An Environmentally Friendly Procedure for Synthesis of Nitrogen-containing Molecules

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Physics Engineering
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Department of Chemistry and Biochemistry, UCSB
Funding source: UCSB & Eli Lilly

Top-selling Pharmaceuticals in 2010

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- Three-quarters contain at least one carbon-nitrogen bond

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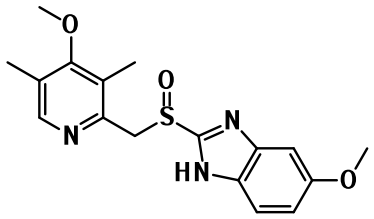
- Examples

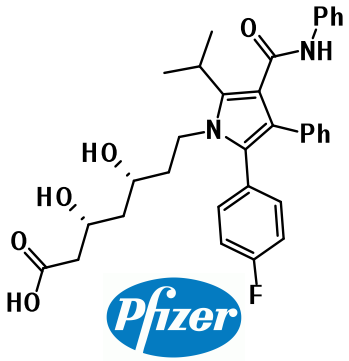
1 Nexium



AstraZeneca

Proton Pump Inhibitor

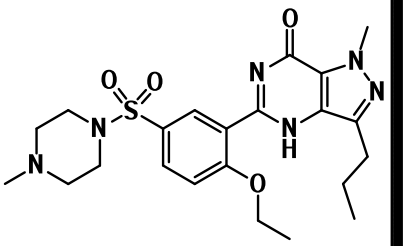
2 Lipitor



Pfizer

Cholesterol Regulator

27 Viagra



Pfizer

Erectile Disfuction PRD

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- Three-quarters contain at least one carbon-nitrogen bond

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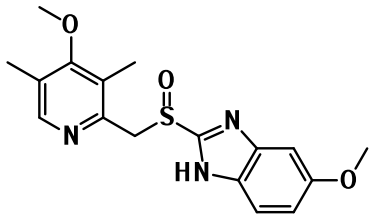

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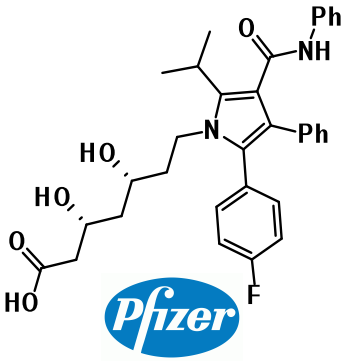

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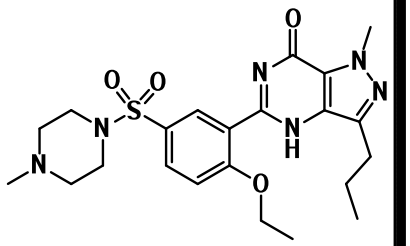


Pfizer

Erectile Disfuction PRD

- Current approaches to construction produce significant waste

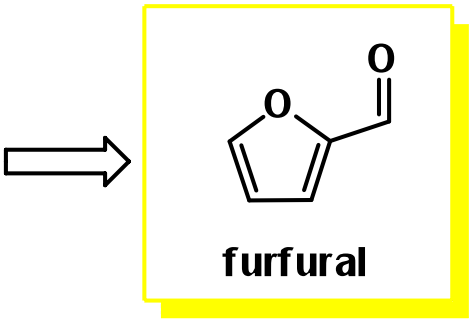
Sustainable Reaction Design

Sustainable Reaction Design

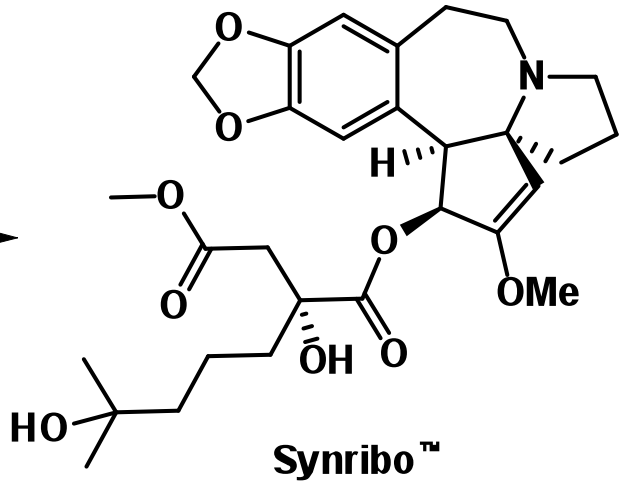
Use Renewable Starting Materials

Sustainable Reaction Design

Courtesy of ORNL



steps



Synribo™
Chronic Mylogenous Leukemia

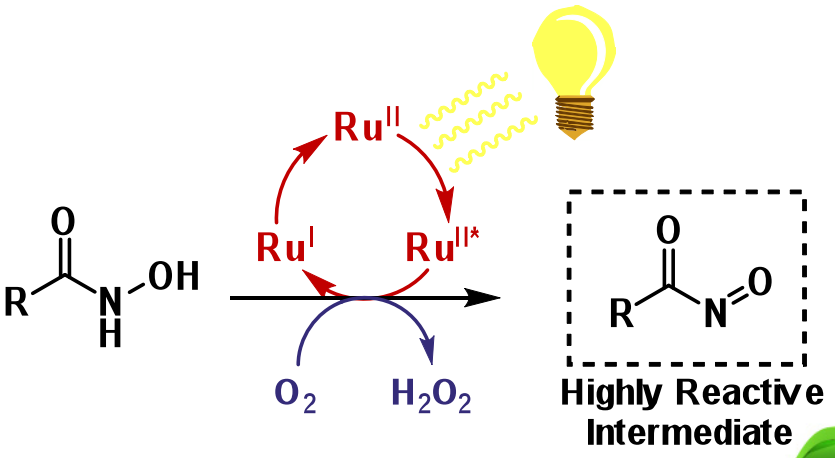
Use Renewable Starting Materials

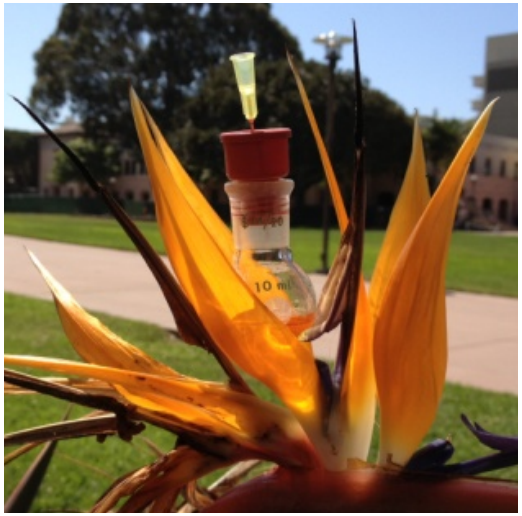
Sustainable Reaction Design

Use Renewable Starting Materials

Use Environmentally Benign Reagents

Sustainable Reaction Design





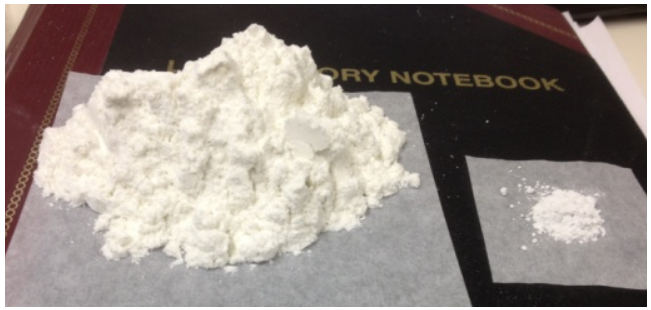
Use Renewable Starting Materials

Use Environmentally Benign Reagents

Sustainable Reaction Design

Minimize Waste By-products & Cost

Typical Catalyst
16.9 g of Bu_4NIO_4
$56



Our Catalyst
0.5 g of CuCl
$0.07

Use Renewable Starting Materials

Use Environmentally Benign Reagents

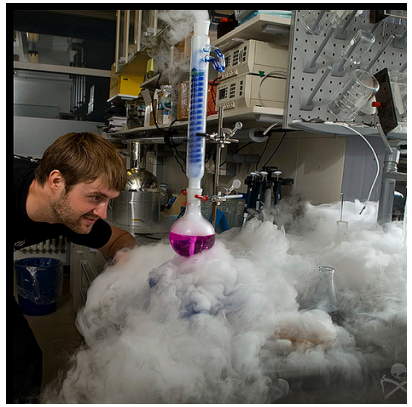
Sustainable Reaction Design

Use Environmentally Benign Reagents

Minimize Waste & Cost

Use Renewable Starting Materials

Develop Novel Chemistry



Sustainable Reaction Design Goal

- Implement green chemistry to construct C-N bonds

  green chemistry = benign methods → less waste

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Expand the organic chemist's toolbox

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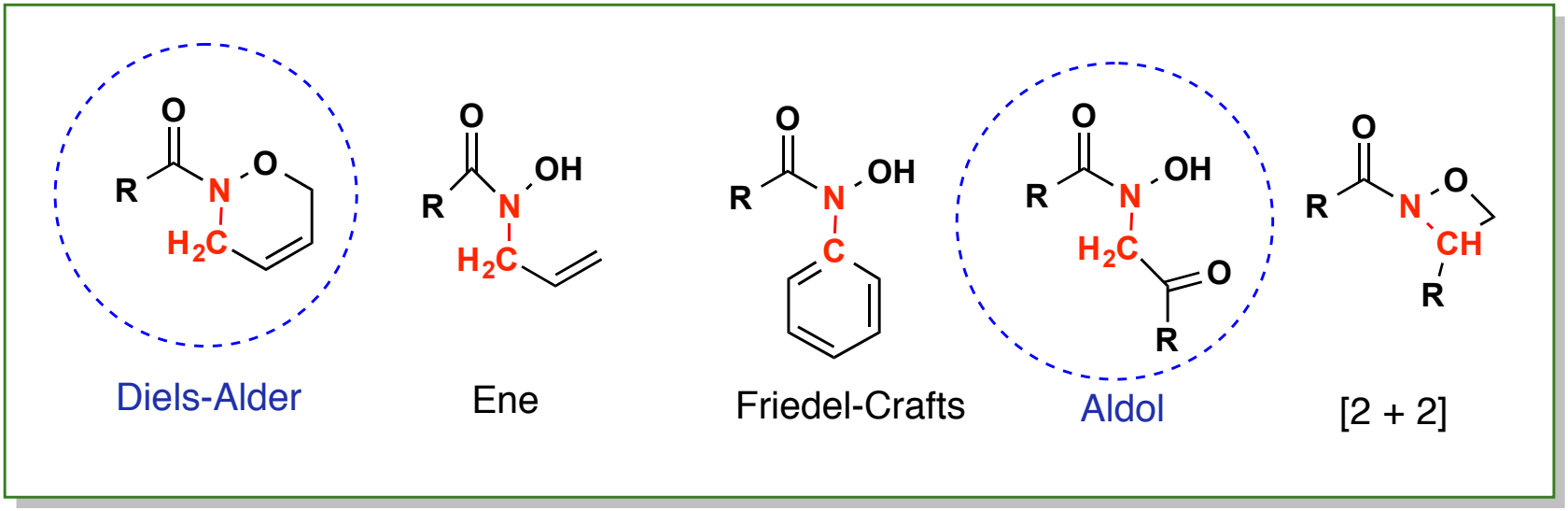
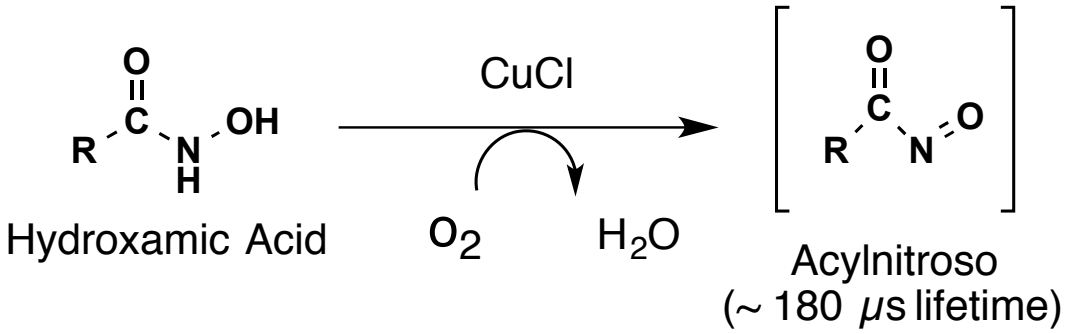
Platforms to Construct Carbon - Nitrogen Bonds



Sustainable Reaction Design Goal

Acylnitroso Project



Hydroxamic Acid

Acylnitroso
(~ 180 μs lifetime)

Sustainable Reaction Design Goal

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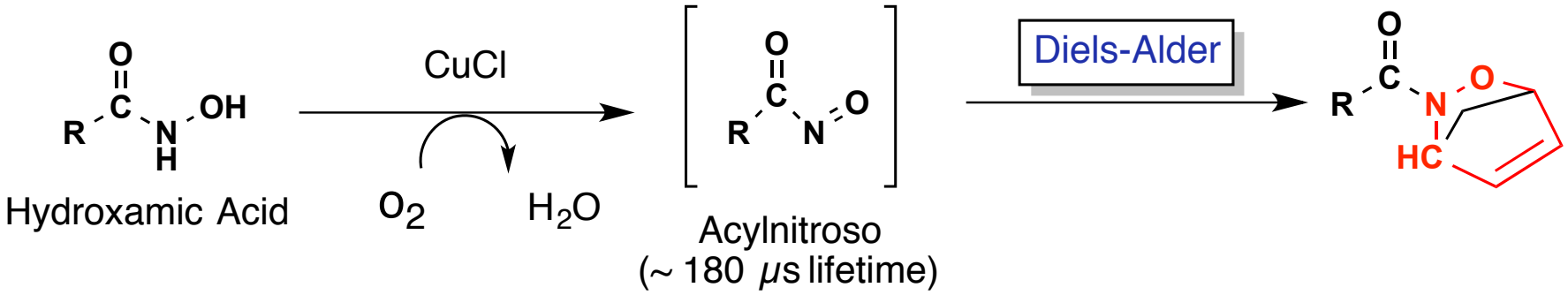

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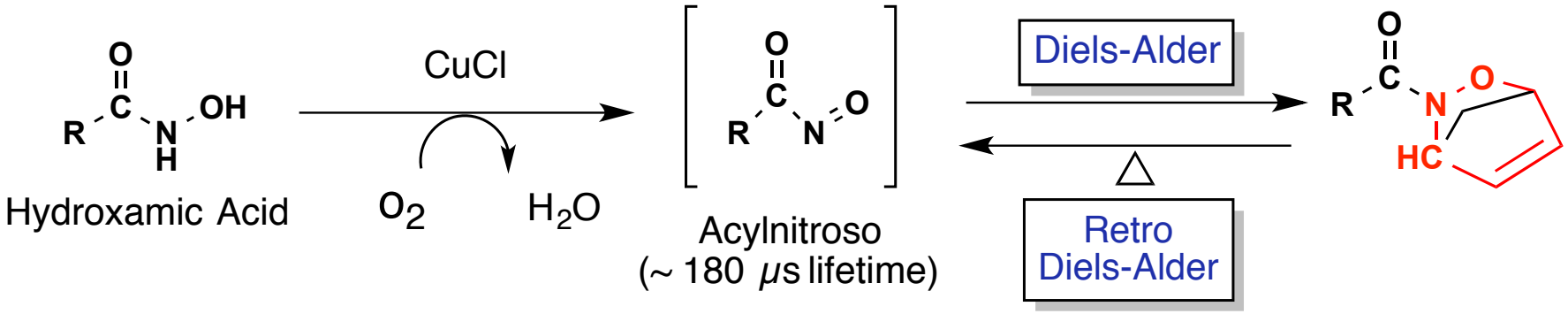

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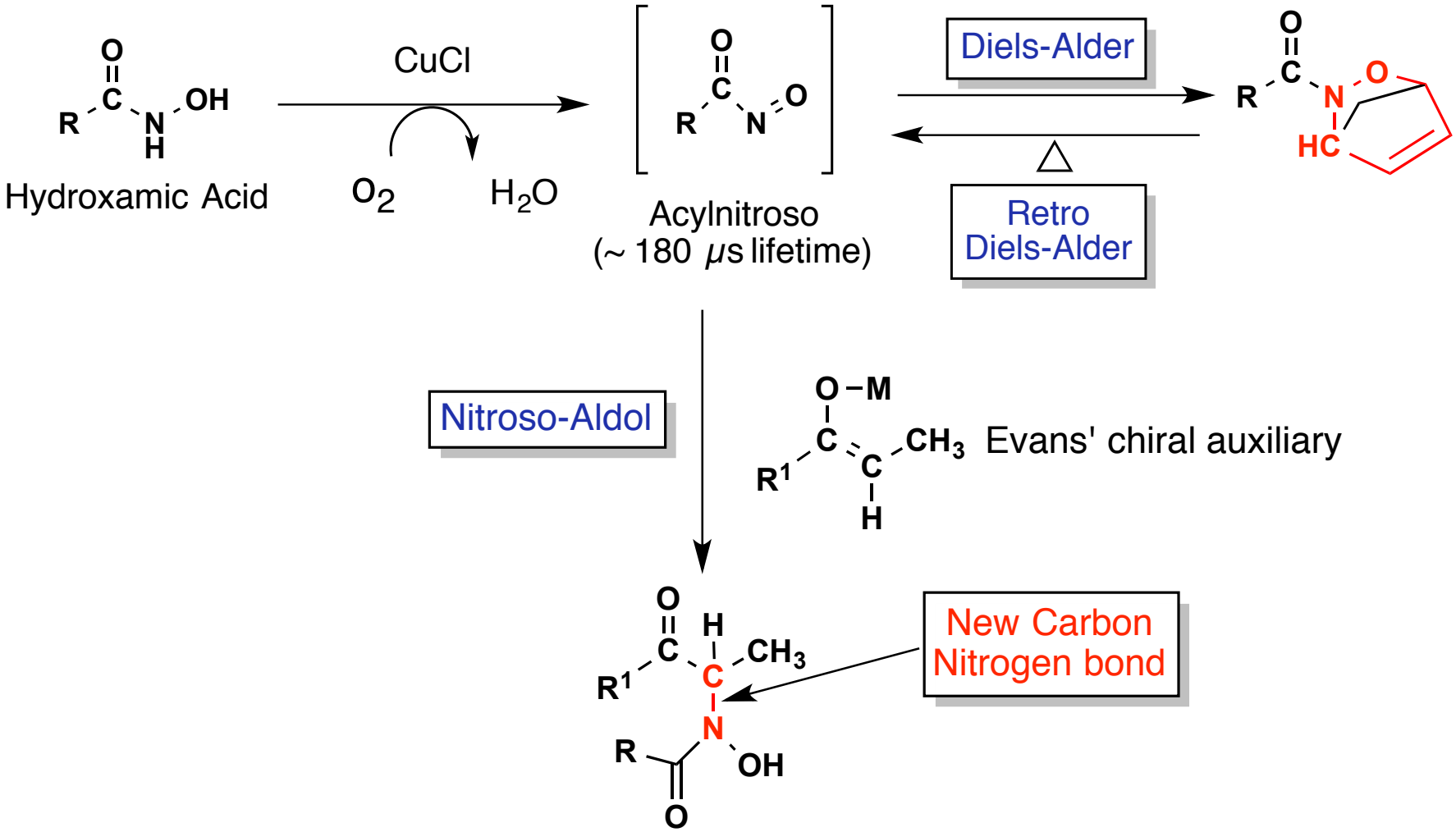
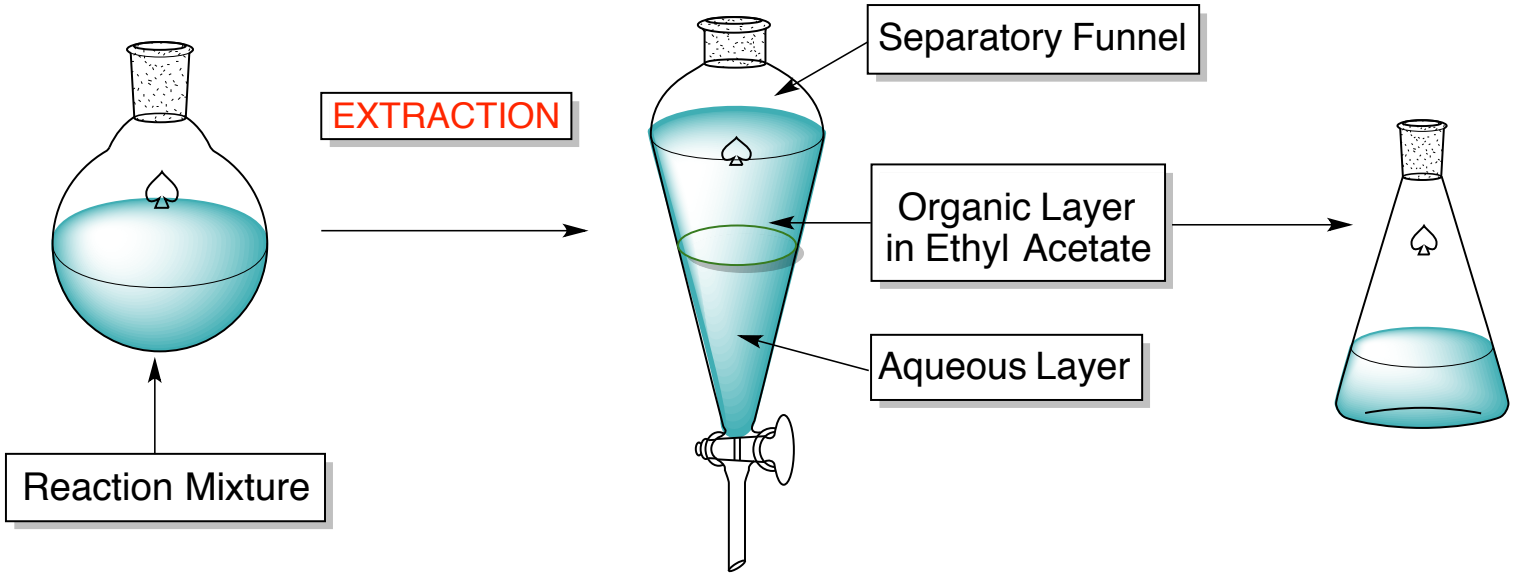


Acylnitroso Separation and Purification Techniques



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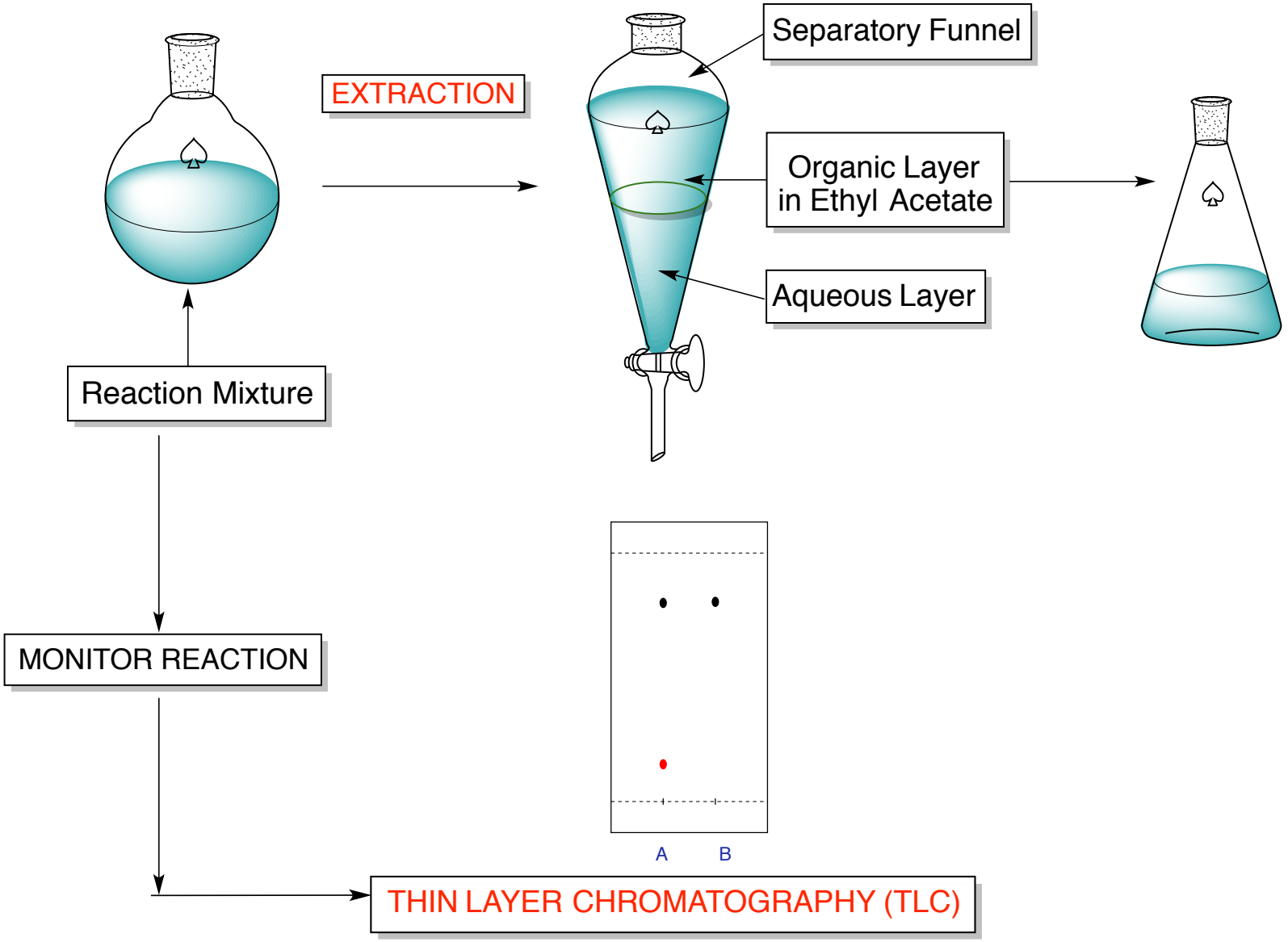

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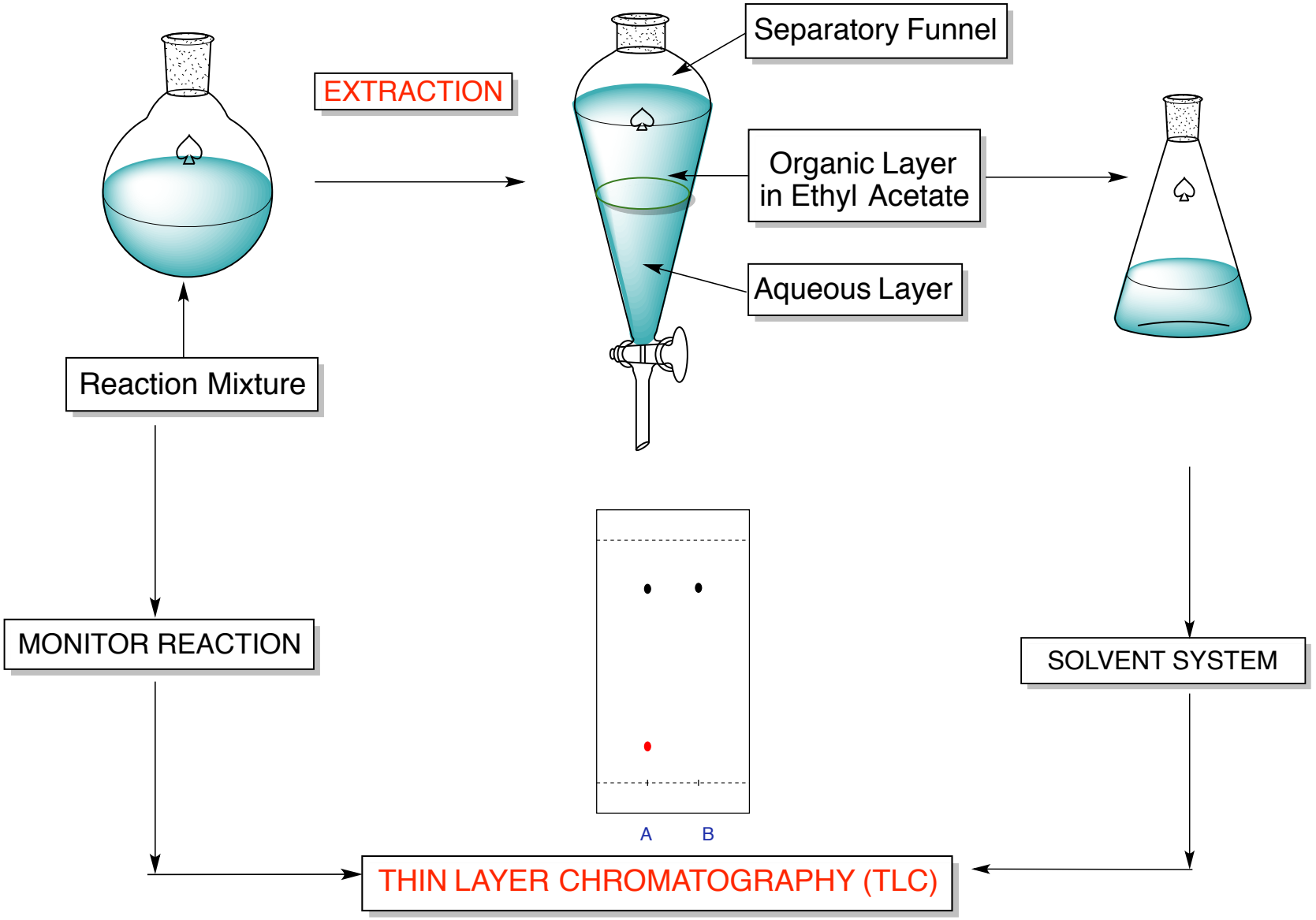

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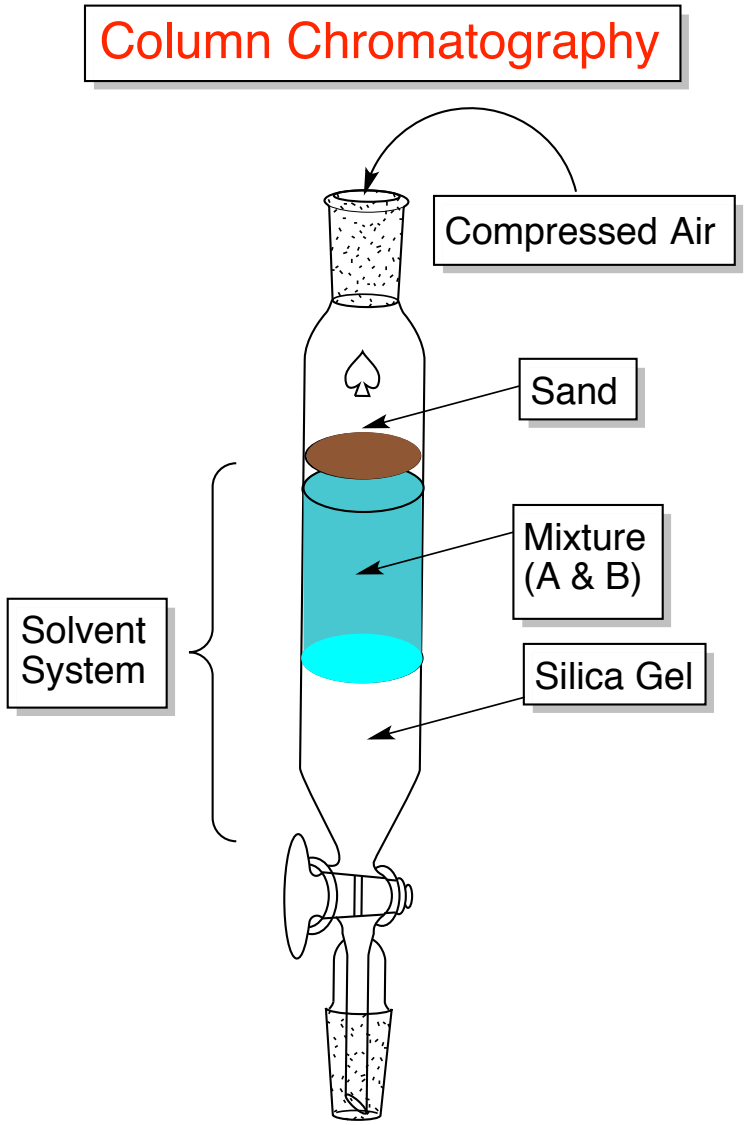
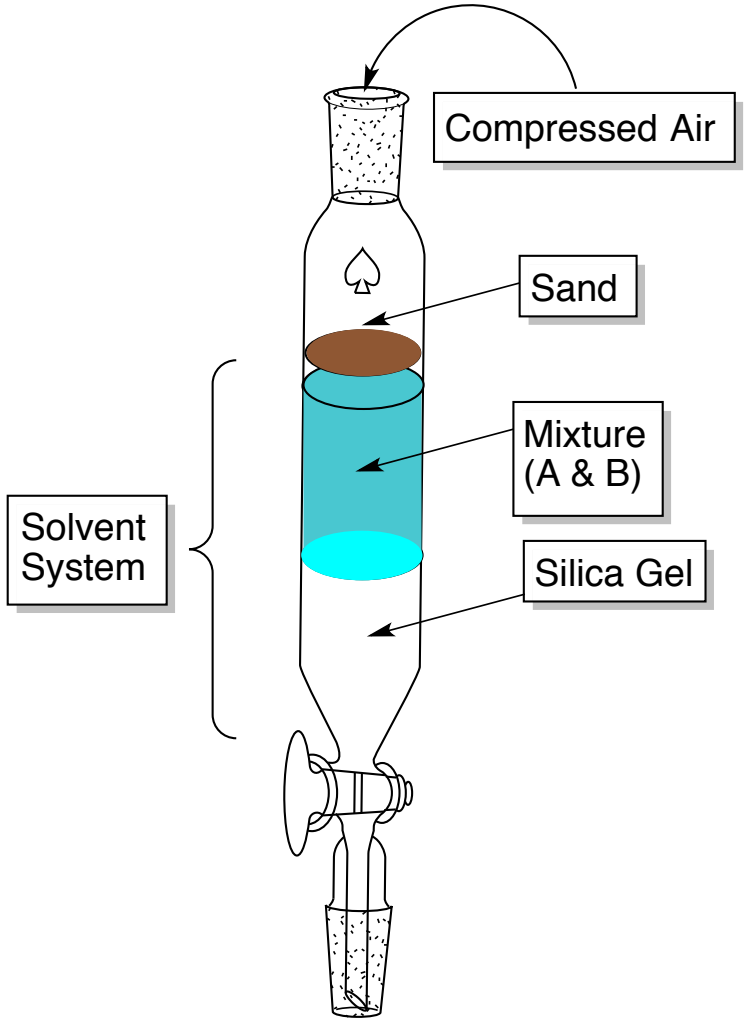
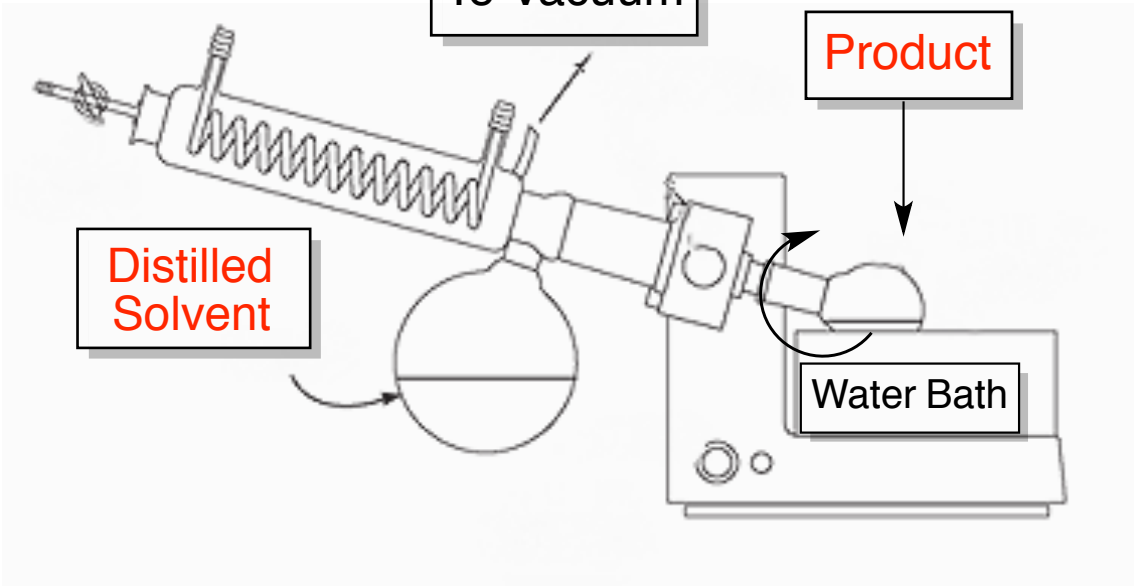


Acylnitroso Separation and Purification Techniques

Column Chromatography



Rotovaporation (Distillation)

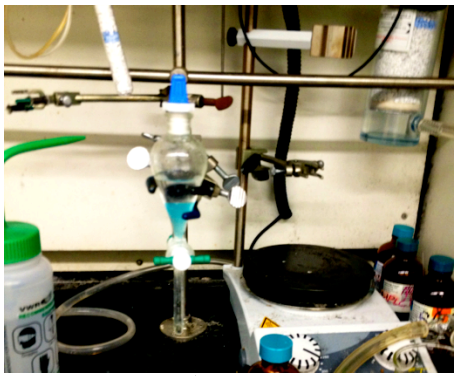


Acylnitroso Separation and Purification Techniques

Technique Pictures at the Read Lab

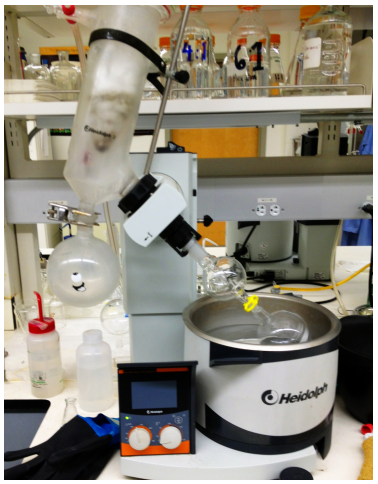
Stirring and Quenching

Extraction



Column Chromatography

Roto-Vaporation



Actual Reaction

Separation and Purification Methods

Nuclear Magnetic Resonance & Infrared Spectroscopy Analysis

To identify an isolated organic compound, the following techniques are primarily used:

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Infrared Spectroscopy (IR)

- used to identify the functional groups in a compound

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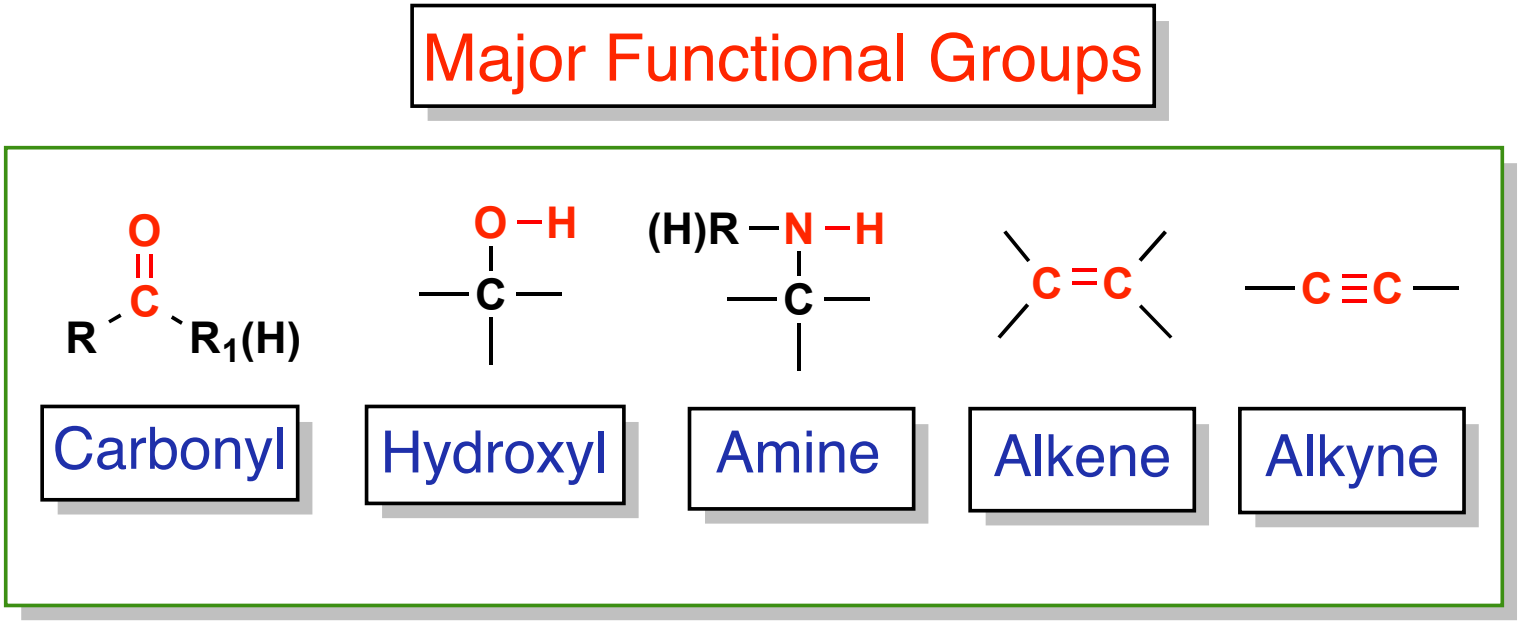
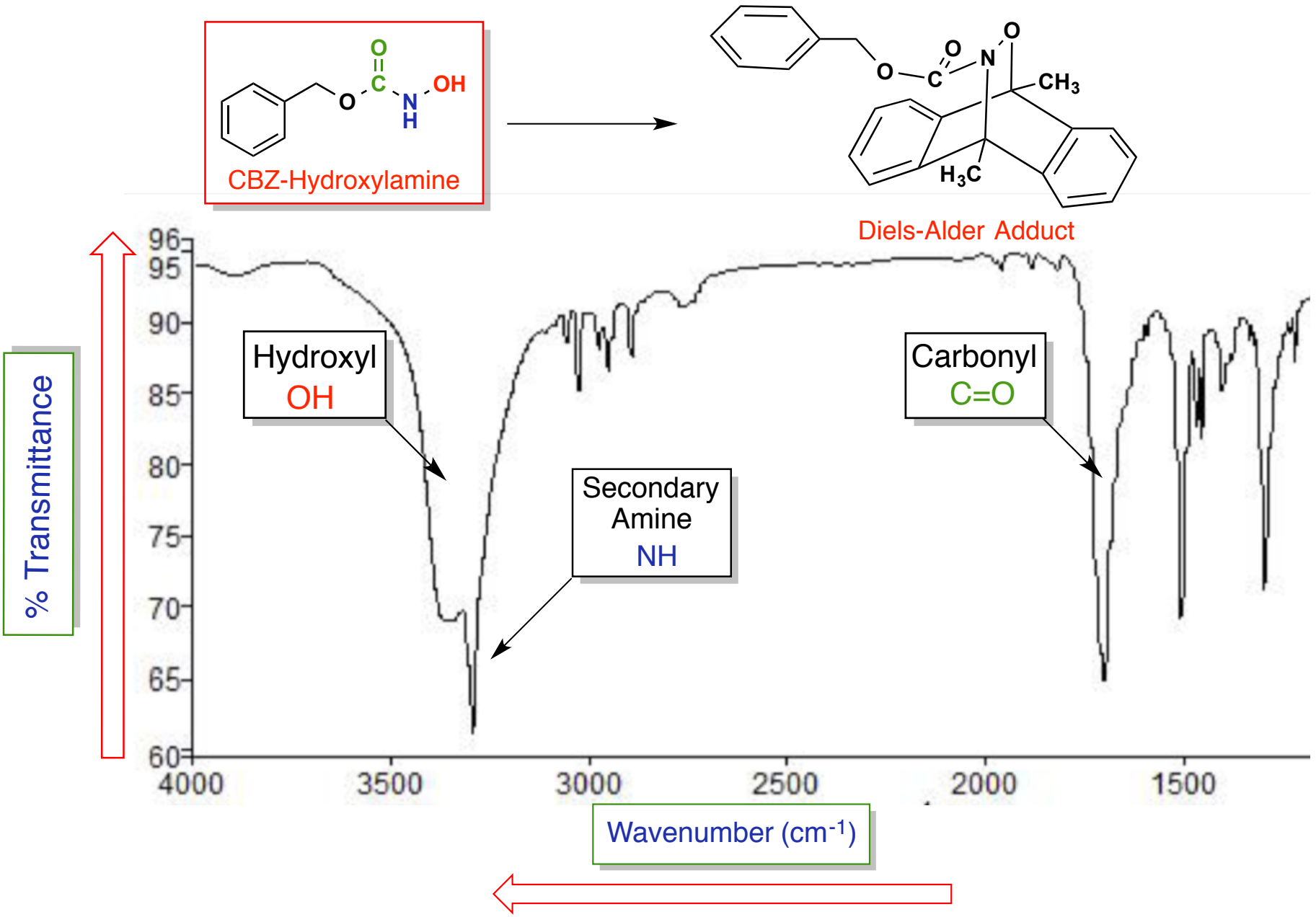
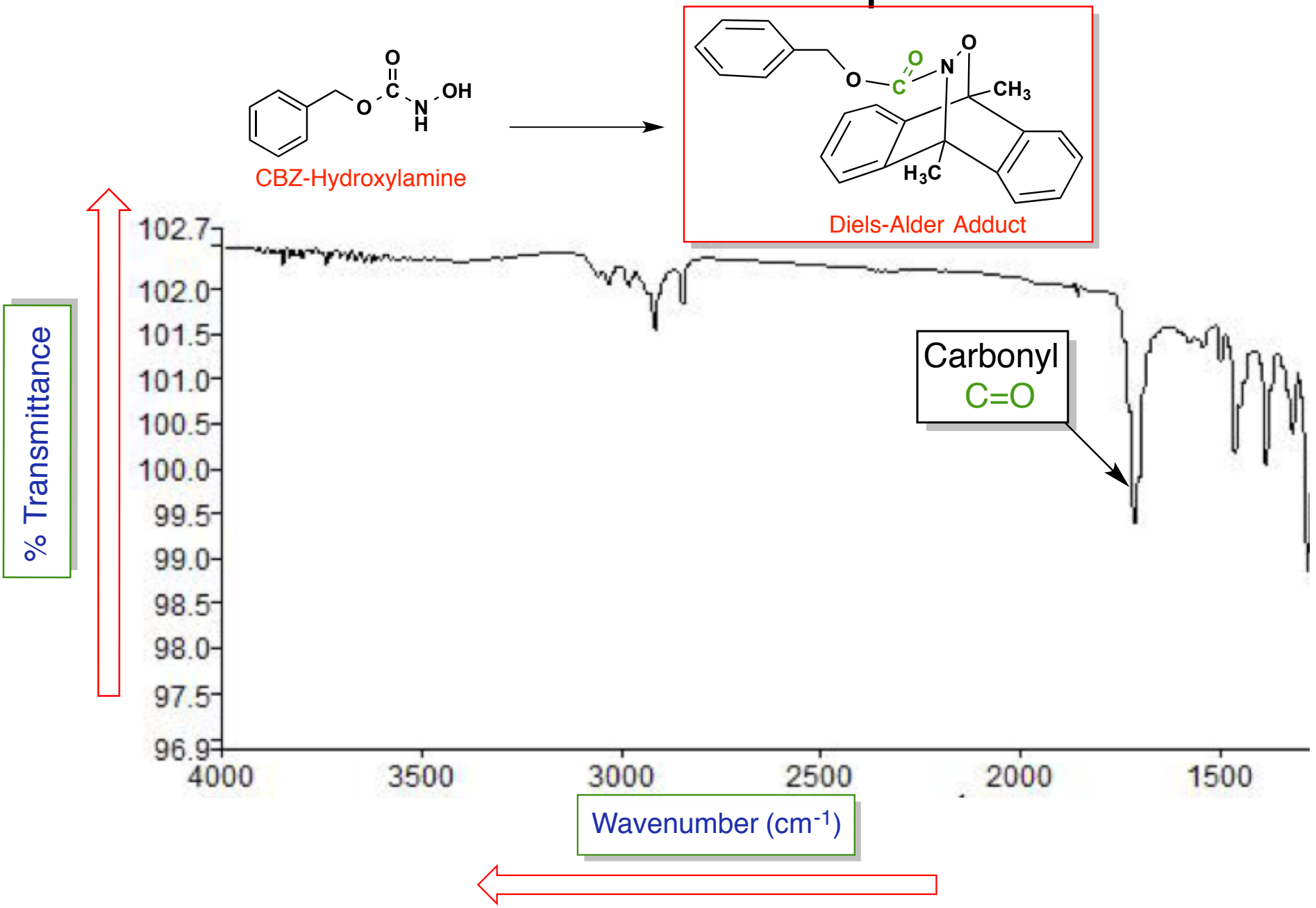


CBZ-Hydroxylamine IR Spectrum



Diels-Alder Adduct IR Spectrum



Nuclear Magnetic Resonance & Infrared Spectroscopy Analysis

Nuclear Magnetic Resonance (NMR)

- ^{1}H NMR (proton NMR)
  used to determine the number and type of hydrogen atoms in a molecule

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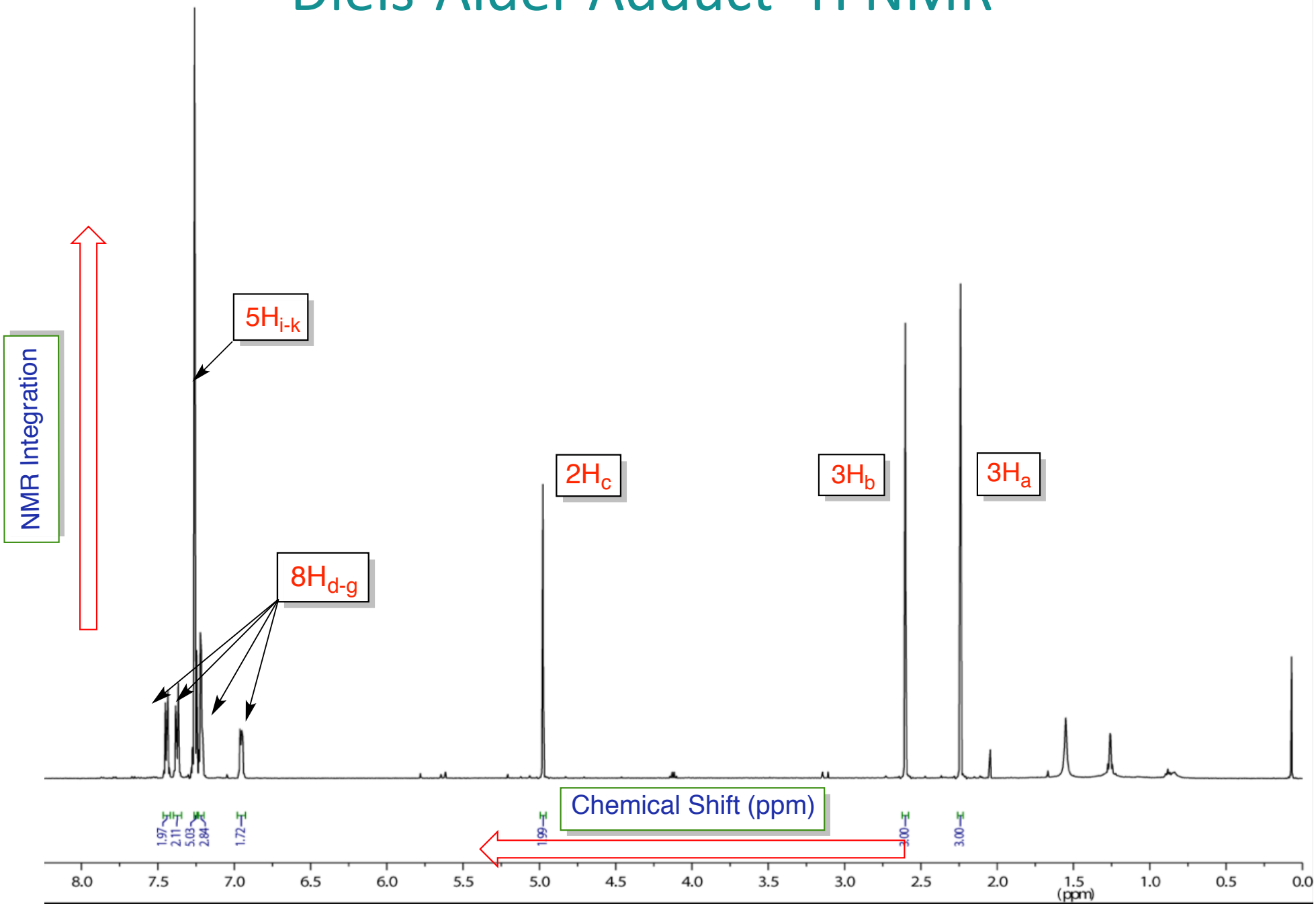
  used to determine the number and type of hydrogen atoms in a molecule

Number of Protons = Area under NMR signal

Types of Protons = Number of major NMR signals
(which depends on the electronic environment of proton)

Diels-Alder Adduct ^{1}H NMR



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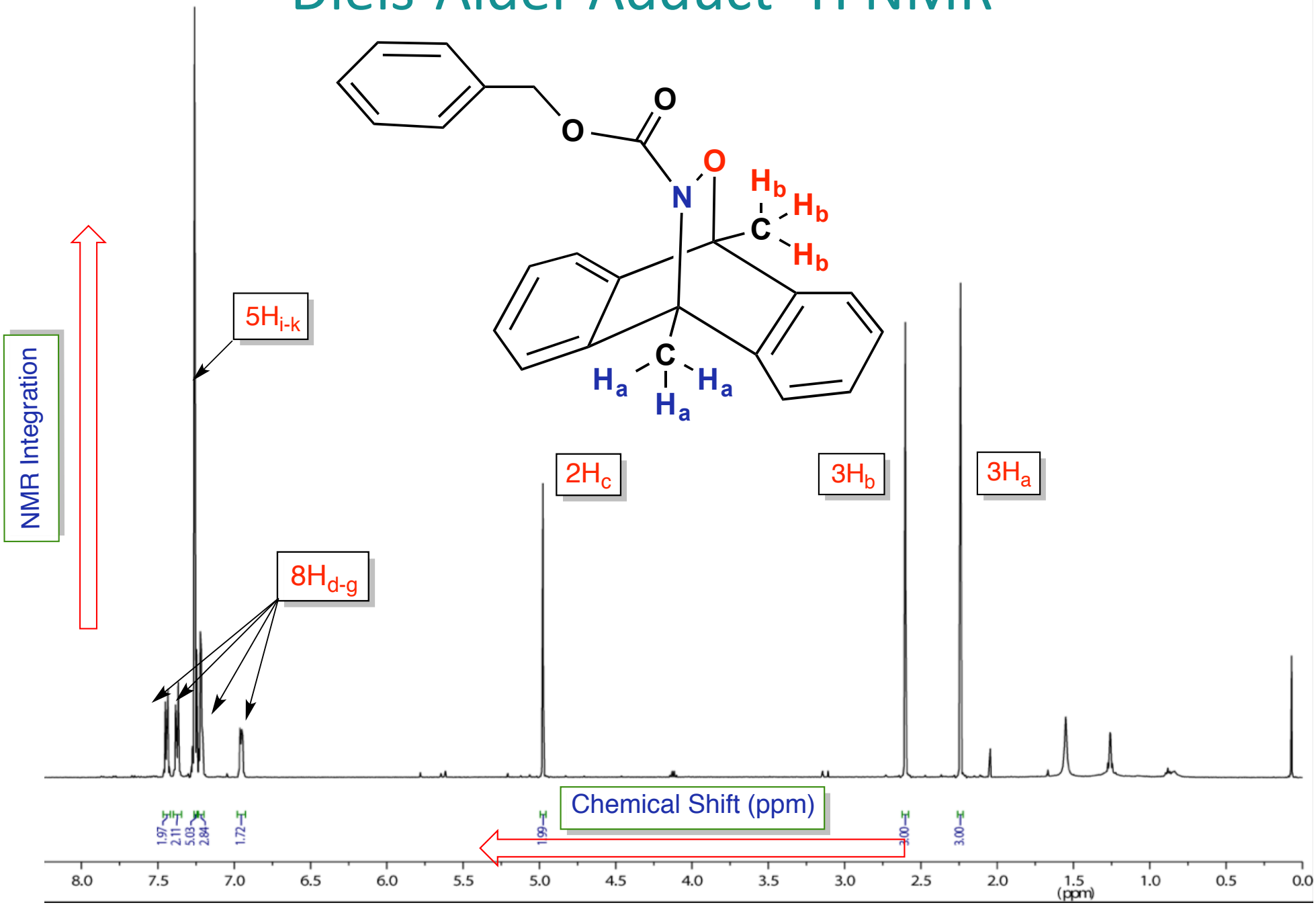
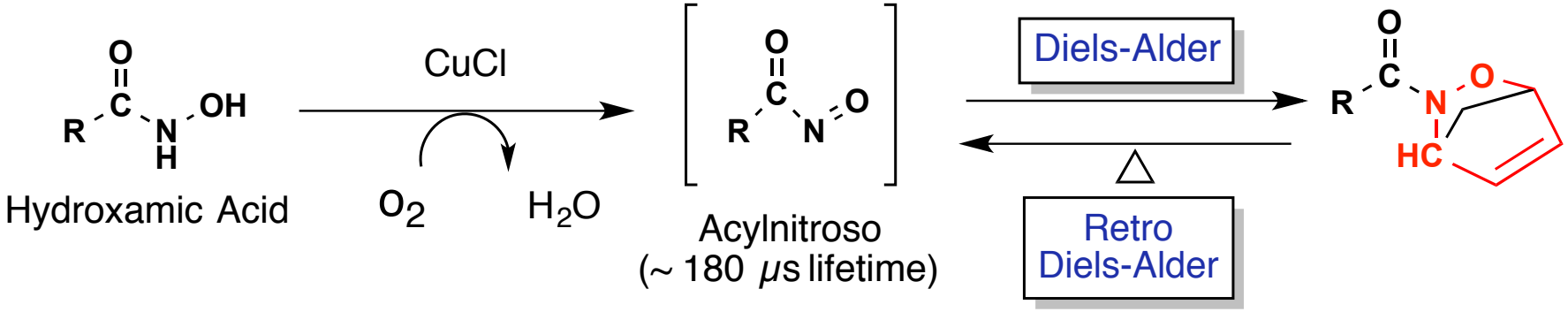


Work Still in Progress …

Acylnitroso Project



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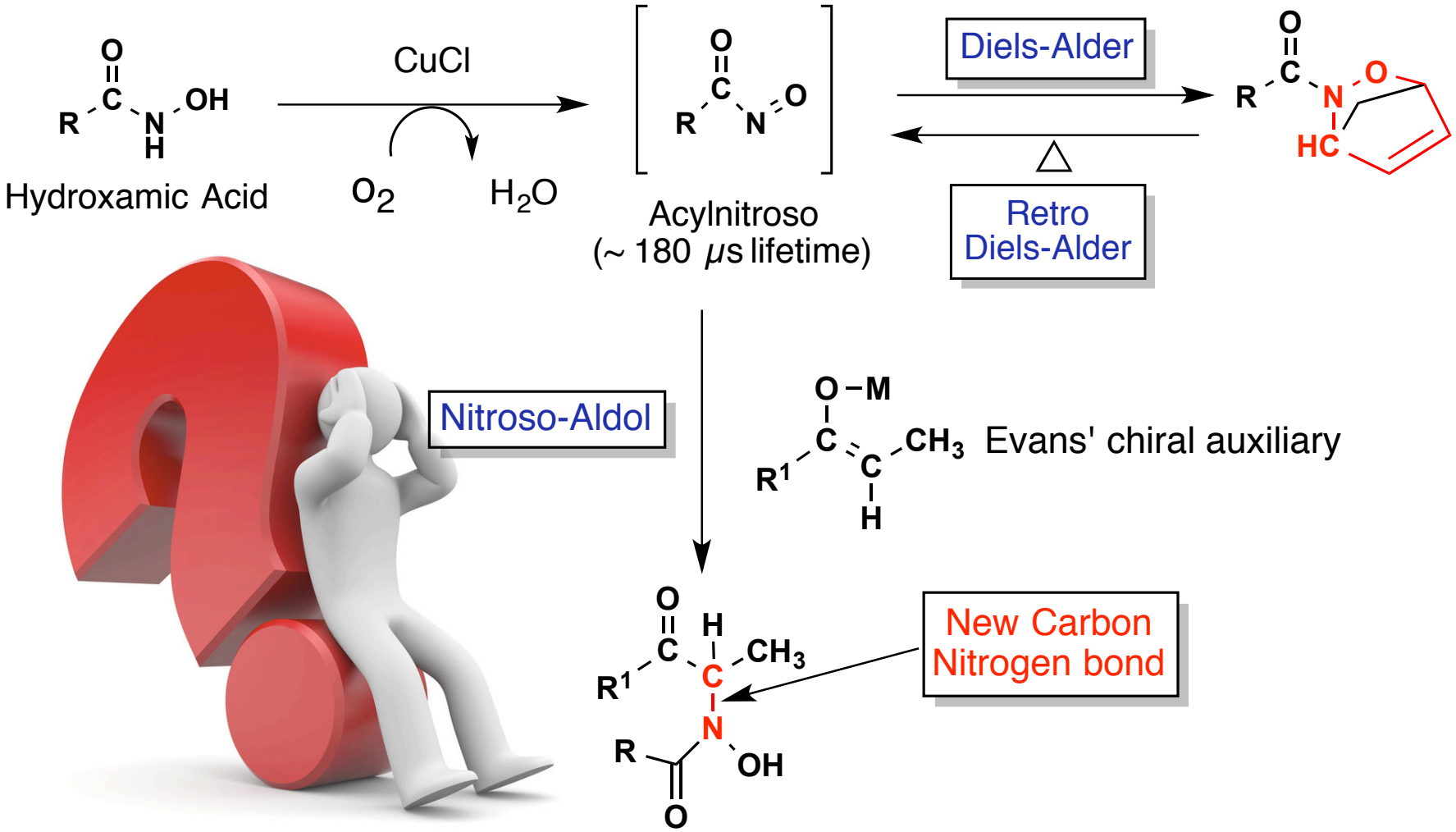
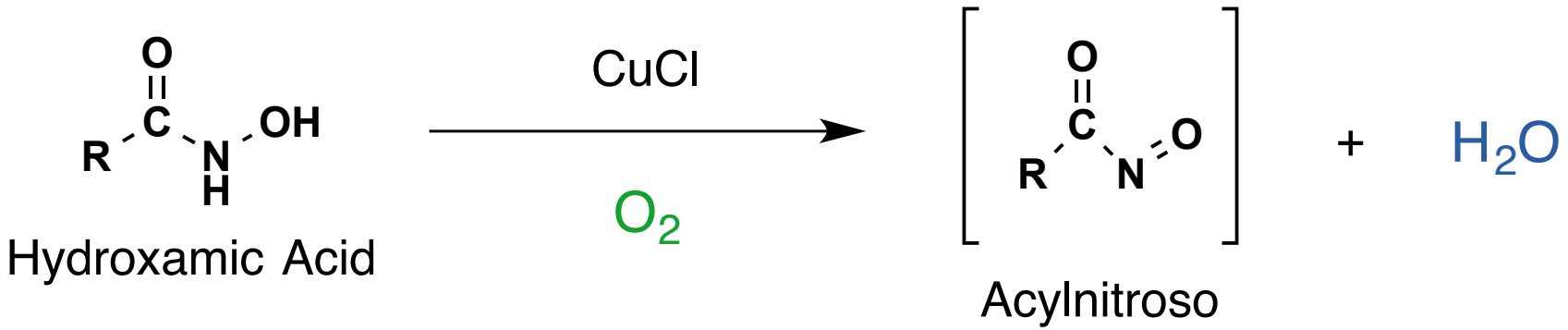


Acylnitroso Project Summary

- Have implemented green chemistry by using air as the terminal oxidant and obtained water as the only by-product



Acylnitroso Project Summary

- Have implemented green chemistry by using air as the terminal oxidant and obtaining water as the only by-product

- Have gained access to unstable nitroso species and locked it in a ring structure using a Diels-Alder transformation

Acylnitroso
(~ 180 μs lifetime)

Acylnitroso Project Summary

- Have implemented green chemistry by using air as the terminal oxidant and obtaining water as the only by-product

- Have used organic chemist's techniques such column chromatography, rotovaporation, and proton NMR to separate, purify and identify organic compounds respectively

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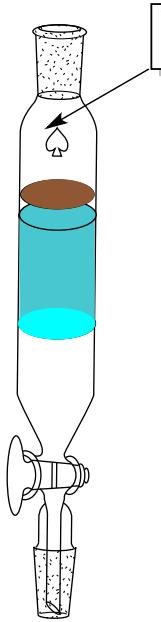
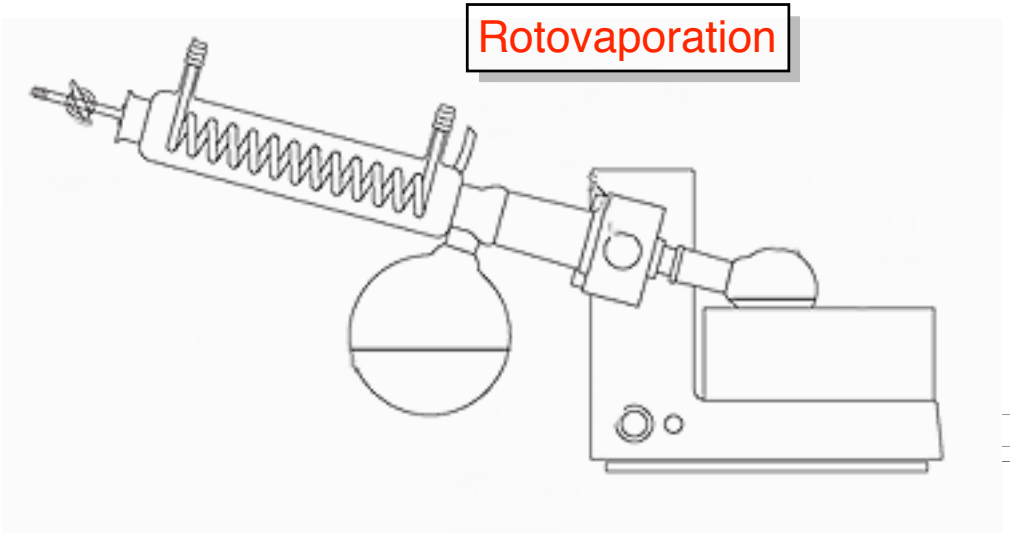
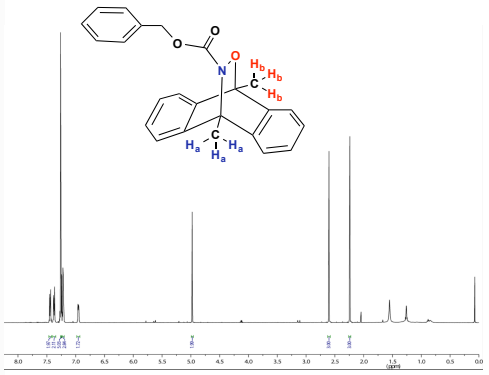


Rotovaporation



^{1}H NMR



Acylnitroso Project Summary

- Have implemented green chemistry by using air as the terminal oxidant and obtaining water as the only by-product
- Have gained access to nitroso species and locked it in a ring structure using a Diels-Alder transformation
- Have used organic chemist's techniques such column chromatography, rotovaporation, and proton NMR to separate, purify and identify organic compounds respectively
- Will continue to run Nitroso-Aldol reactions to find out if it is possible to construct Carbon-Nitrogen bonds using green chemistry

Acknowledgements

Read Group

Prof. Javier Read de Alaniz

Charles Frazier

Benjamin Newmeyer

Robert Lewis

Gesine Veits

Donald Wenz

Andrey Samoshin

Jimmy Hemmer

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Jens-Uwe Kuhn

Nicholas Arnold

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