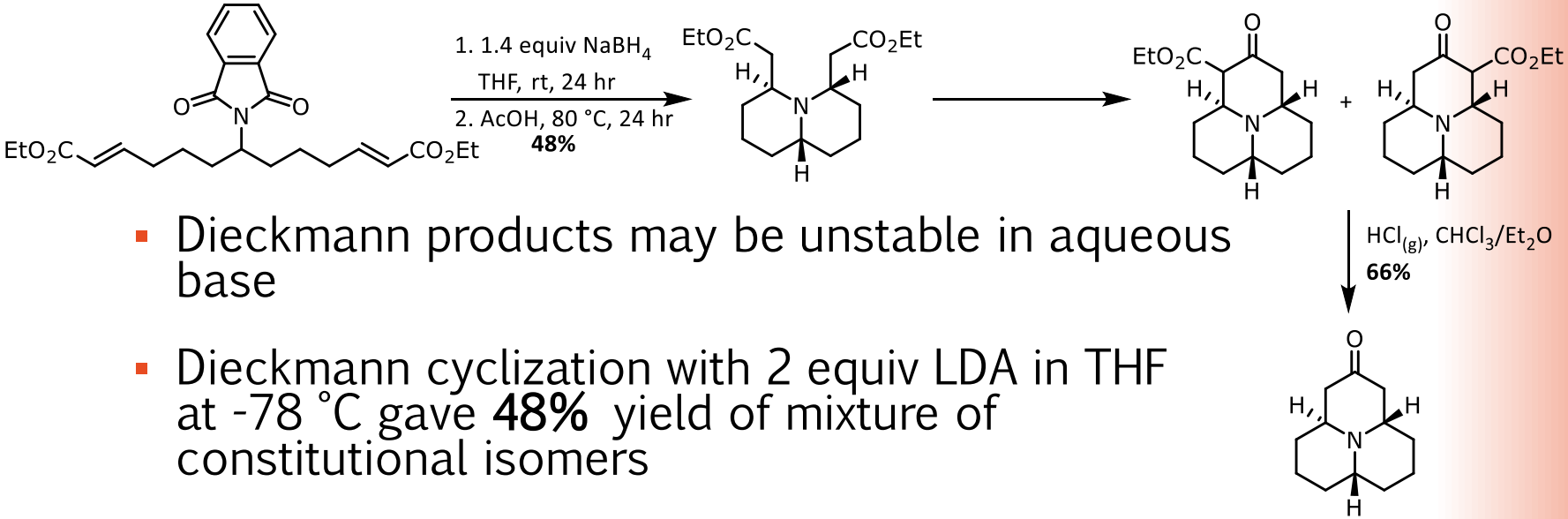
- Two-dimensional synthesis followed by desymmetrization strategy

Methods for alkene oxidation to diester (yields over 2 steps)	
6 equiv $NaIO_4$, 2 mol% OsO_4	**76%** on large scale
4 equiv $NaIO_4$, 4.1 mol% $RuCl_3$	**71%**, dependent on cat quality
O_3 then Me_2S, PPh_3	**45%** on large scale

Stockman and coworkers – Org. Biomol. Chem. 2005, 3, 73-83

Hippodamine synthesis

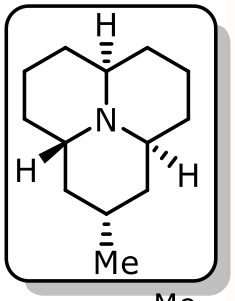


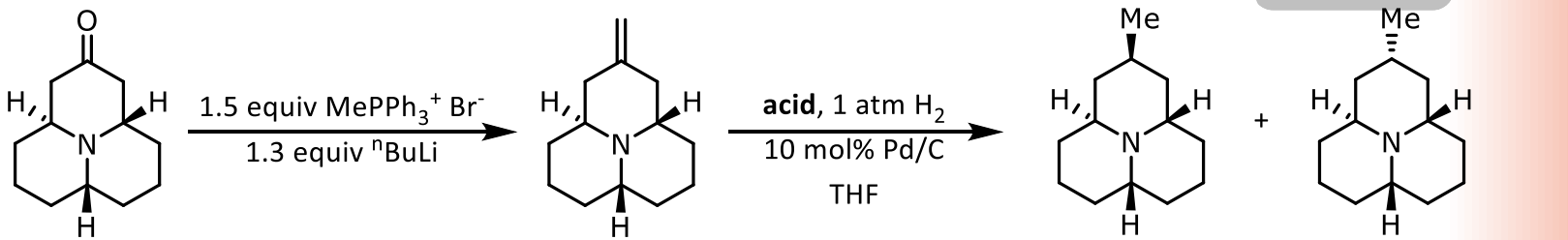


- Dieckmann products may be unstable in aqueous base
- Dieckmann cyclization with 2 equiv LDA in THF at -78 °C gave **48%** yield of mixture of constitutional isomers
- Alternative method with 2 equiv KO^{t}Bu in benzene (120 °C, 2 hr) with Dean-Stark trap charged with Li to remove EtOH produced gave **84%** yield (mixture of isomers)

Stockman and coworkers – Org. Biomol. Chem. 2005, 3, 73-83

Hippodamine synthesis



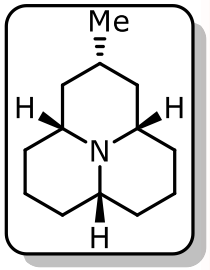


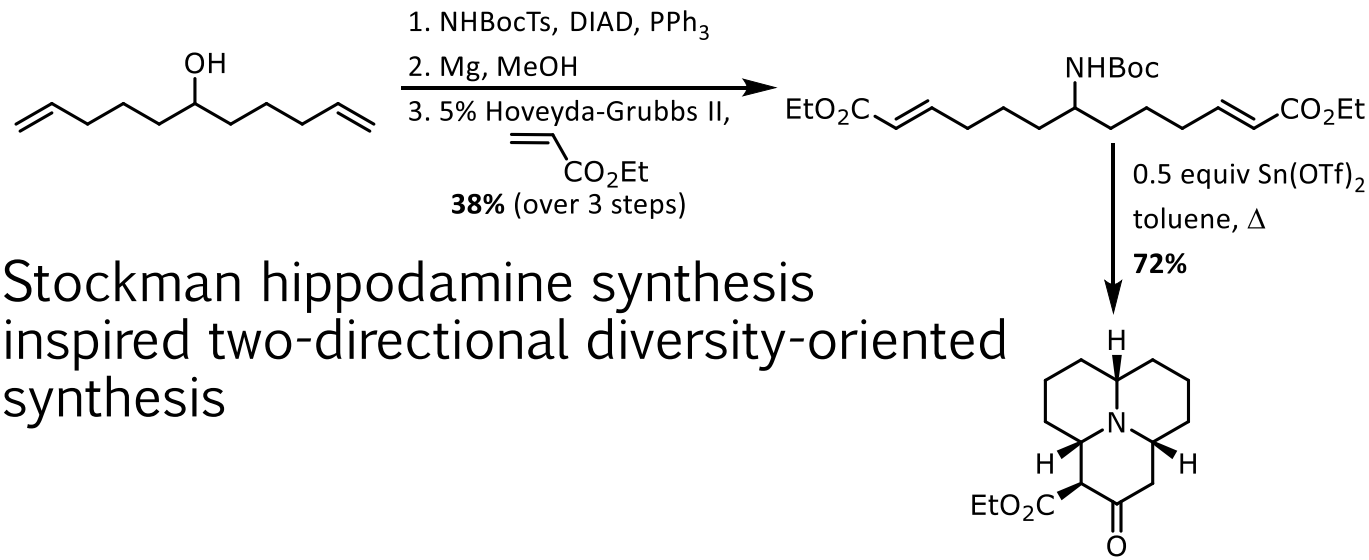
hippodamine *epi*-hippodamine

- Hydrogenation without acid additive favored *epi*-hippodamine
- Various acids screened; mesitylenesulfonic acid in THF gave 93% combined yield of products in 3.5 : 1 ratio
- Formation of a xanthate ester and Barton-McCombie deoxygenation gave 46% combined yield in 2.3 : 1 ratio
- Hippodamine in **7.2%** overall yield, over 8 steps

Stockman and coworkers – Org. Biomol. Chem. 2005, 3, 73-83

Spring's myrrhine synthesis

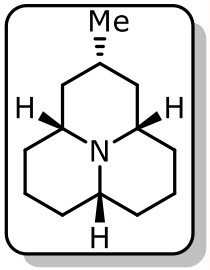


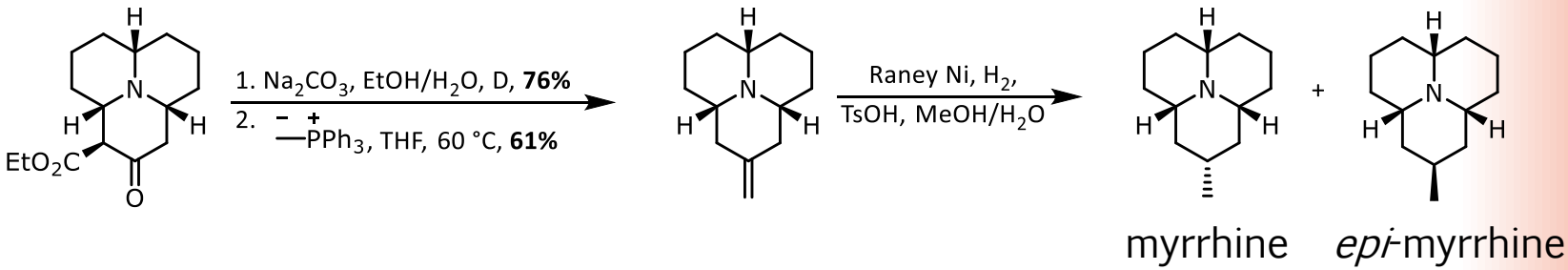


- Stockman hippodamine synthesis inspired two-directional diversity-oriented synthesis

Spring and coworkers – Beilstein J. Org. Chem. 2012, 8, 850-860

Myrrhine synthesis





- Hydrogenation gave **57%** combined yield of 10.4 : 1 product ratio
- Myrrhine in **6.6%** overall yield over 8 steps
- Myrrhine is the most thermodynamically stable of the coccinellid alkaloids

Spring and coworkers – Beilstein J. Org. Chem. 2012, 8, 850-860

Outline

- Methods of synthesis
- Uses and properties of cyclazines
- The perhydroazaphenalene natural products
  - Stevens's coccinelline synthesis
  - Stockman's hippodamine synthesis
  - Spring's myrrhine synthesis
- Summary

Summary

- Aromatic cyclazines have been well-studied for their optical properties
- Potential uses for saturated cyclazine derivatives exist as cryptands, chiral bases and tripodal ligands
- Coccinellids have medicinal potential
- All of the coccinellid alkaloids have now been synthesized asymmetrically or racemically

Reviews

- Science of Synthesis: Houben-Weyl methods of molecular transformations Vol. 17, Chapter 4
- Boekelheide and coworkers – J. Am. Chem. Soc. 1959, 81 (6), 1459-1465
- Flitsch and Krämer - Adv. Heterocycl. Chem. 1978, 22, 321-365
- Review on coccinellid chemistry:
  Glisan King and Meinwald – Chem. Rev. 1996, 96 (3), 1105-1122