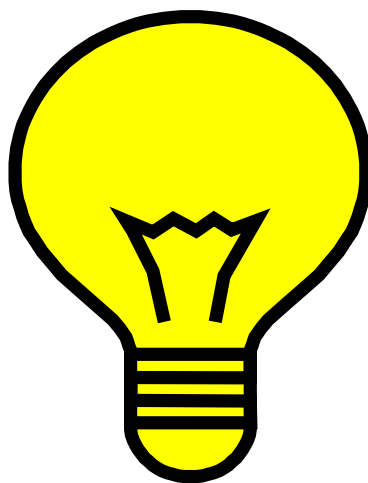


The Current State of Synthetic Organic Photochemistry

Frontiers in Chemistry Series



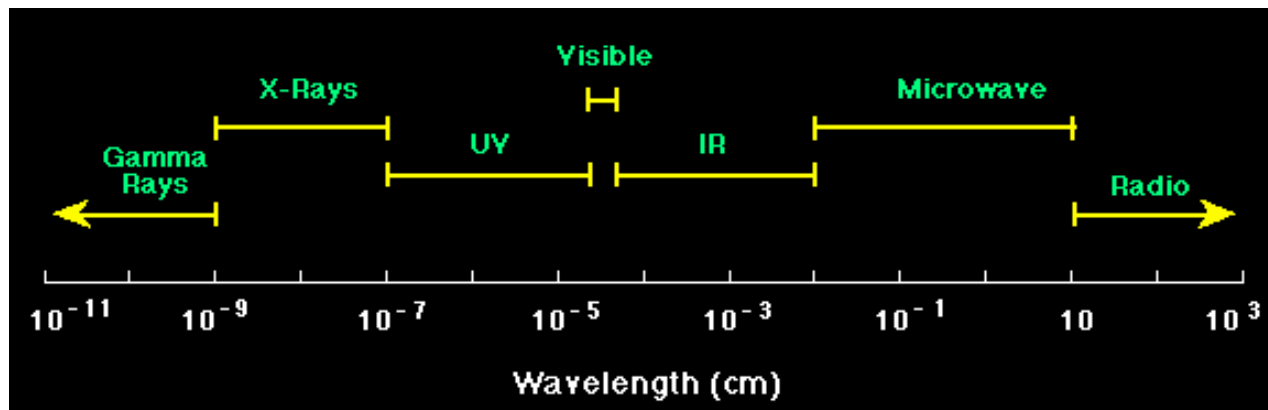
Stephen Lynch

1/24/04

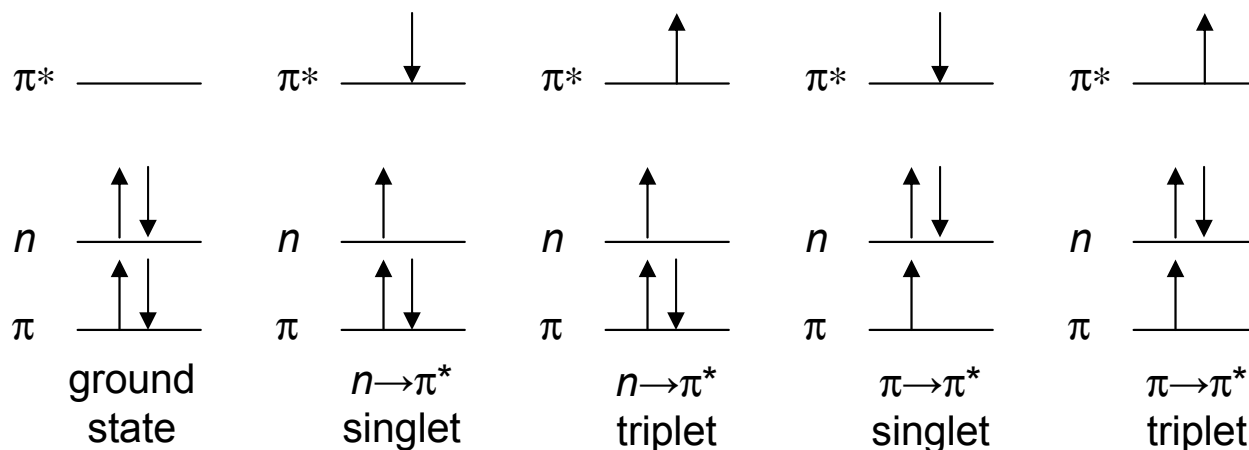
The Current State of Synthetic Organic Photochemistry

- ▶ Introduction to Photochemistry
- ▶ Some Historical Aspects
- ▶ Recent Applications of Photochemistry in Organic Synthesis
 - Isomerizations
 - Cycloadditions
 - Rearrangements
 - Cyclizations
- ▶ New Directions in Organic Photochemistry
 - Photoactivated Scavengers
 - Photolabile Protecting Groups
 - Photochirogenesis
- ▶ Summary

Overview of Photochemistry

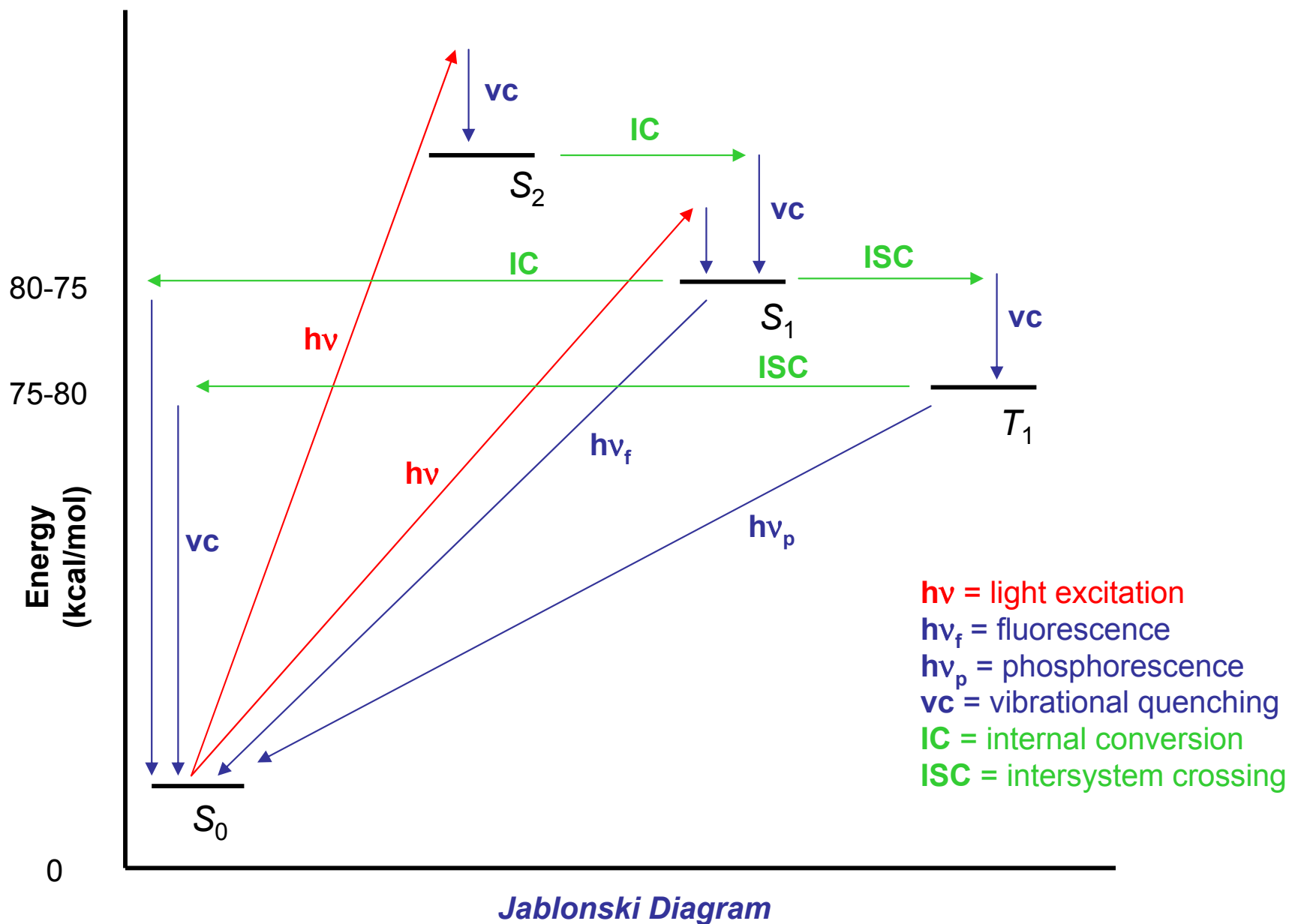


- *Molecules absorb radiation which results in excited electronic states.*
→ usually C=C and C=O
- *Chemically useful light is generally in the range of 200-400 nm.*
- *Often employ filters to regulate the wavelength of the radiation.*



- *Triplet state lower in energy than singlet state (due to Hund's rule)*

What is the Fate of an Excited Molecule?



Physical Processes Undergone by Excited Molecules



Excitation

Vibrational Relaxation

Fluorescence

Internal Conversion

Intersystem Crossing

Vibrational Relaxation

Phosphorescence

Intersystem Crossing

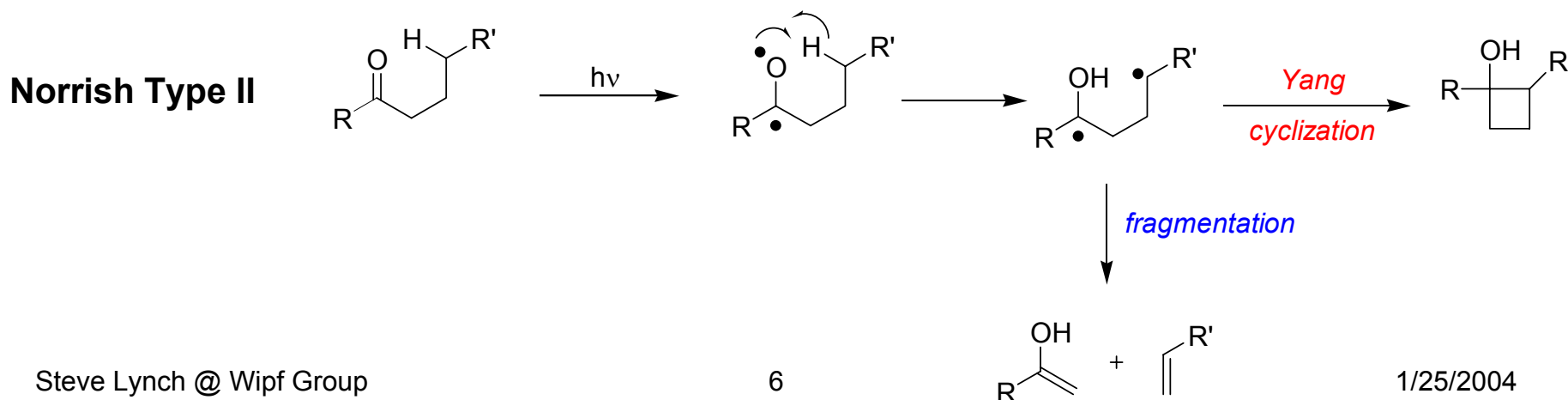
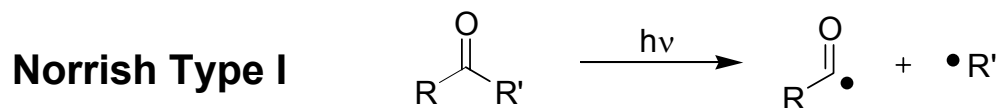
Singlet-Singlet Transfer

Triplet-Triplet Transfer

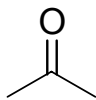
photosensitization

Chemical Processes Undergone by Excited Molecules

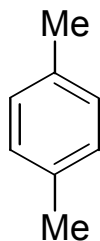
- | | |
|---|-------------------------------|
| 1. (A-B-C) \rightarrow A-B \cdot + C \cdot | Simple Cleavage into Radicals |
| 2. (A-B-C) \rightarrow E + F | Decomposition into Molecules |
| 3. (A-B-C) \rightarrow A-C-B | Intramolecular Rearrangement |
| 4. (A-B-C) \rightarrow A-B-C' | Photoisomerization |
| 5. (A-B-C) \xrightarrow{RH} A-B-C-H + R \cdot | Hydrogen-atom Abstraction |
| 6. (A-B-C) \rightarrow (ABC) $_2$ | Photodimerization |
| 7. (A-B-C) \xrightarrow{A} ABC + A* | Photosensitization |



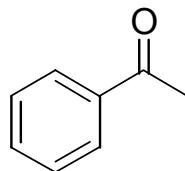
Some Common Photosensitizers



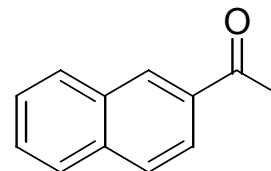
acetone



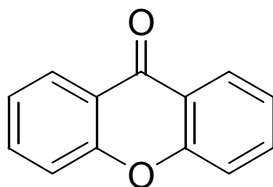
p-xylene



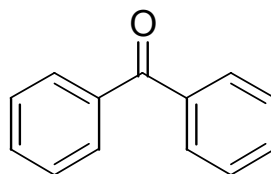
acetophenone



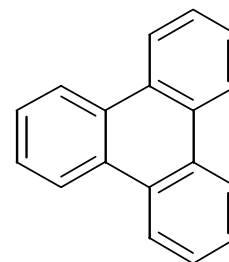
acetonaphthone



xanthone



benzophenone



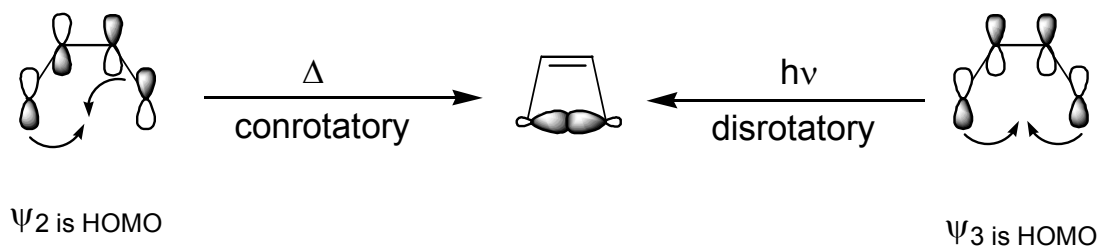
triphenylene

A good sensitizer must:

- absorb light entirely in order to avoid concurrent reactions
- not undergo chemical alteration until reaction is complete
- be easily eliminated from the reaction mixture upon completion

Woodward-Hoffman Rules and Orbital Symmetry

Number of π electrons	Thermal	Photochemical
2	disrotatory	conrotatory
4	conrotatory	disrotatory
6	disrotatory	conrotatory
8	conrotatory	disrotatory



Stereochemical outcome will be impacted!

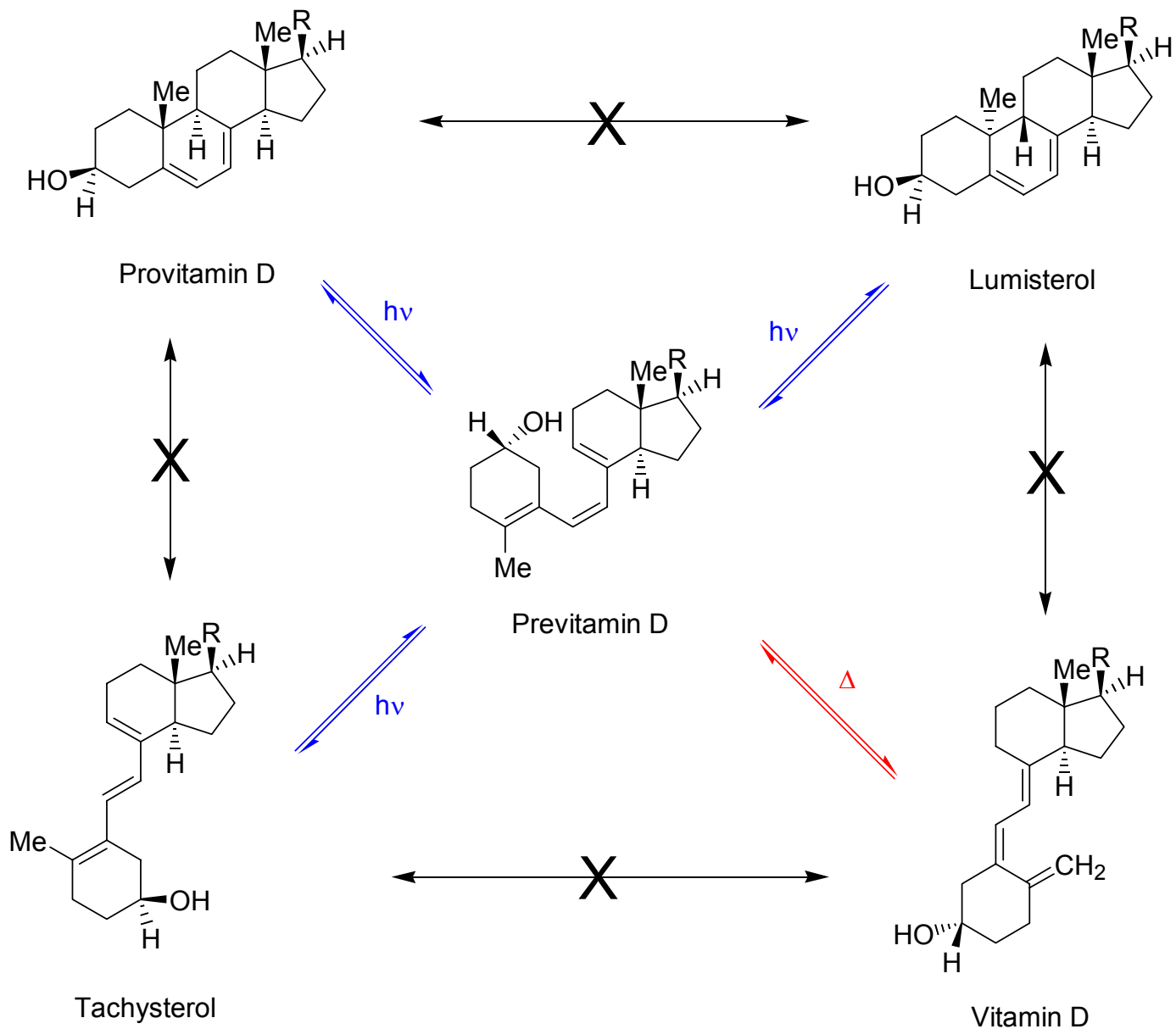
Why Use Photochemistry?

- ✓ Overcome large kinetic barriers in a short amount of time
- ✓ Produce immense molecular complexity in a single step
- ✓ Form thermodynamically disfavored products
- ✓ Allows reactivity that would otherwise be inaccessible by almost any other synthetic method
- ✓ The reagent (light) is cheap, easily accessible, and renewable

Drawbacks?

- ✗ Reactivity is often unpredictable
- ✗ Many substrates are not compatible
- ✗ Selectivity and conversion are sometimes low

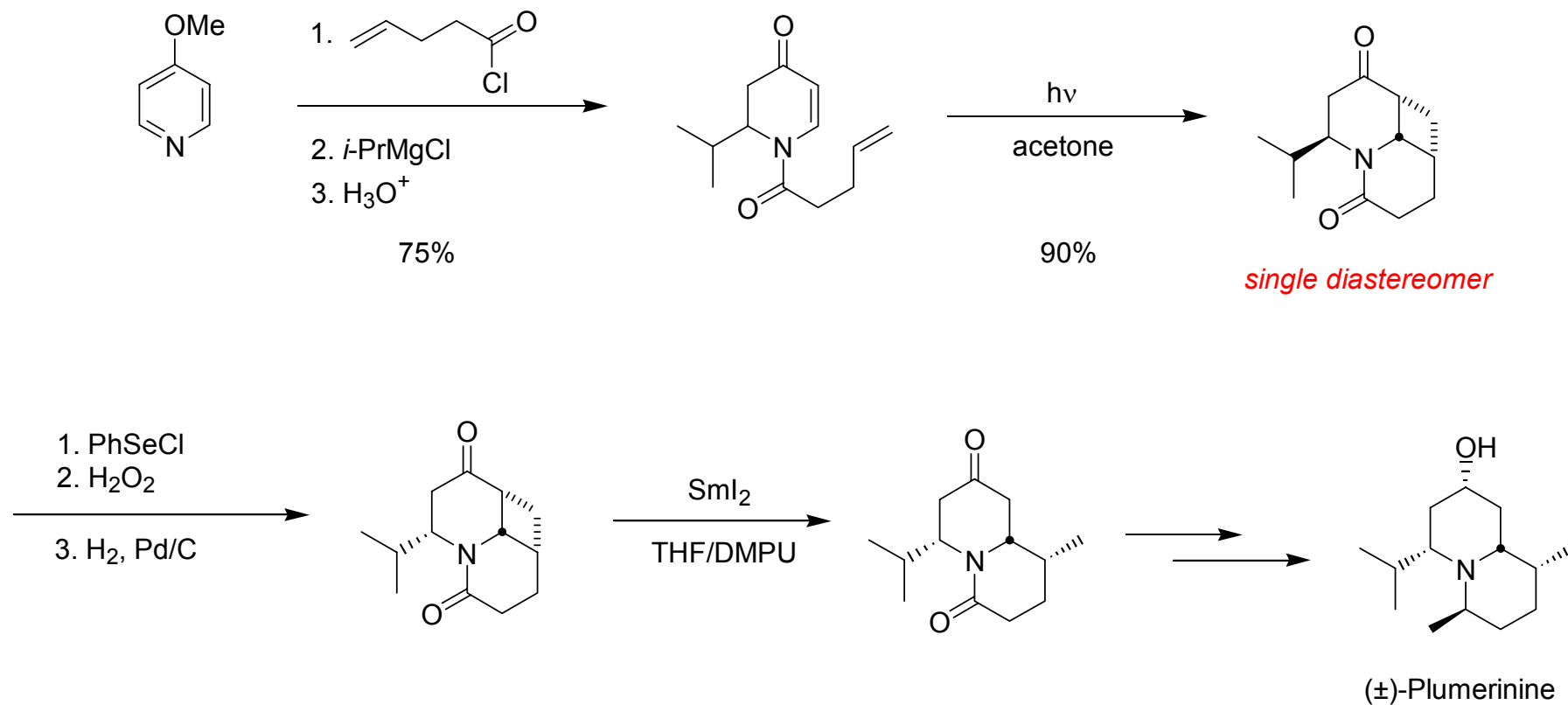
Emergence of Photochemistry in Natural Product Synthesis



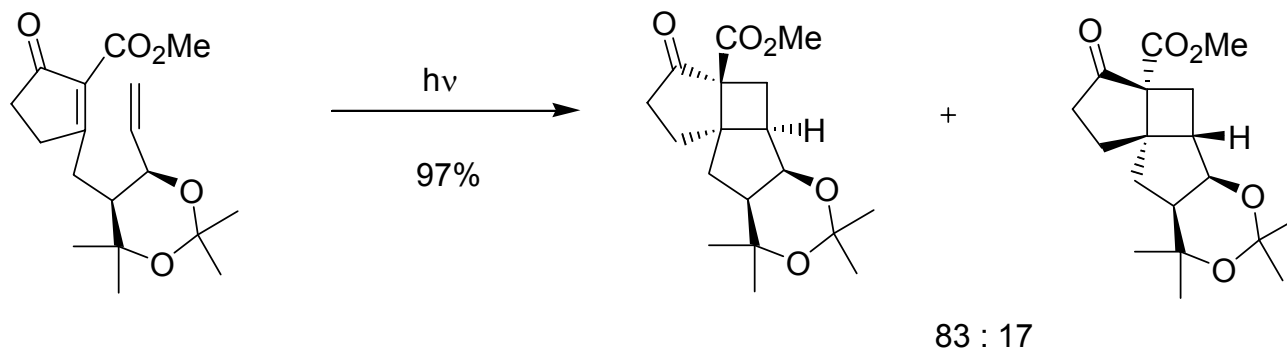
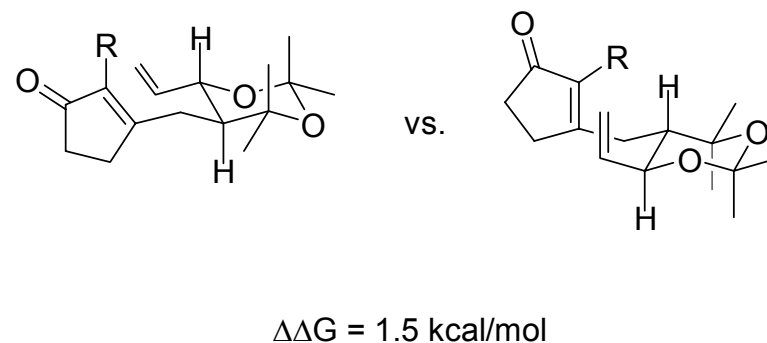
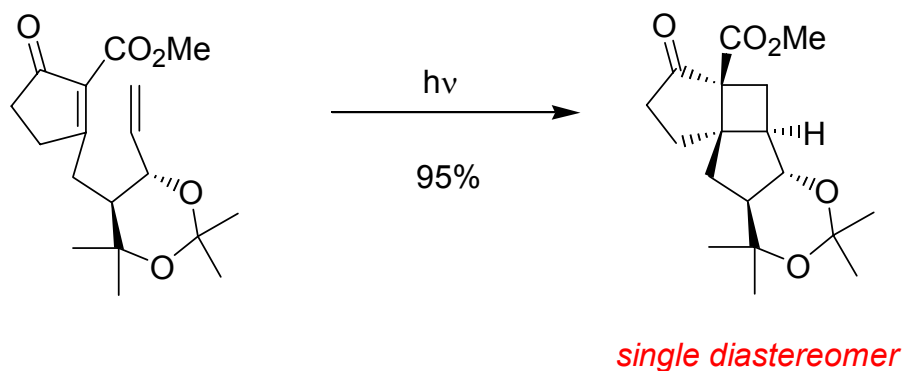
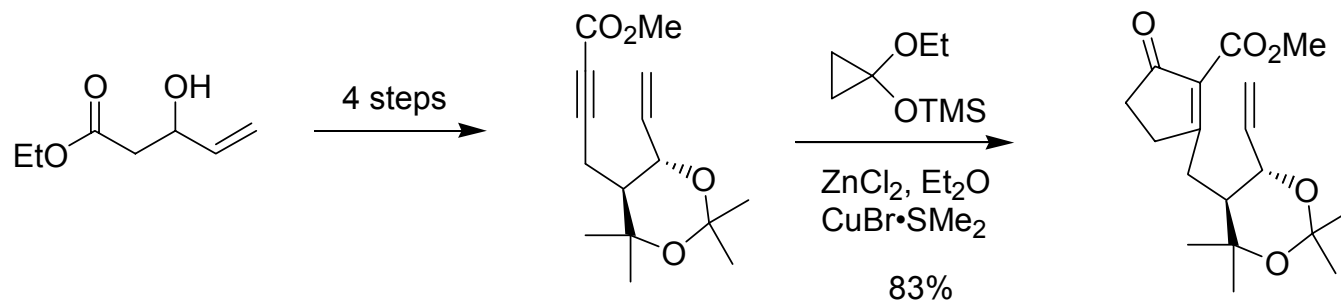
Recent Applications of Traditional Photochemical Methodology

- [2+2] Cycloadditions
- [4+2] Cycloadditions
- Photoisomerizations
- Photoenolizations
- Photorearrangements
- Electrocyclizations

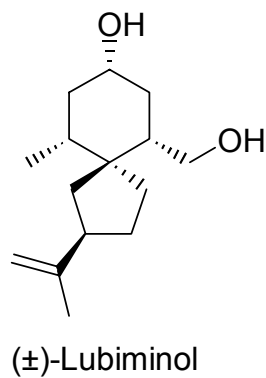
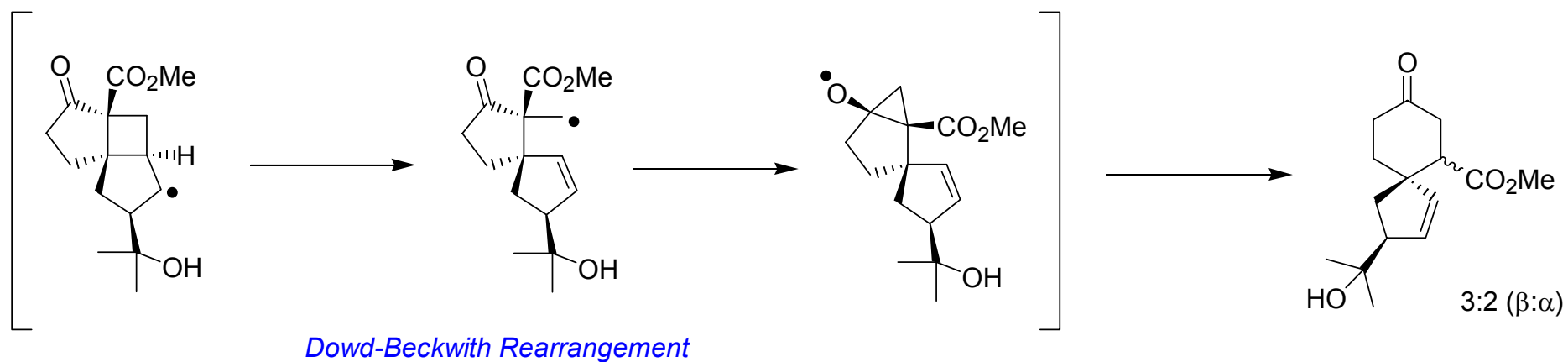
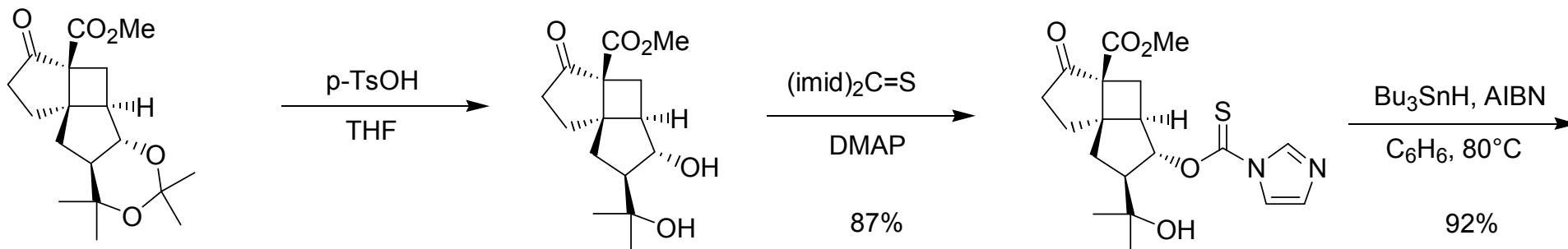
Highly Facial Selective Intramolecular [2+2] Photocyclization



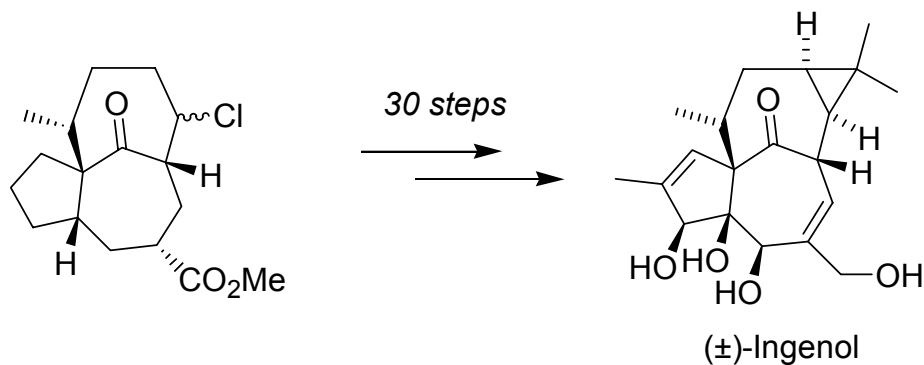
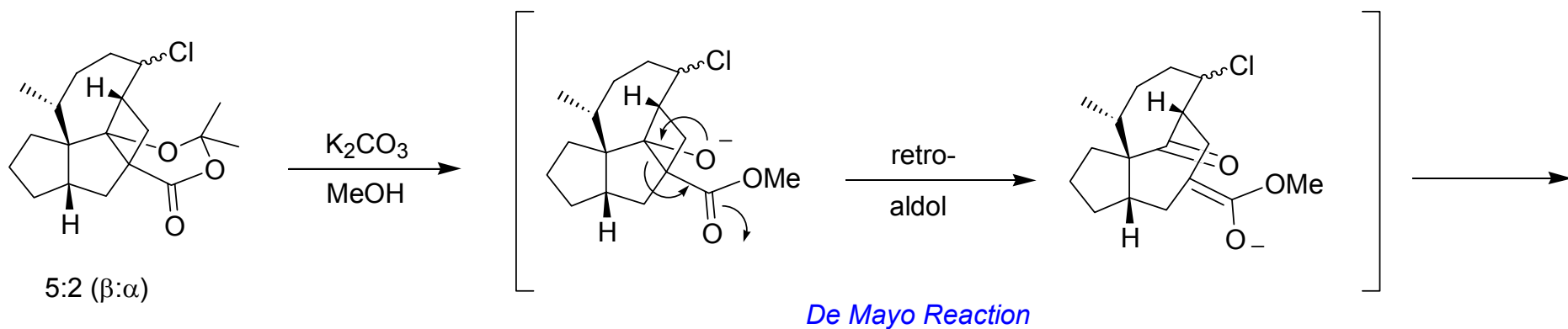
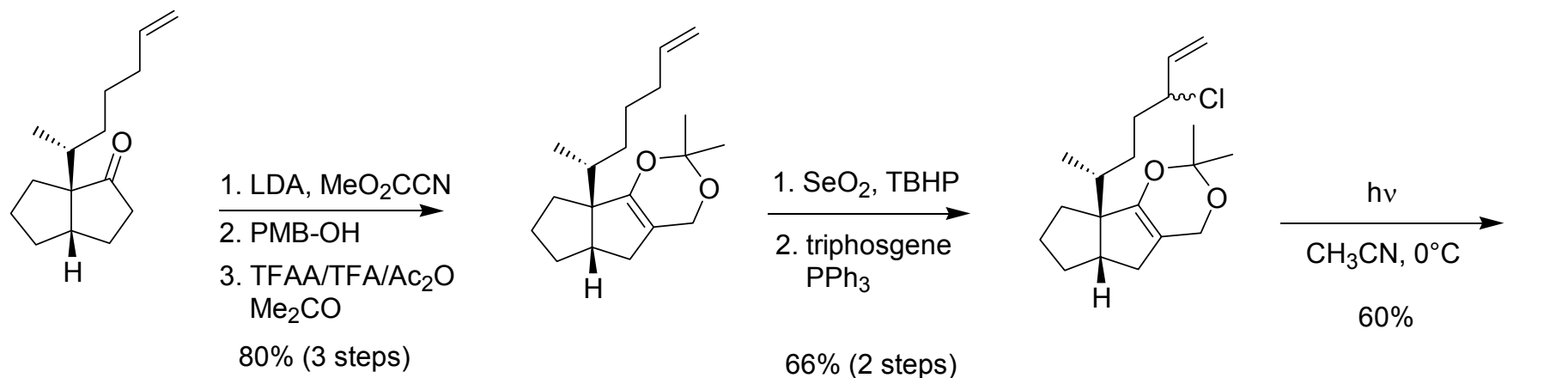
Highly Diastereoselective Intramolecular Photocycloaddition



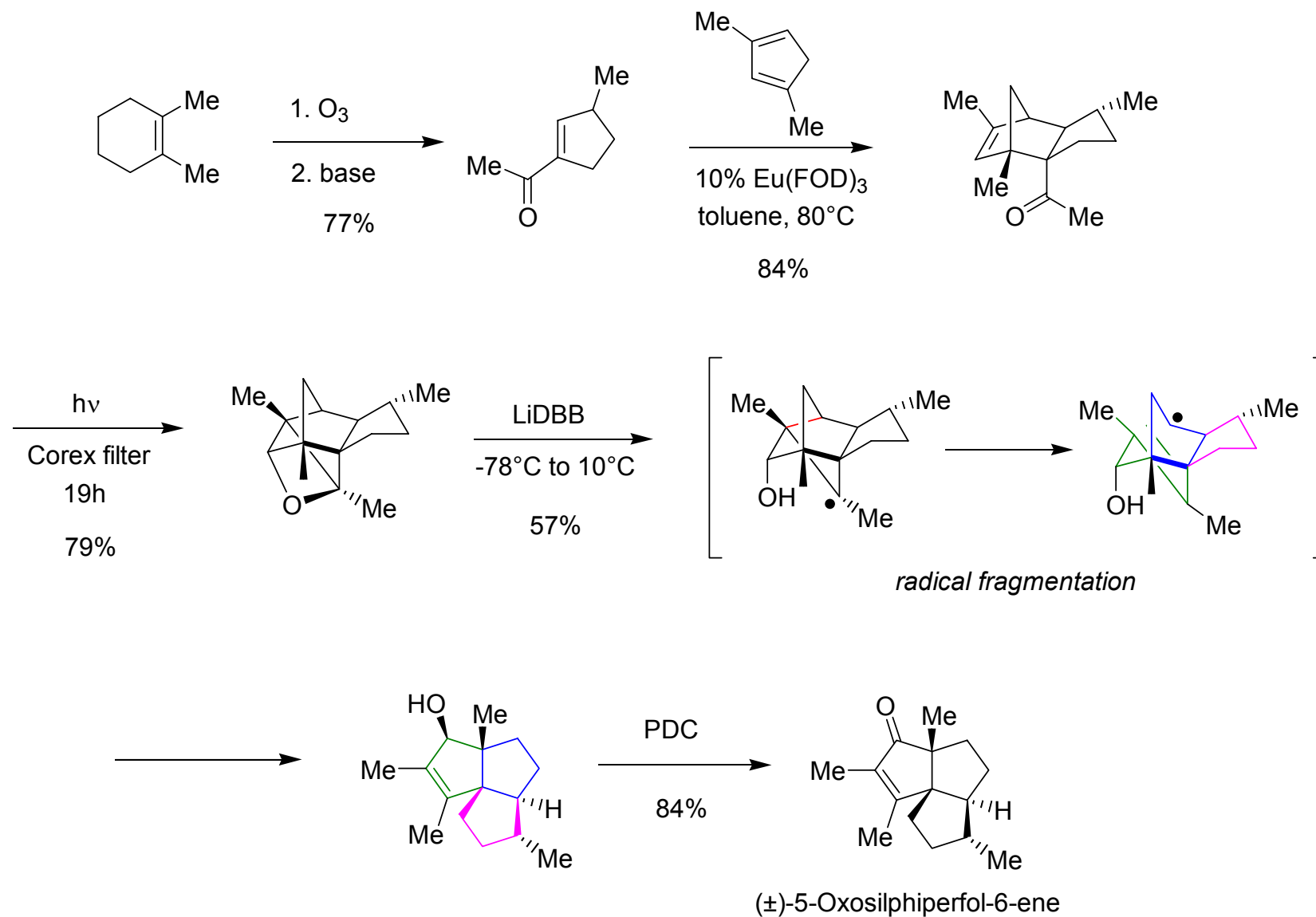
Elaboration of the Photocycloadduct



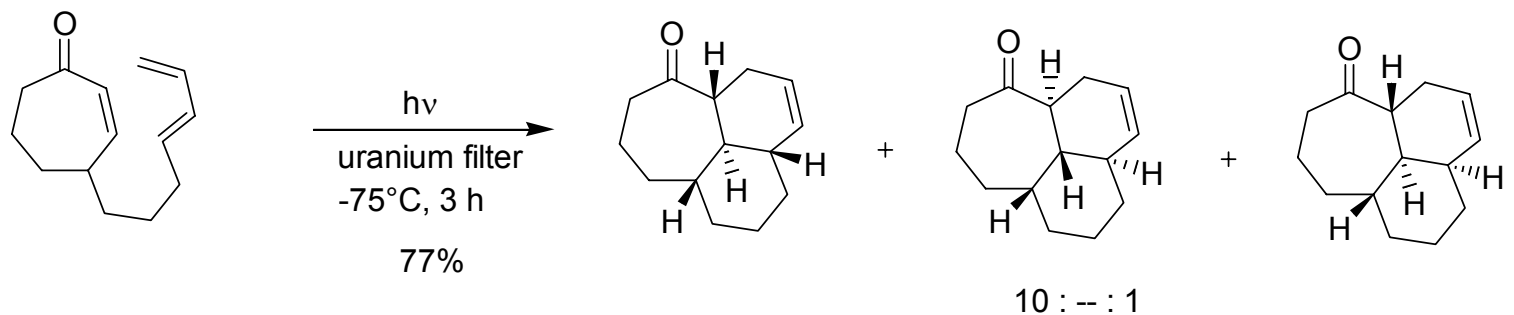
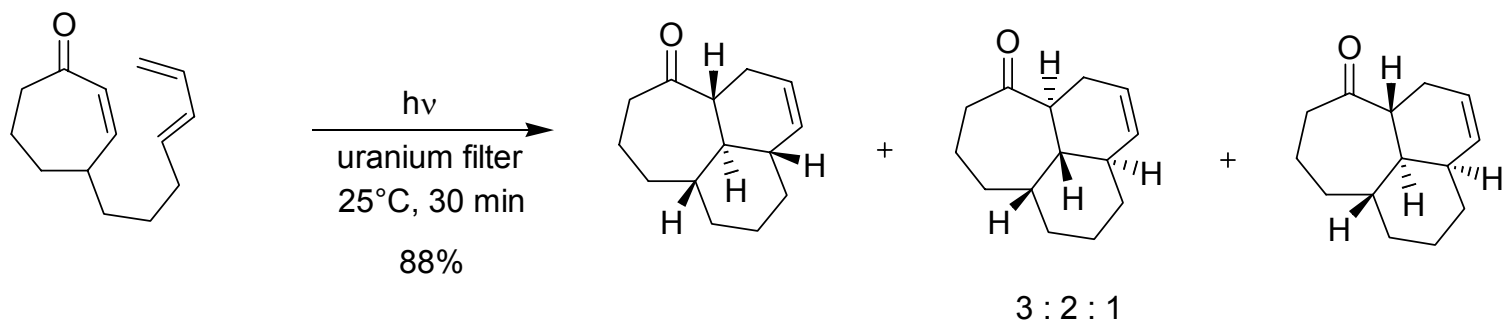
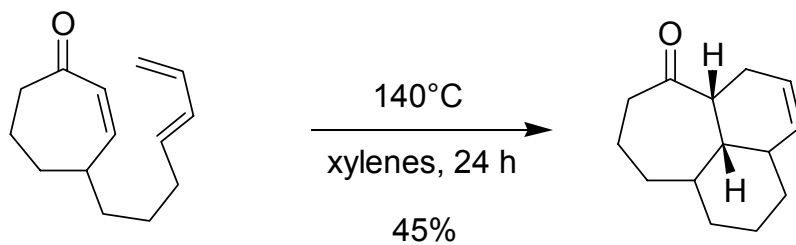
Photocycloaddition/Fragmentation Sequence



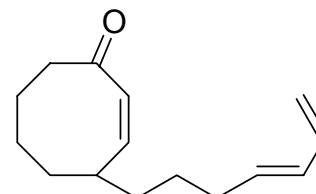
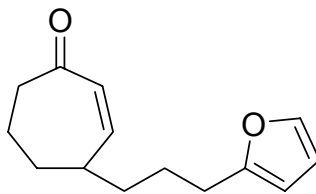
Paterno-Büchi Type Photocycloaddition/Fragmentation



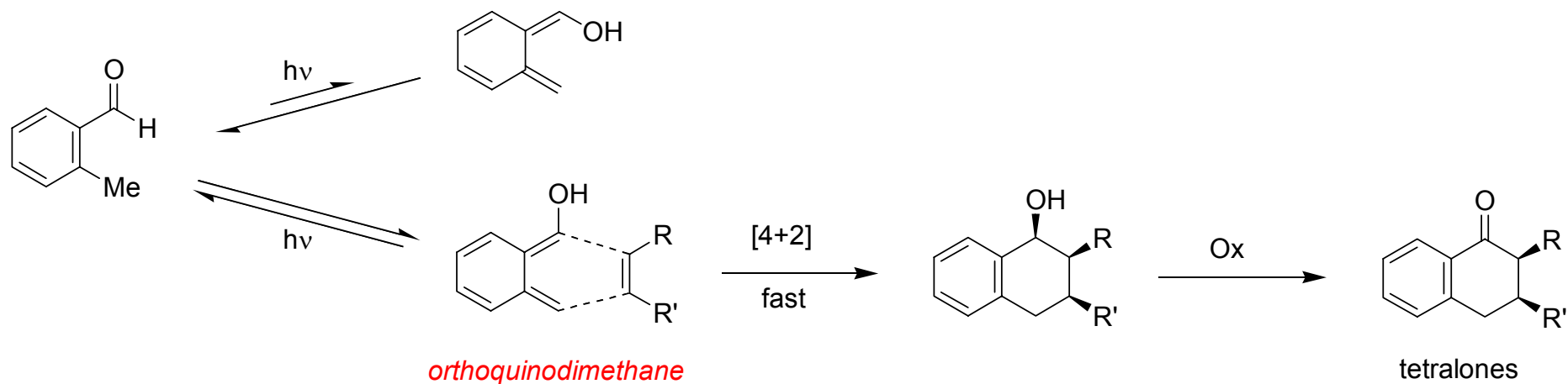
Photoisomerization Diels-Alder Reactions



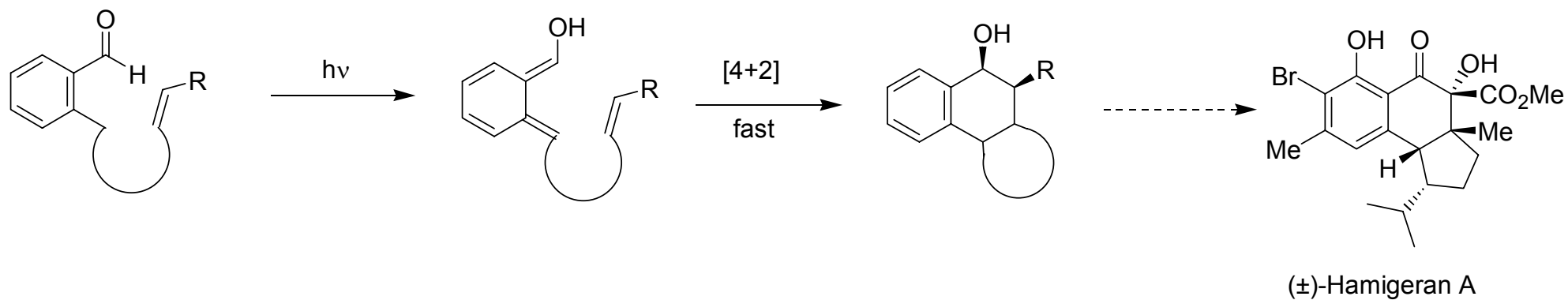
Additional Substrates:



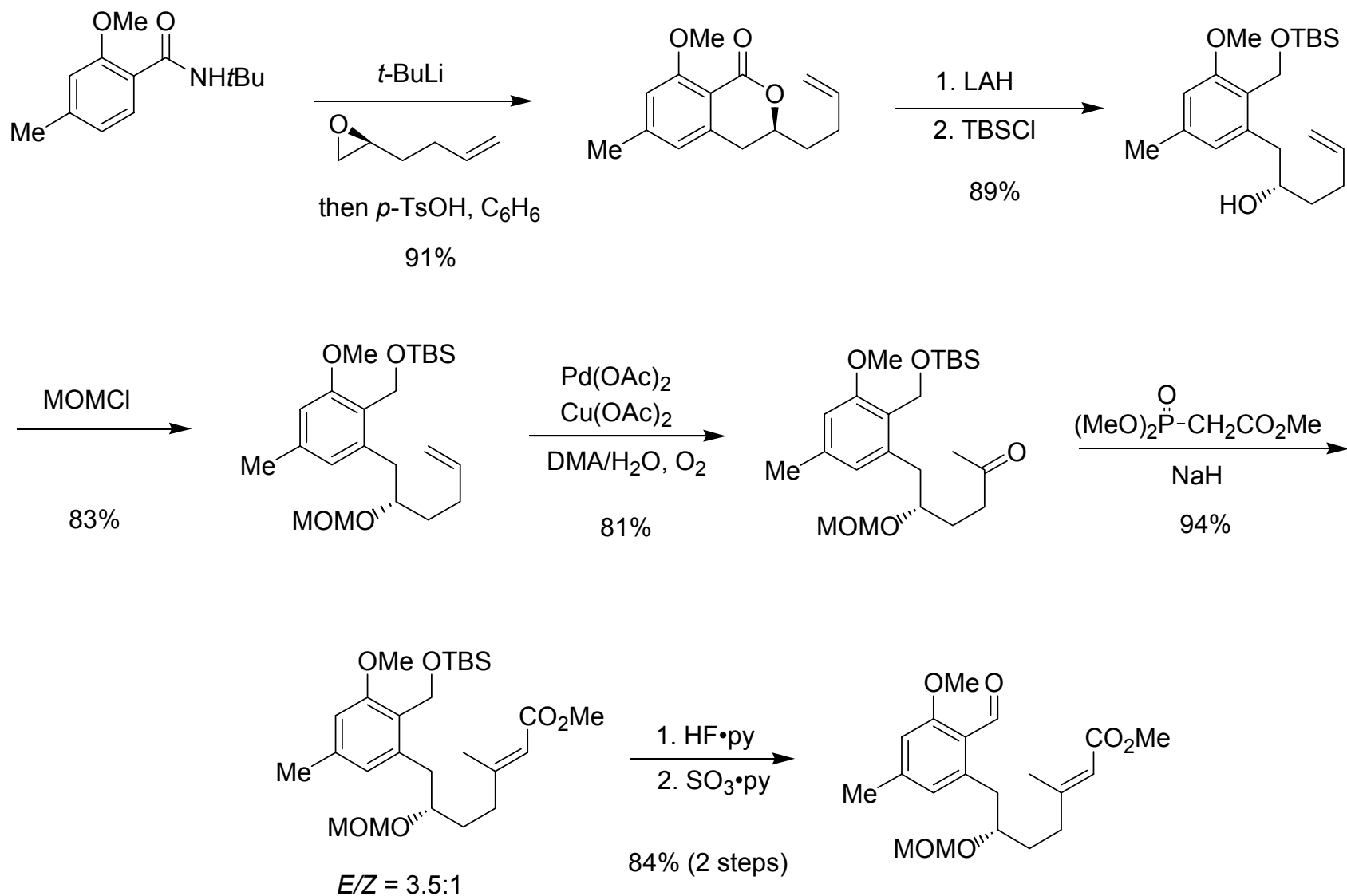
Application of Photoenolization Diels-Alder Reaction



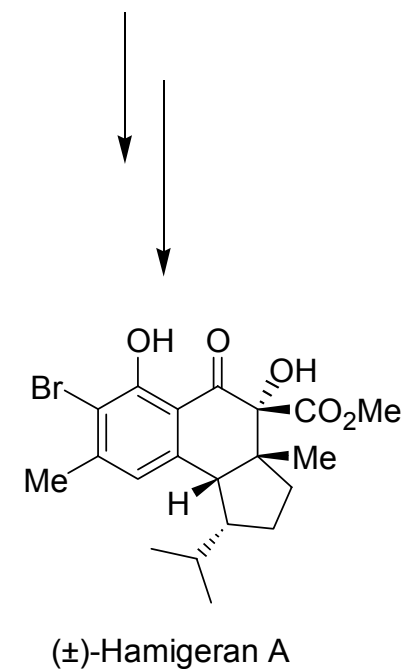
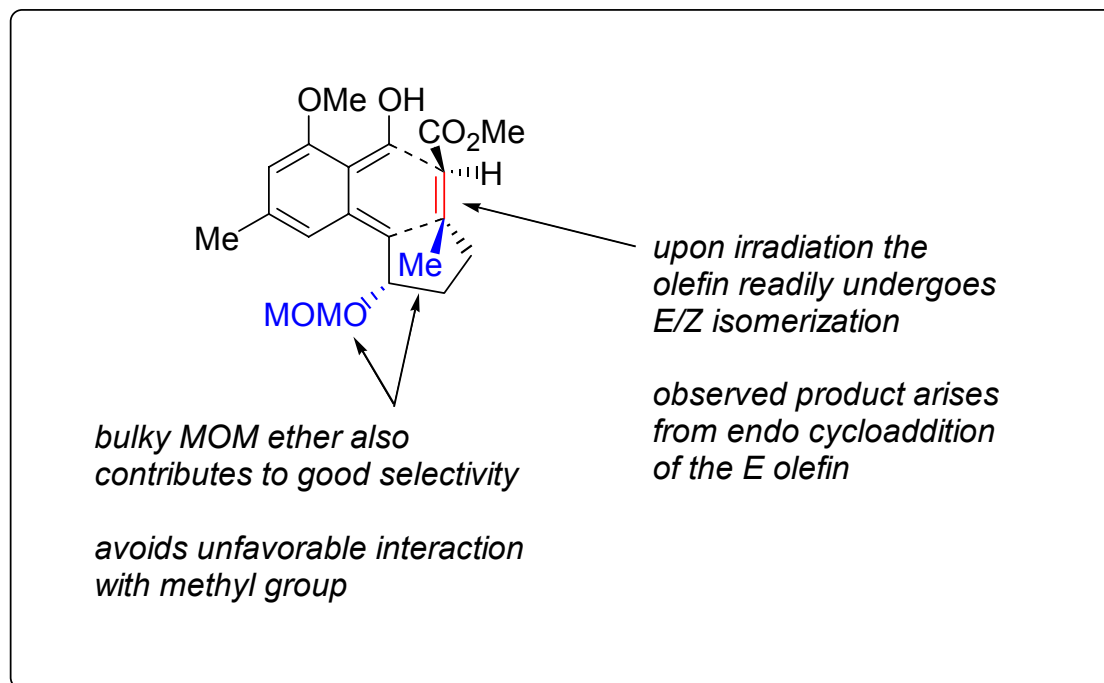
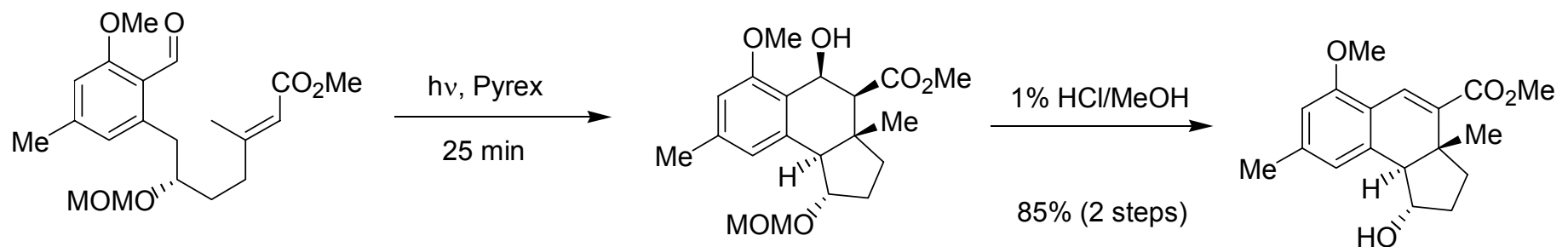
R = electron withdrawing group



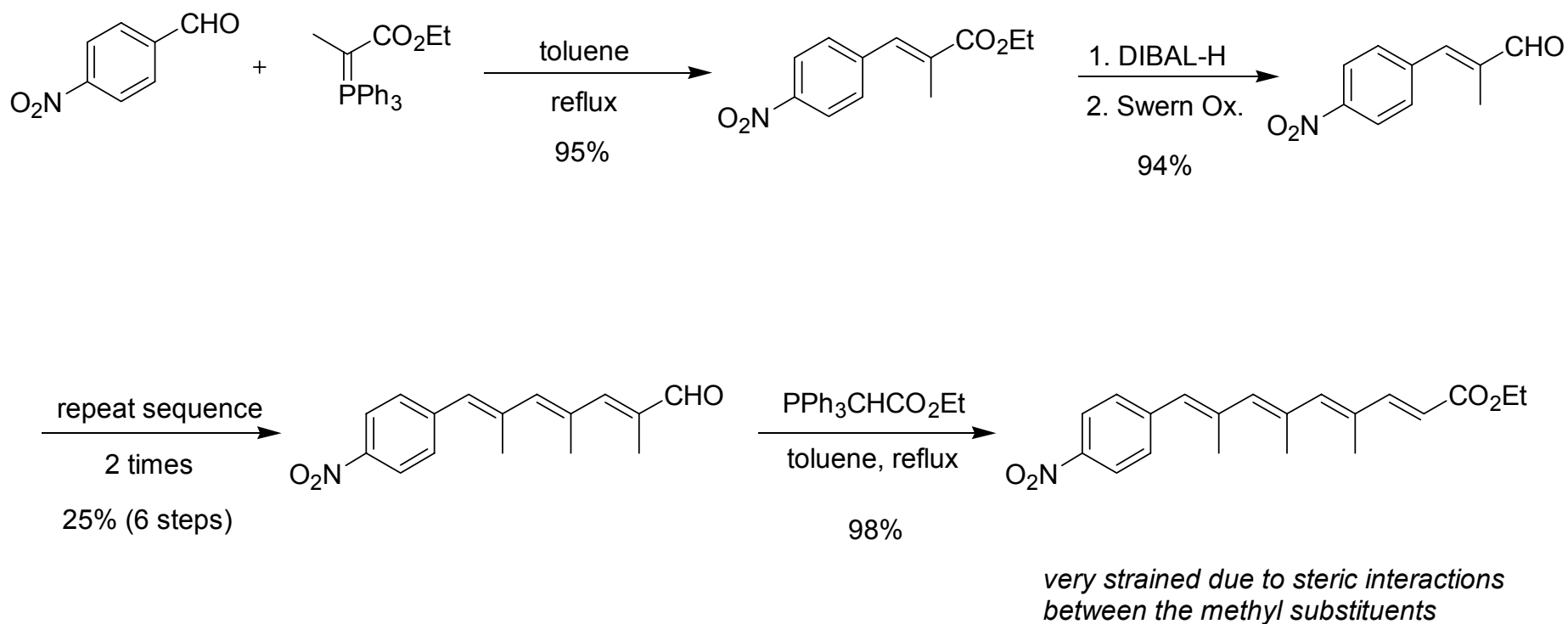
Application of Photoenolization Diels-Alder Reaction



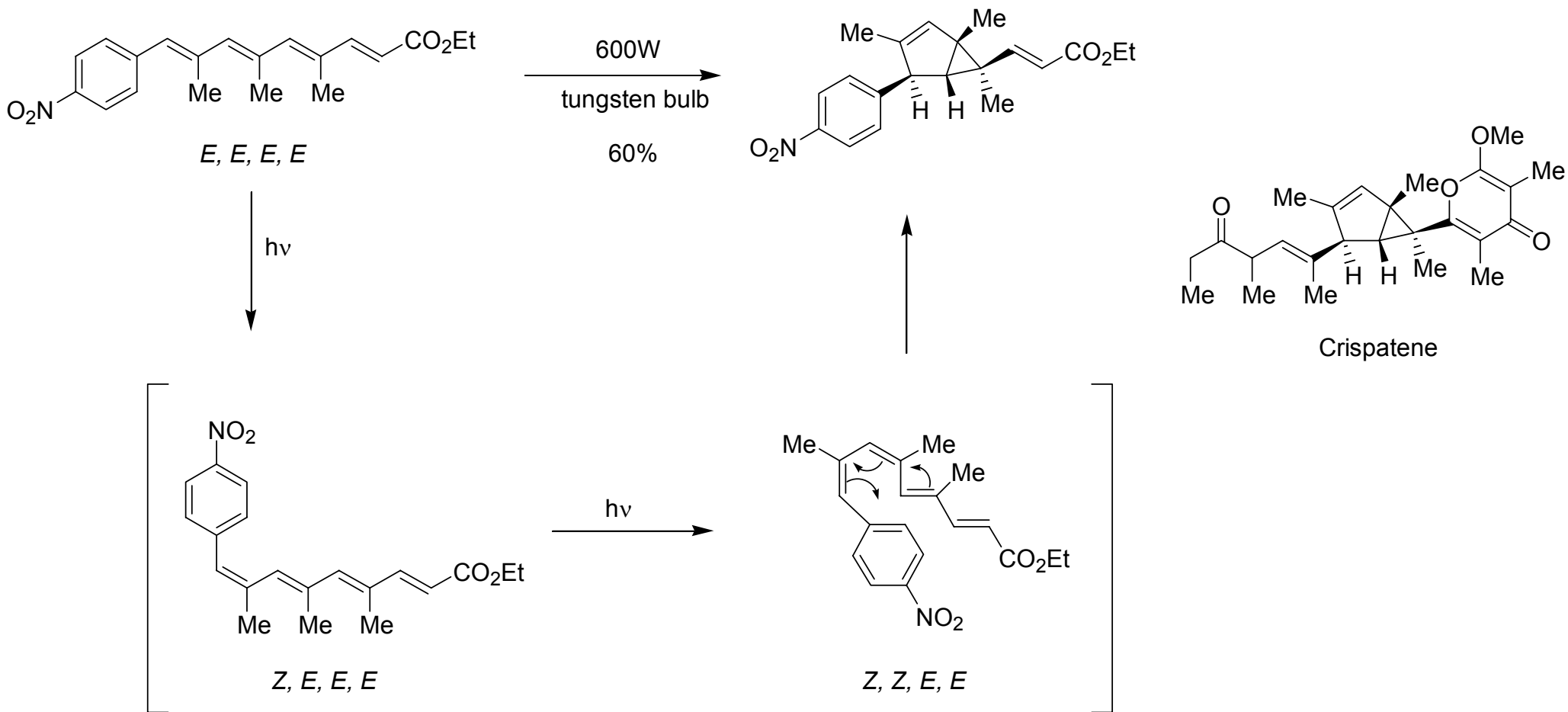
Application of Photoenolization Diels-Alder Reaction



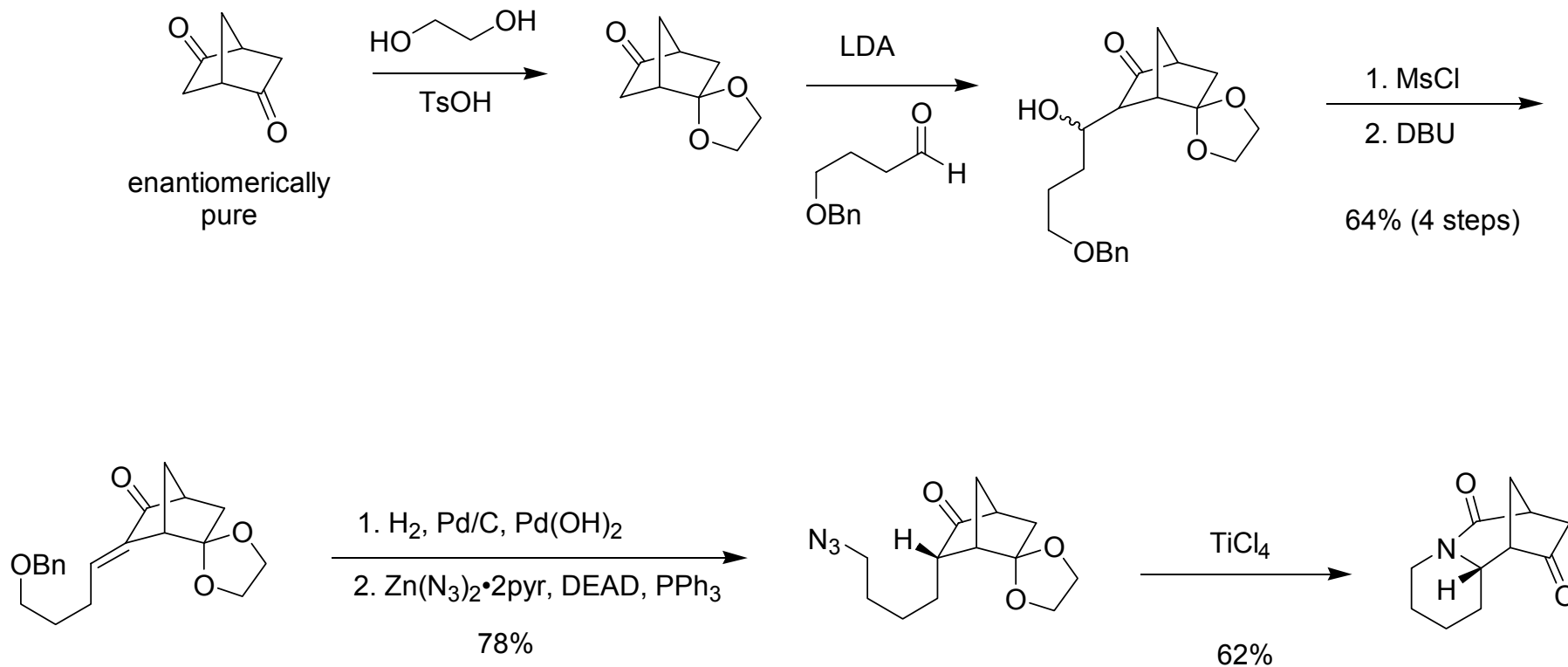
Photochemical Isomerization/Diels-Alder Cycloaddition Applied to Biomimetic Synthesis



Photochemical Isomerization/Diels-Alder Cycloaddition Applied to Biomimetic Synthesis

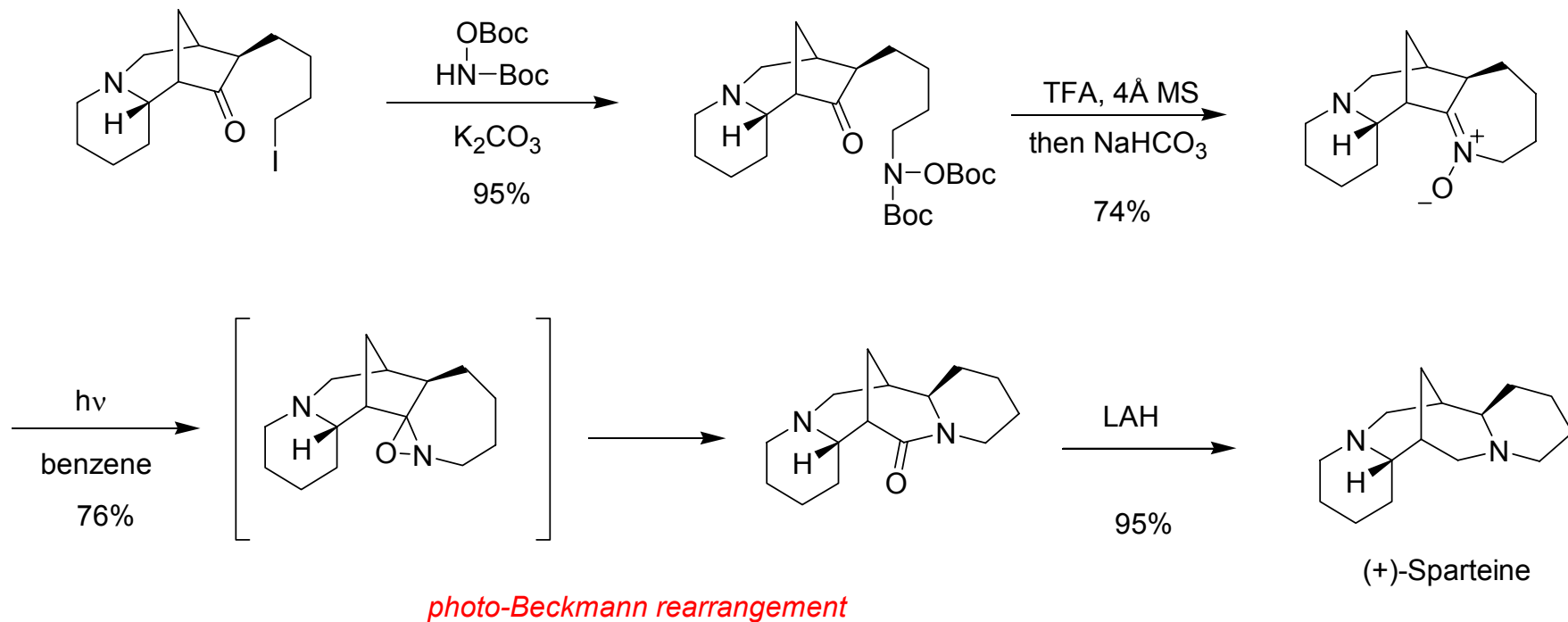
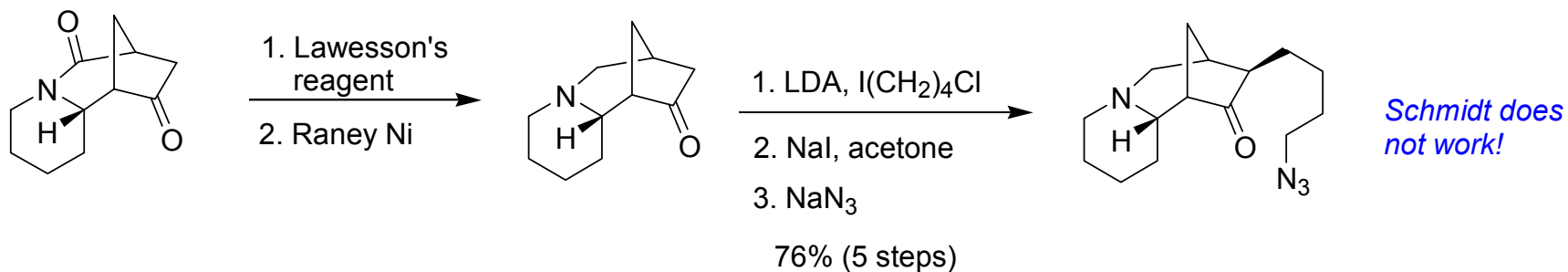


Photochemistry Completes First Asymmetric Total Synthesis of (+)-Sparteine

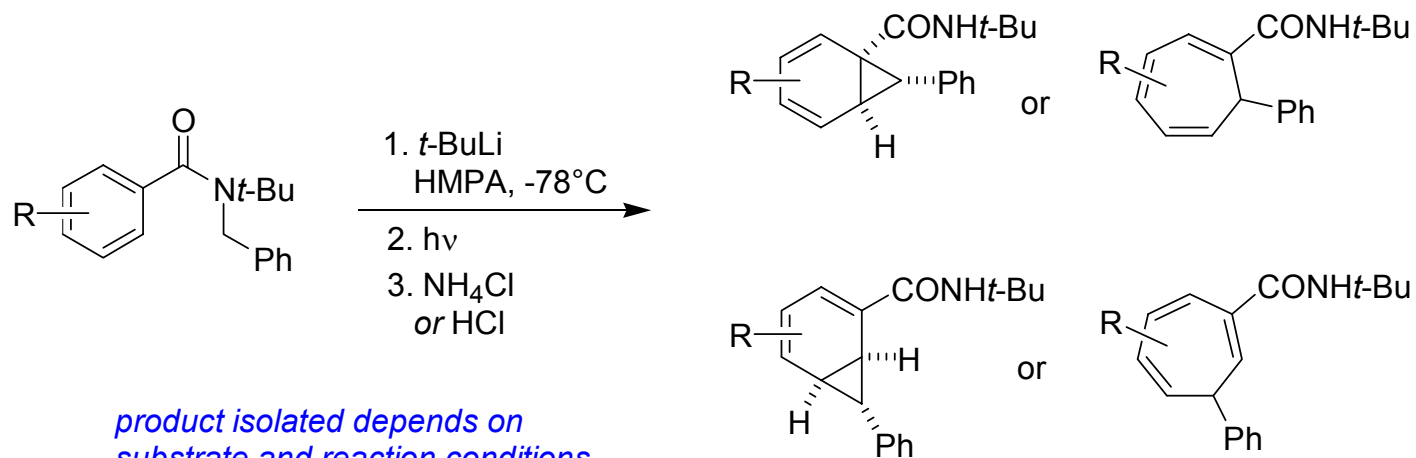
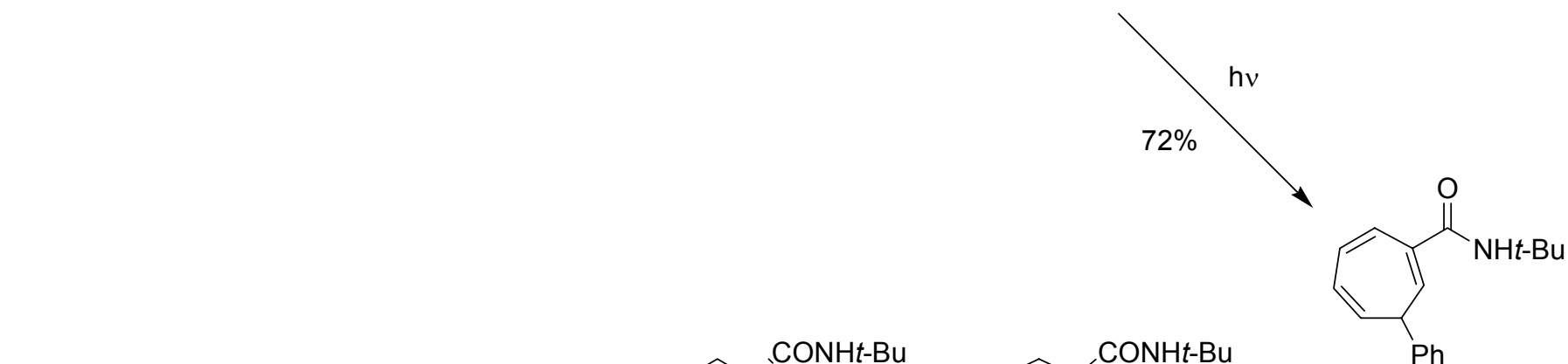
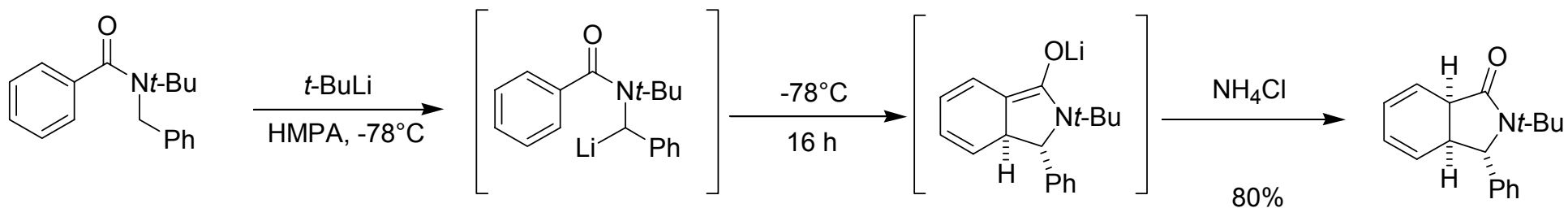


Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577.

Photochemistry as a Key Step in (+)-Sparteine Total Synthesis



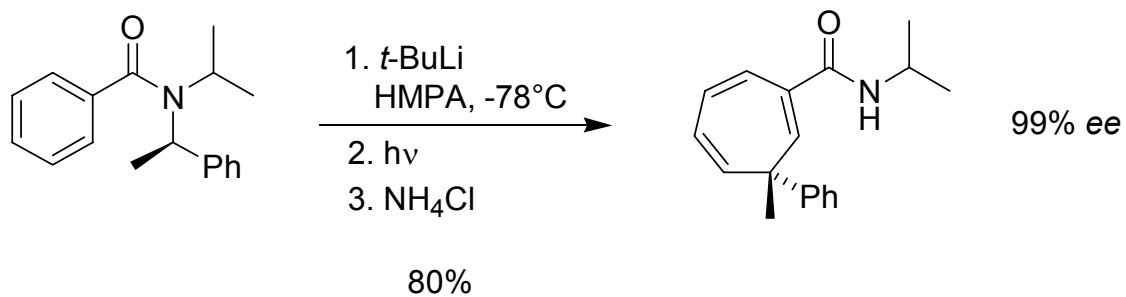
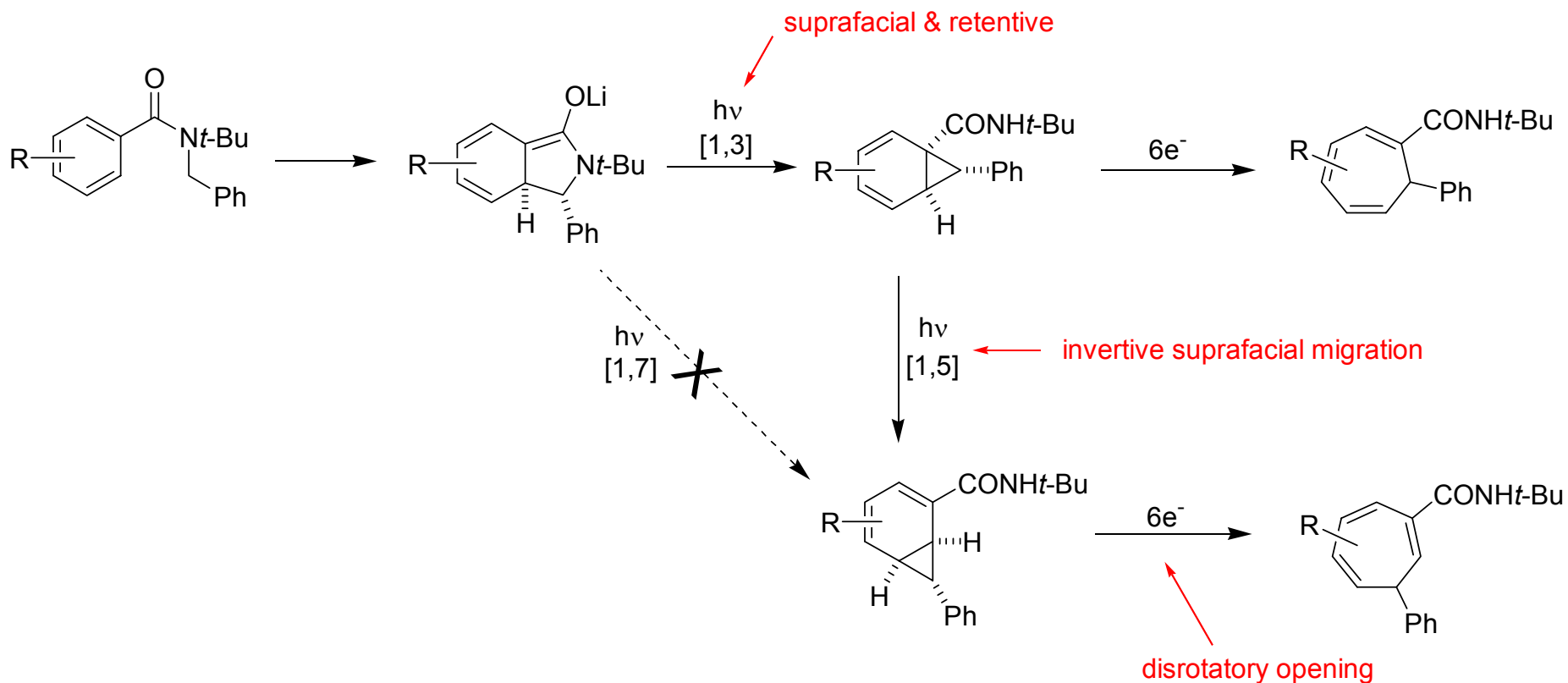
Photochemically Induced Ring Expansion



product isolated depends on substrate and reaction conditions

24 - 80 % yield

Photochemically Induced Ring Expansion

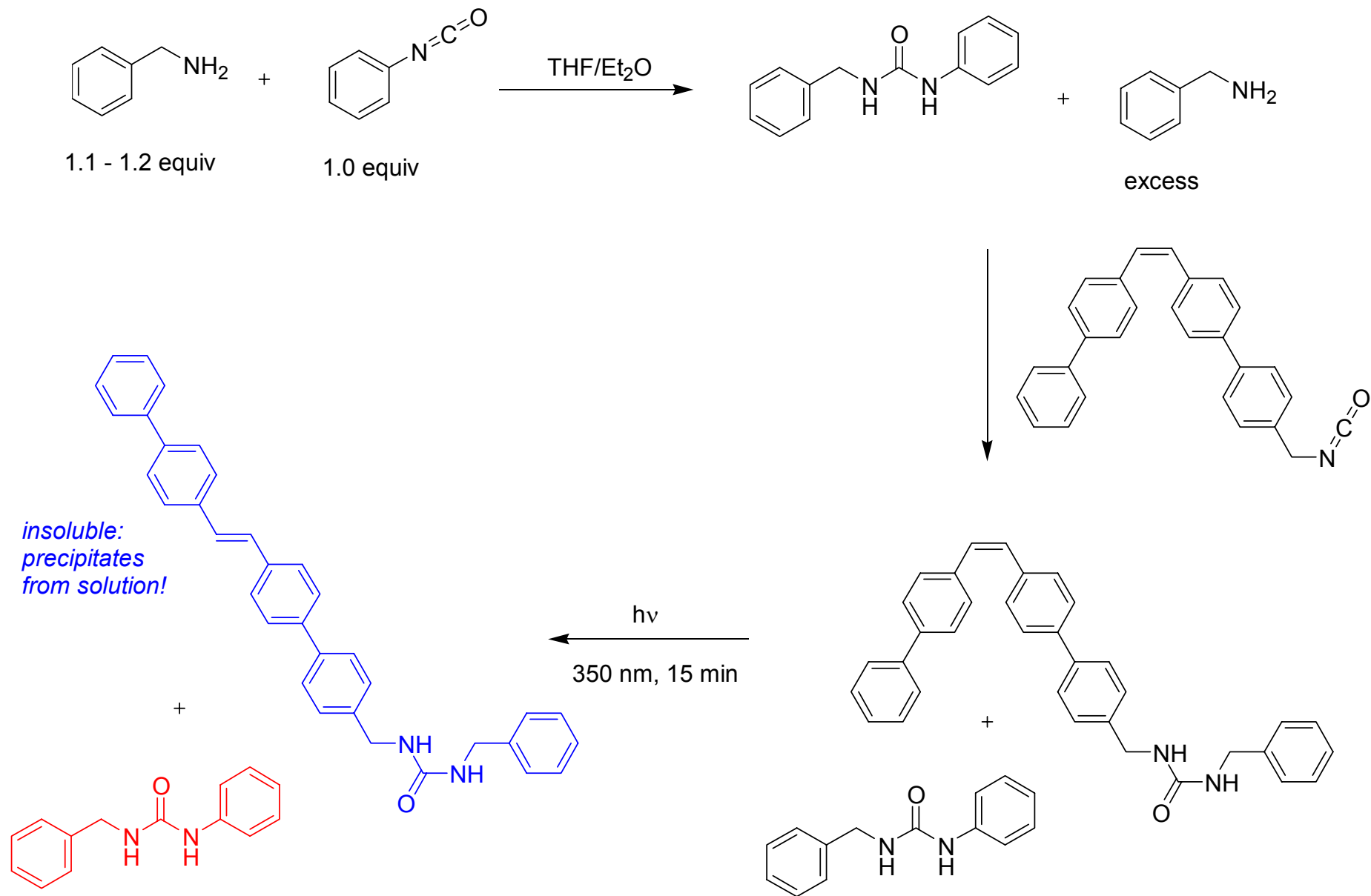


Stereospecificity persists through deprotonation, cyclization, and rearrangement!

New Directions in Organic Photochemical Methodology

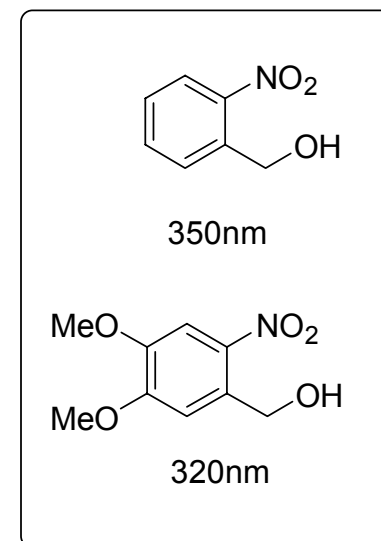
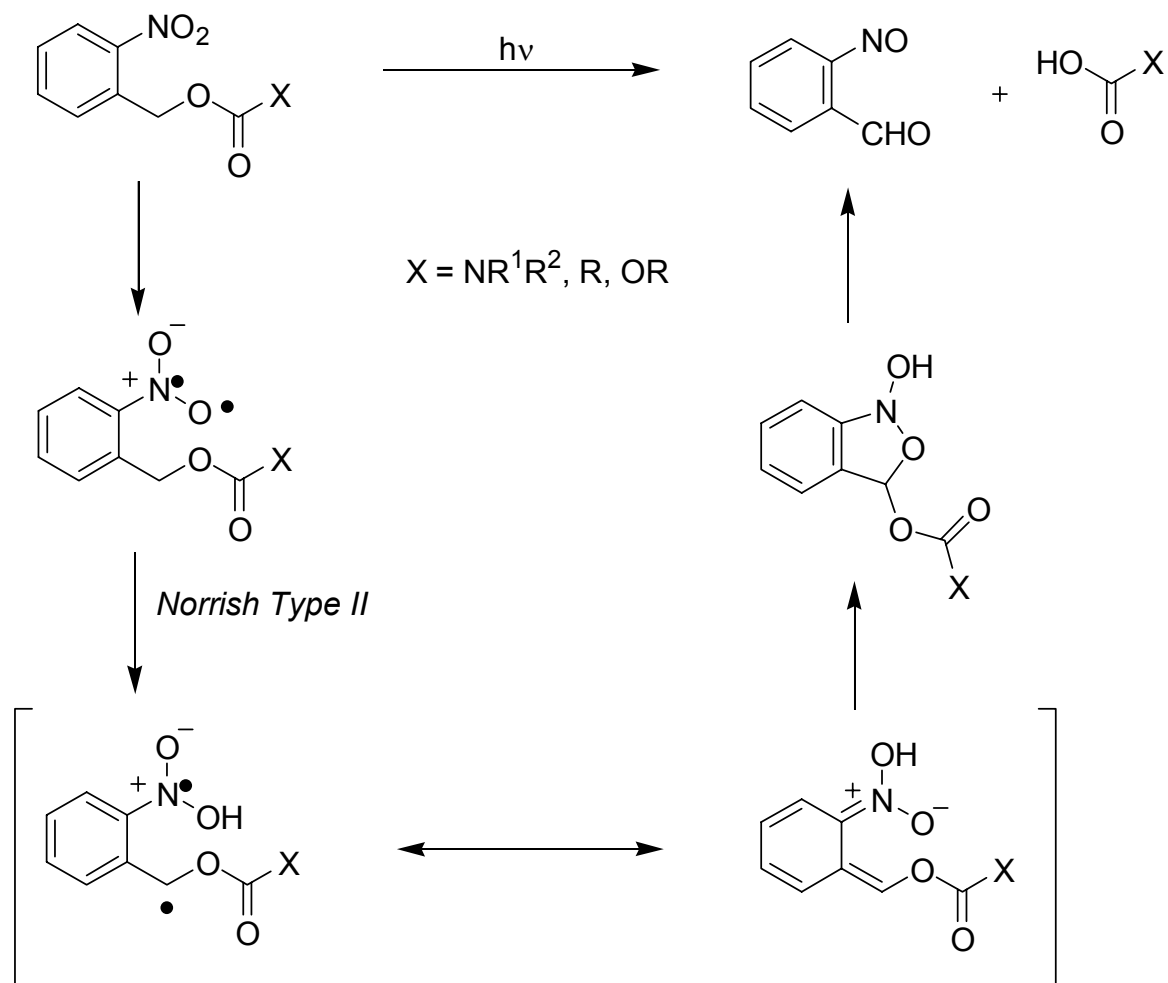
- Photoactivated Reagent Scavengers
- Photolabile Protecting Groups
- Photoreleasable “Caged” Molecules
- Photochirogenesis (Asymmetric Photochemistry)

Photoactivated Reagent Scavengers (Precipitons)



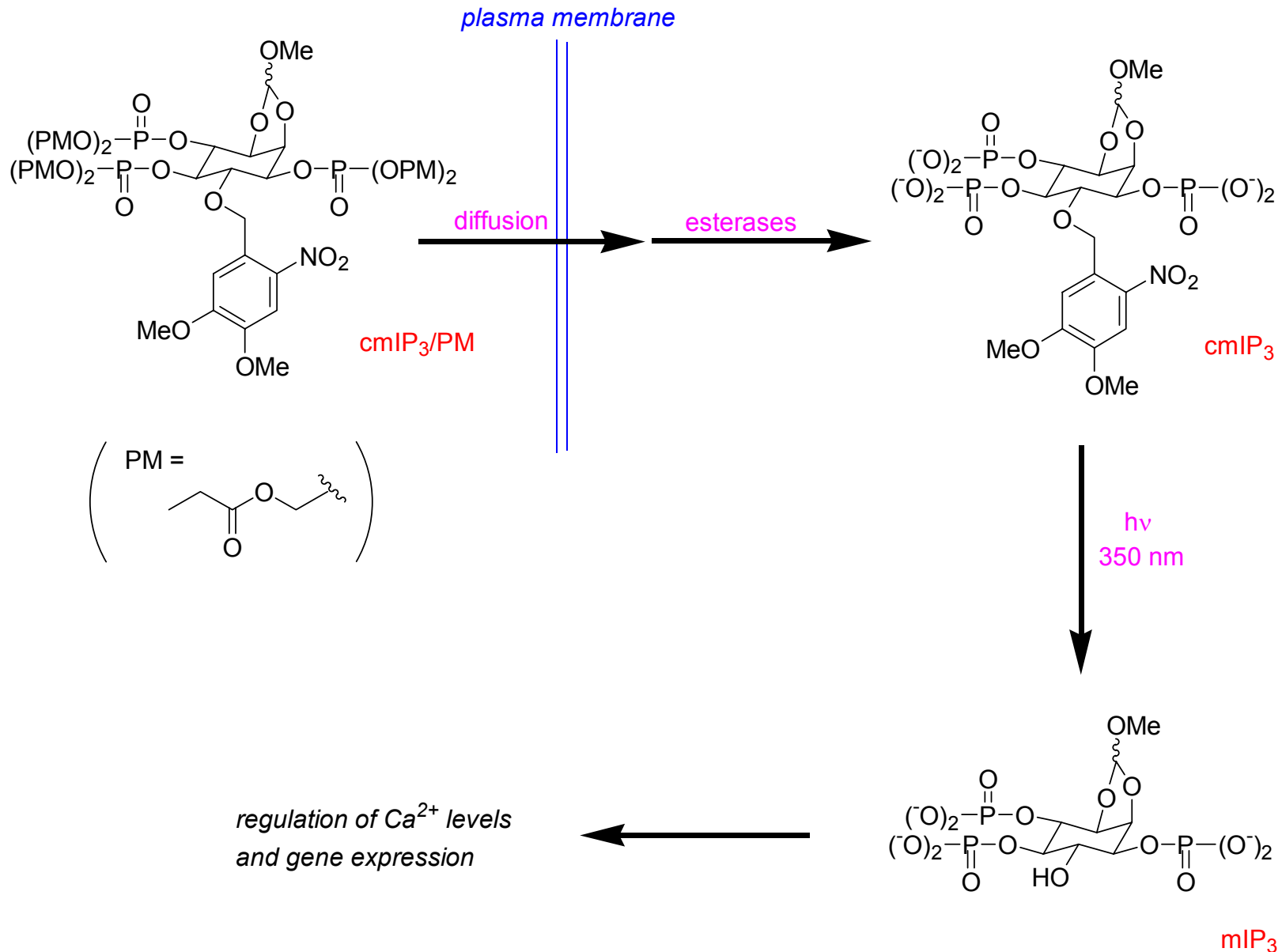
95% yield
>95% pure

Photolabile Protecting Groups

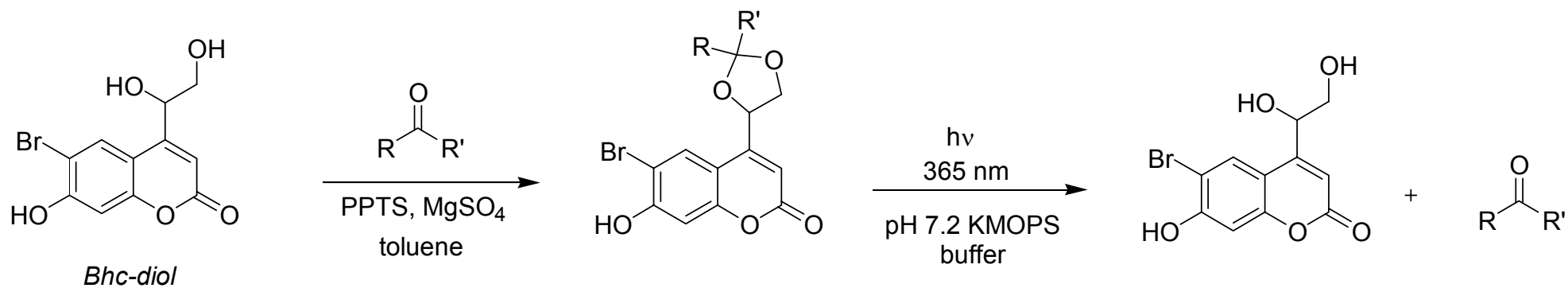


Photochemical Release of "Caged" Molecules

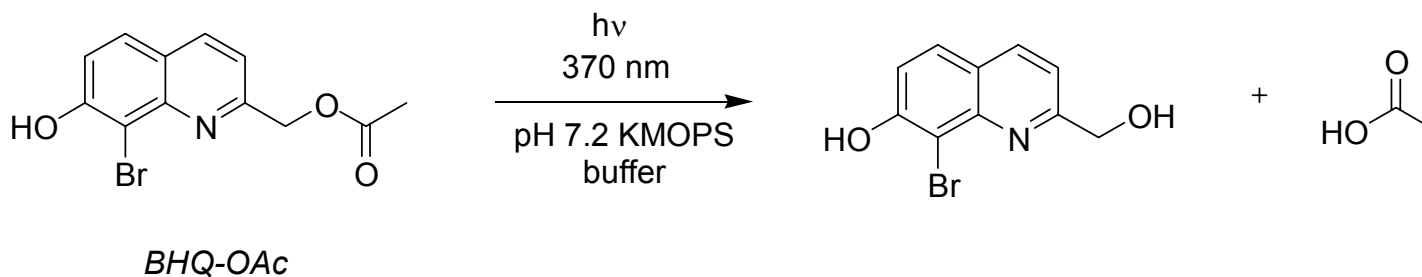
Inositol Triphosphate ($InsP_3$)



Photochemical Release of "Caged" Molecules



Lu, M.; Fedoryak, O. D.; Moister, B. R.; Dore, T. M. *Org. Lett.* **2003**, 5, 2119.



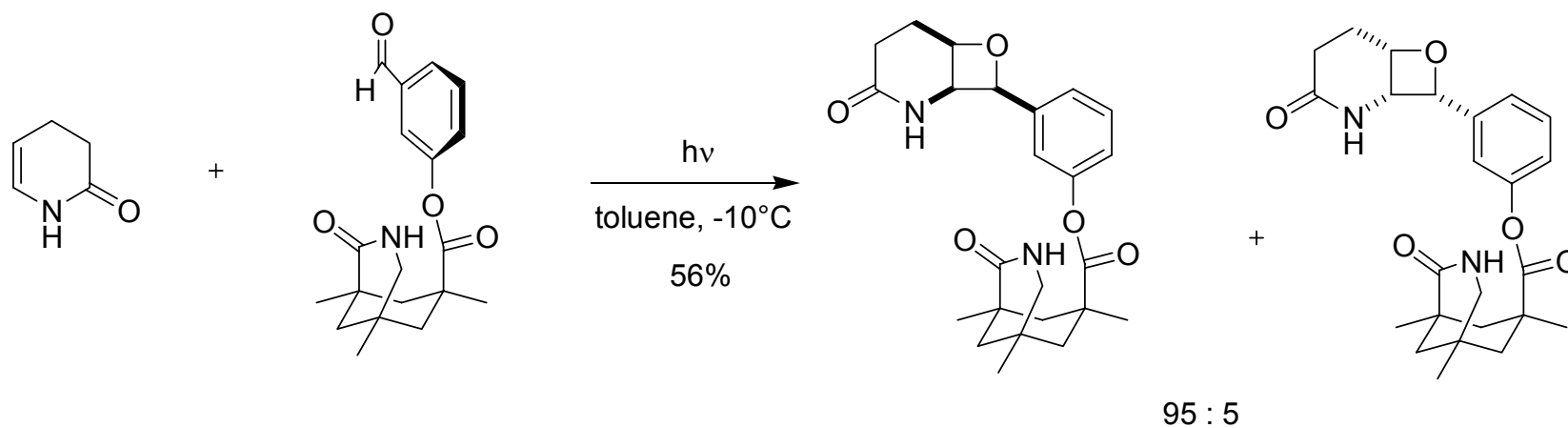
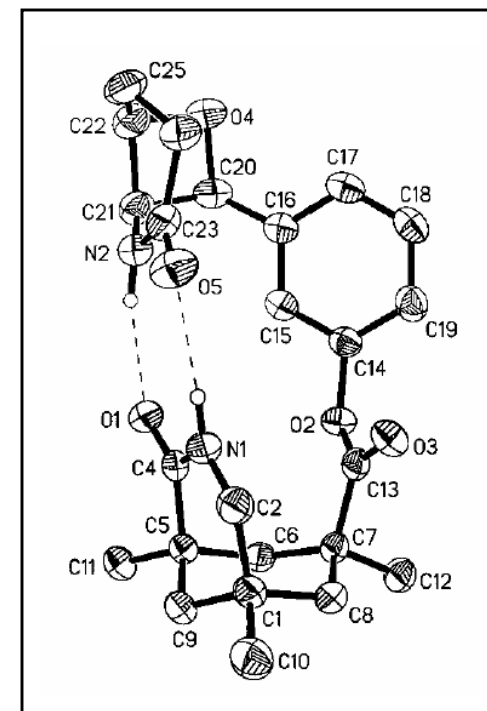
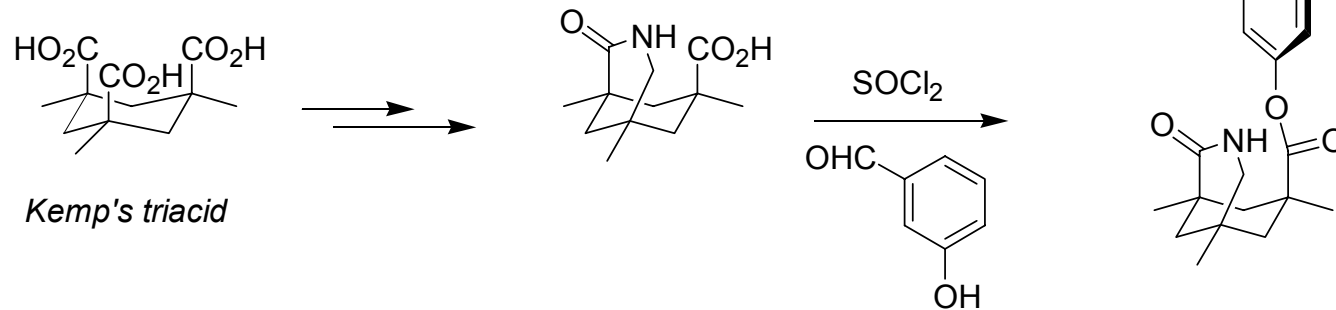
Fedoryak, O. D.; Dore, T. M. *Org. Lett.* **2002**, 4, 3419.

Attempts at Asymmetric Photochemistry

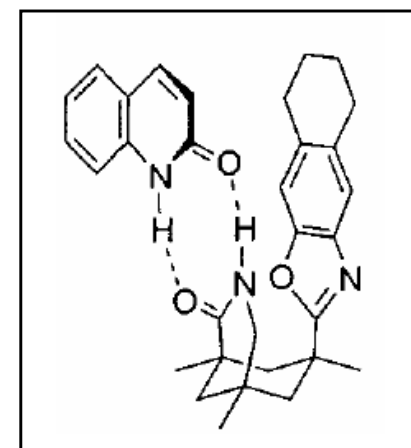
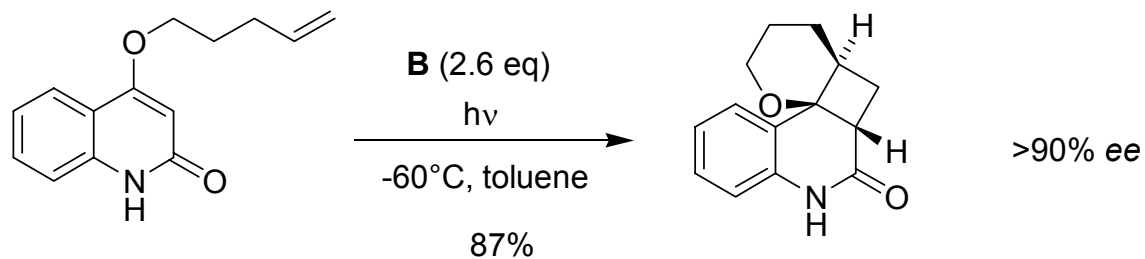
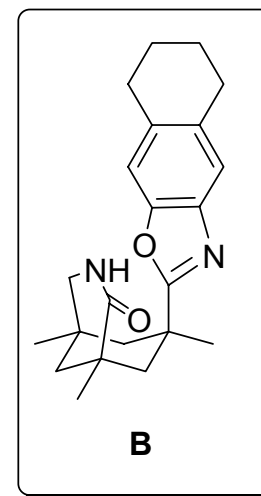
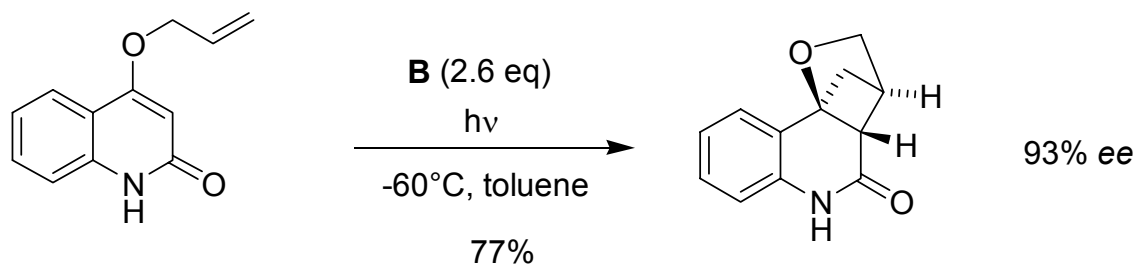
- Stoichiometric chirality transfer from pre-existing stereocenters present in the substrate
- Use of chiral auxiliaries
- Solid state photochemical transformations in clays and chirally modified zeolites
- Chiral solvents, liquid crystalline phases and polymer matrices
- Chiral molecular receptors
- Circularly polarized light
- Chiral photosensitizers

Review: Inoue, Y.; Wada, T.; Asaoka, S.; Sato, H.; Pete, J.-P. *J. Chem. Soc., Chem. Commun.* **2000**, 251.

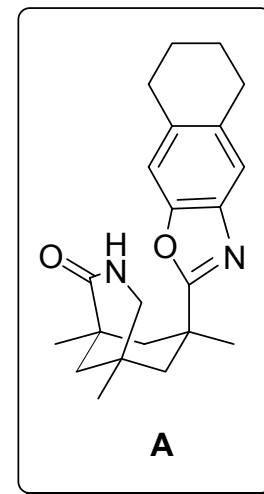
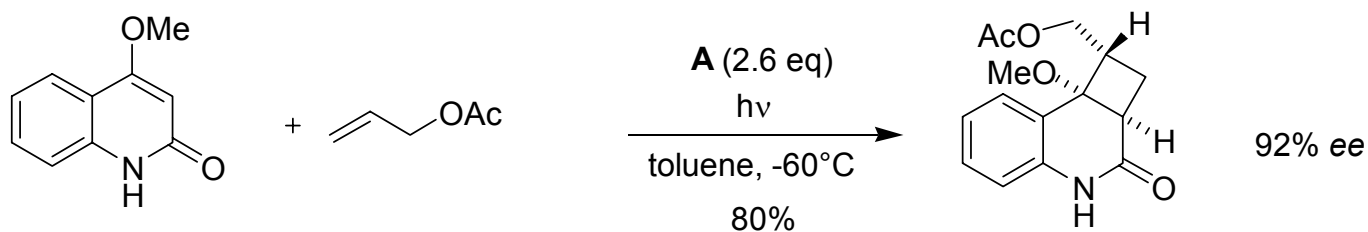
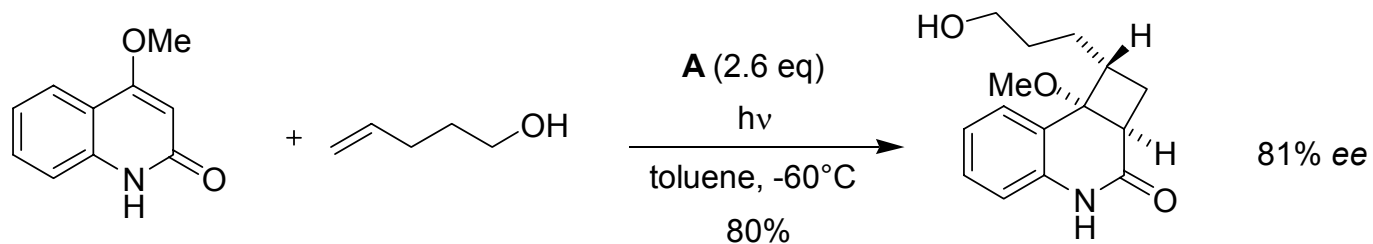
Chiral Auxiliary



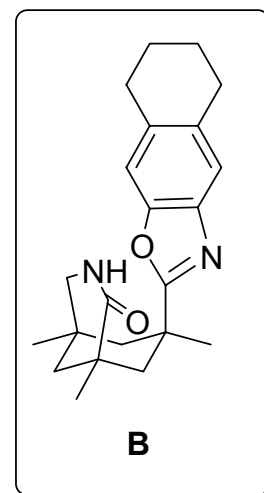
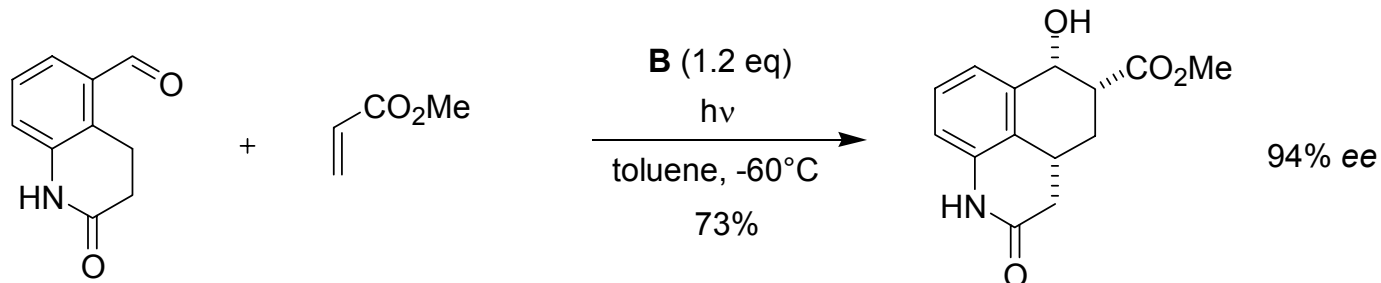
Chiral Molecular Receptors (Host-Guest Systems)



Chiral Molecular Receptors (Host-Guest Systems)

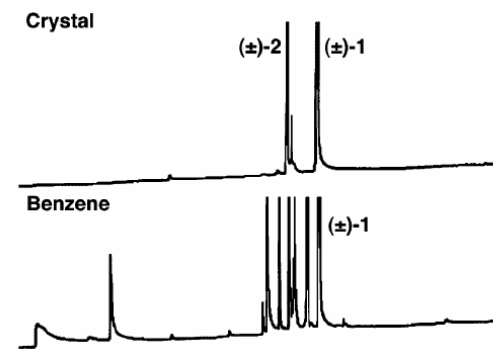
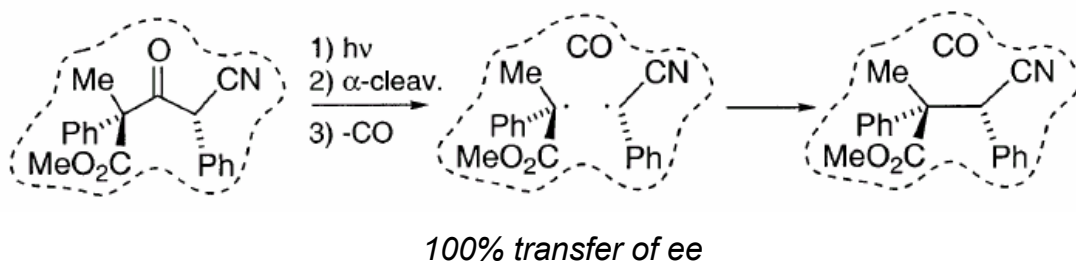


Bach, T.; Bergmann, H.; Grosch, B.; Harms, K. *J. Am. Chem. Soc.* **2002**, *124*, 7982.

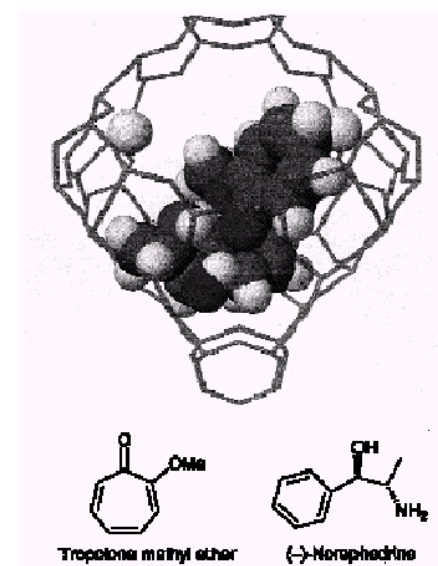
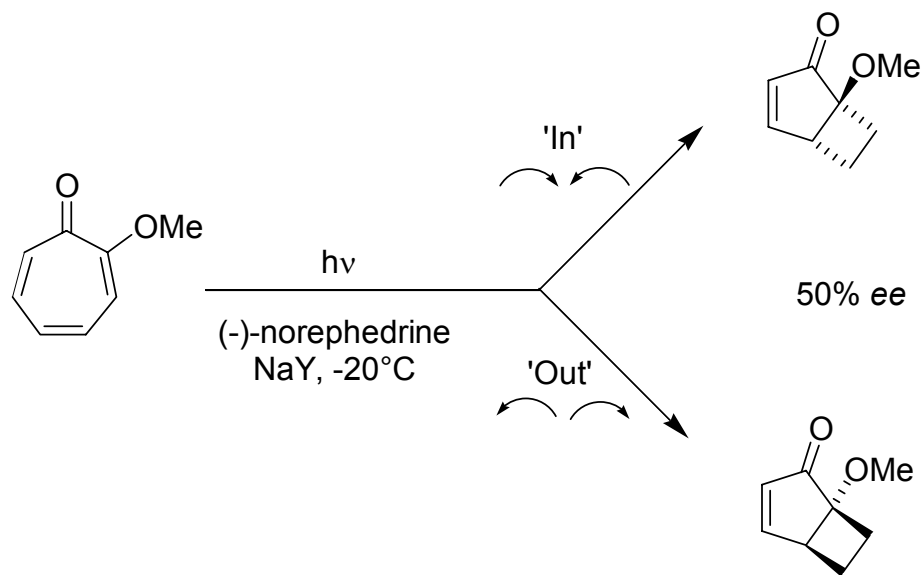


Grosch, B.; Orlebar, C. N.; Herdtweck, E.; Masa, W.; Bach, T. *Angew. Chem. Int. Ed.* **2003**, *42*, 3693.

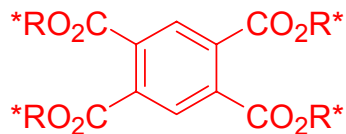
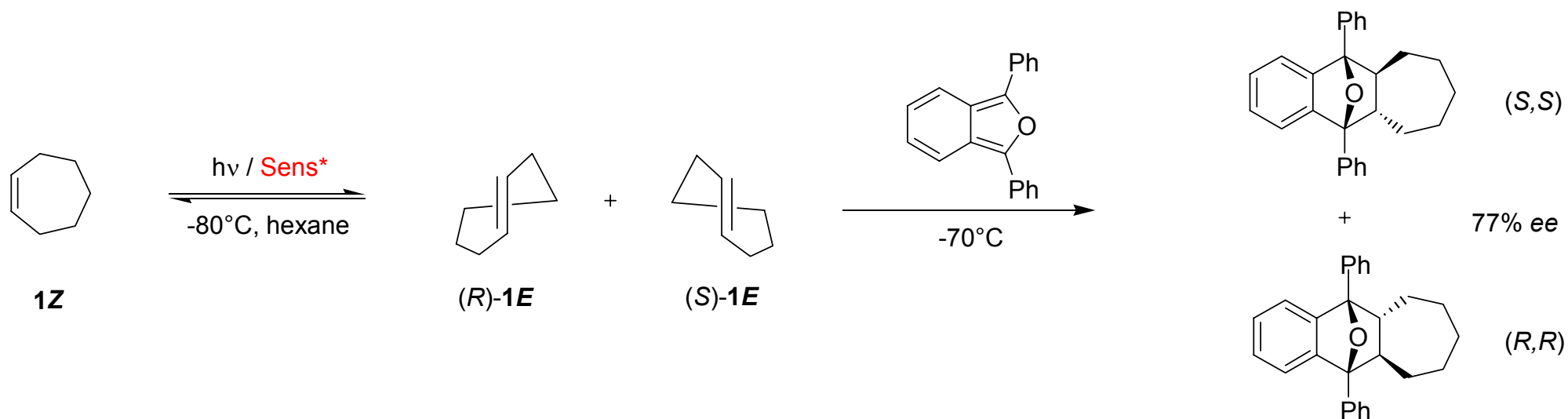
Solid State or Crystalline Reactions Can Induce Asymmetry



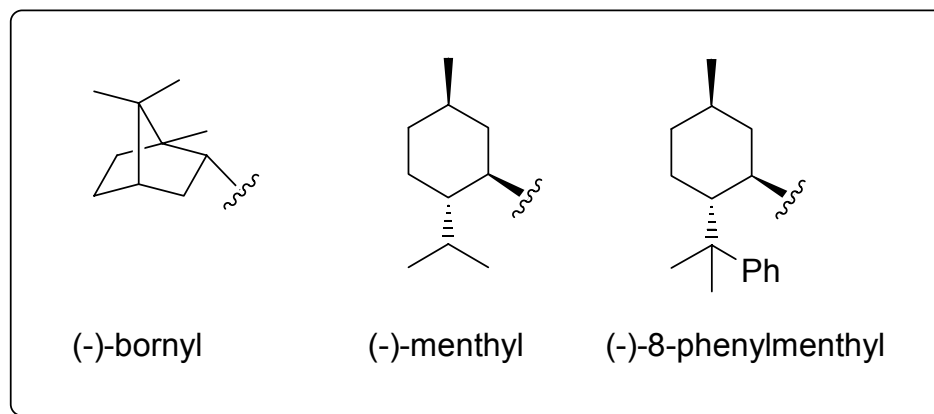
Ellison, M. E.; Ng, D.; Dang, H.; Garcia-Garibay, M. A. *Org. Lett.* **2003**, 5, 2531.



Sensitization by Chiral Aromatic Esters



Sensitizer*



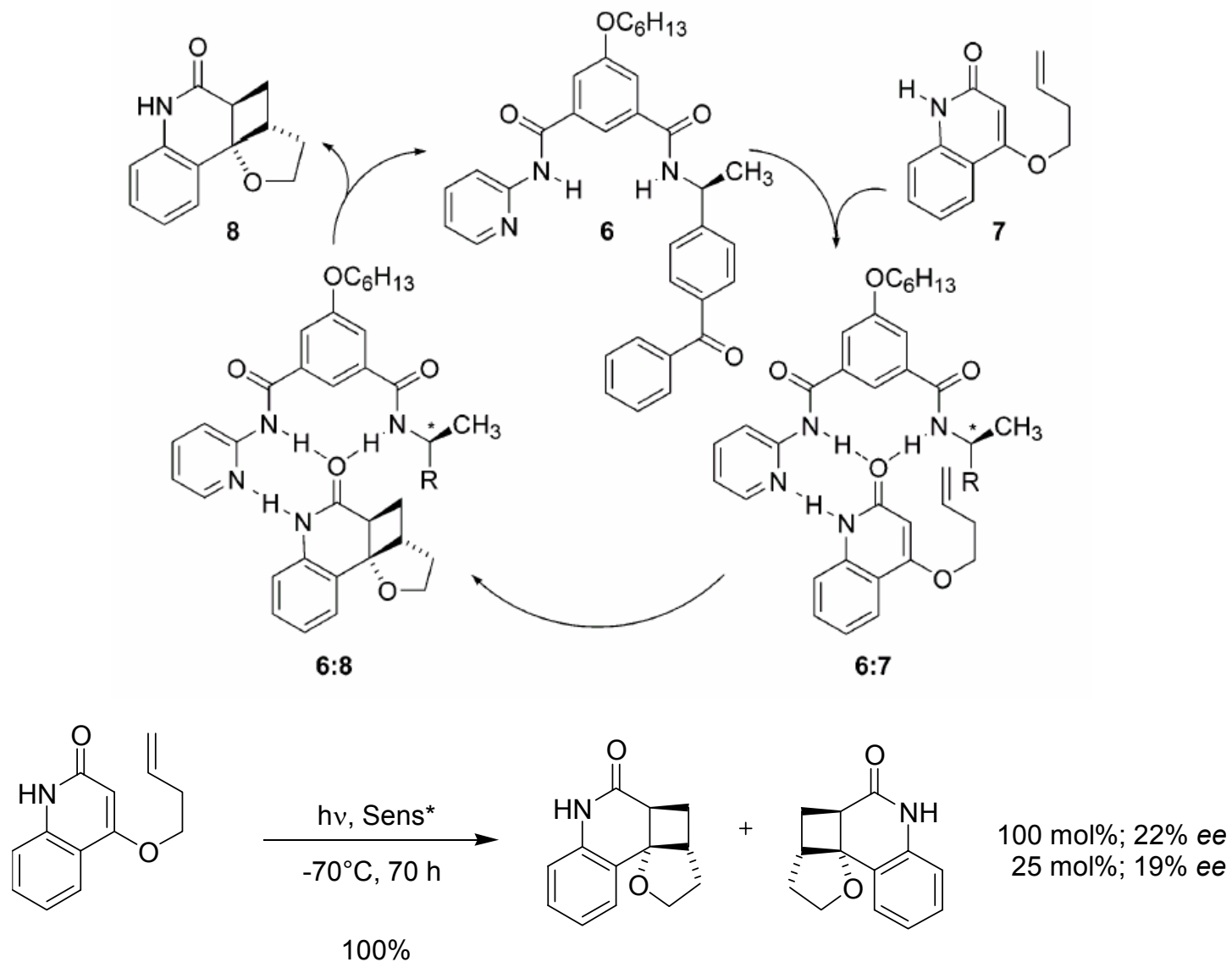
Designing a Catalytic Asymmetric Sensitizing Receptor

Requirements for such an endeavor:

1. The substrate must be placed in a well-defined chiral micro-environment upon binding to a template
 - *Host-guest system where hydrogen bonding dictates orientation in predictable fashion*
2. Substrate-template binding confers a kinetic advantage to the transformation of interest
 - *Sensitizer which contains a highly localized sphere of energy transfer (exciplex)*

If the lifetime of the exciplex is comparable to the rate of desired reaction, the exciplex formation can be enantiodiscriminating!

Designing a Catalytic Asymmetric Sensitizing Receptor



Summary

- ▶ Traditional photochemistry will continue to occupy a unique niche in the realm of organic synthesis.
 - *New and creative applications of established reactions will continue to solve important synthetic problems*
 - *Photochemistry allows access to reactive intermediates that would prove difficult to achieve by almost any other synthetic method.*
- ▶ The field of photochirogenesis will continue to be developed with hopes of unlocking its full potential, especially in applications toward total synthesis.
- ▶ New directions in organic photochemistry will likely focus on more contemporary biological and analytical applications.