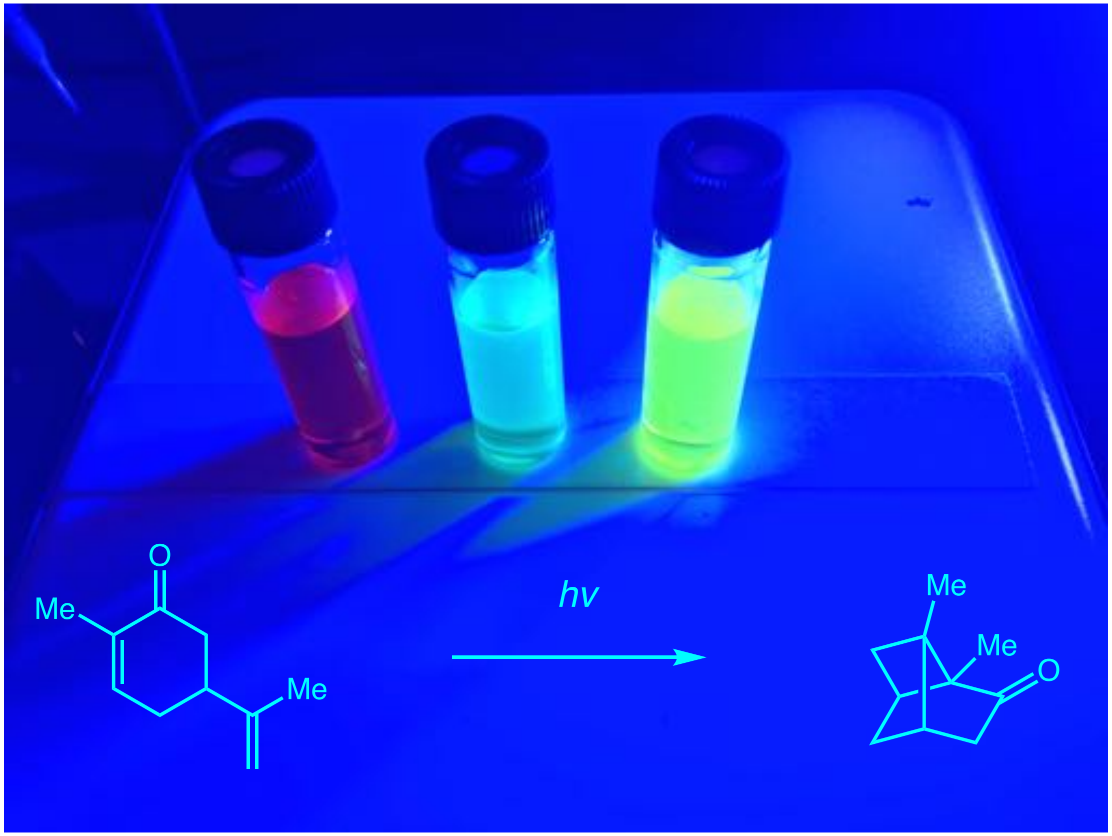
Complex Molecule Synthesis Enabled by Photochemistry



Joseph Badillo

MacMillan Group Meeting

March 23, 2017

Complex Molecule Synthesis Enabled by Photochemistry

Outline

General outline

1) Why are photochemical reactions interesting?

2) 2+2 cycloaddtions and cyclobutane ring-opening reactions

3) Norrish type I and II applications to complex architectures

4) Oxa-di-π-methane rearrangement

5) Paternò–Büchi reaction

6) meta-photocycloaddition reaction in total synthesis

7) Photoredox applications to complex molecule synthesis

8) Summary

Complex Molecule Synthesis Enabled by Photochemistry

why photochemistry?

- Why are photochemical reactions interesting?

1) Since excited states are rich in energy, highly endothermic reactions are possible.
   Such as highly strained (up-hill) targets!

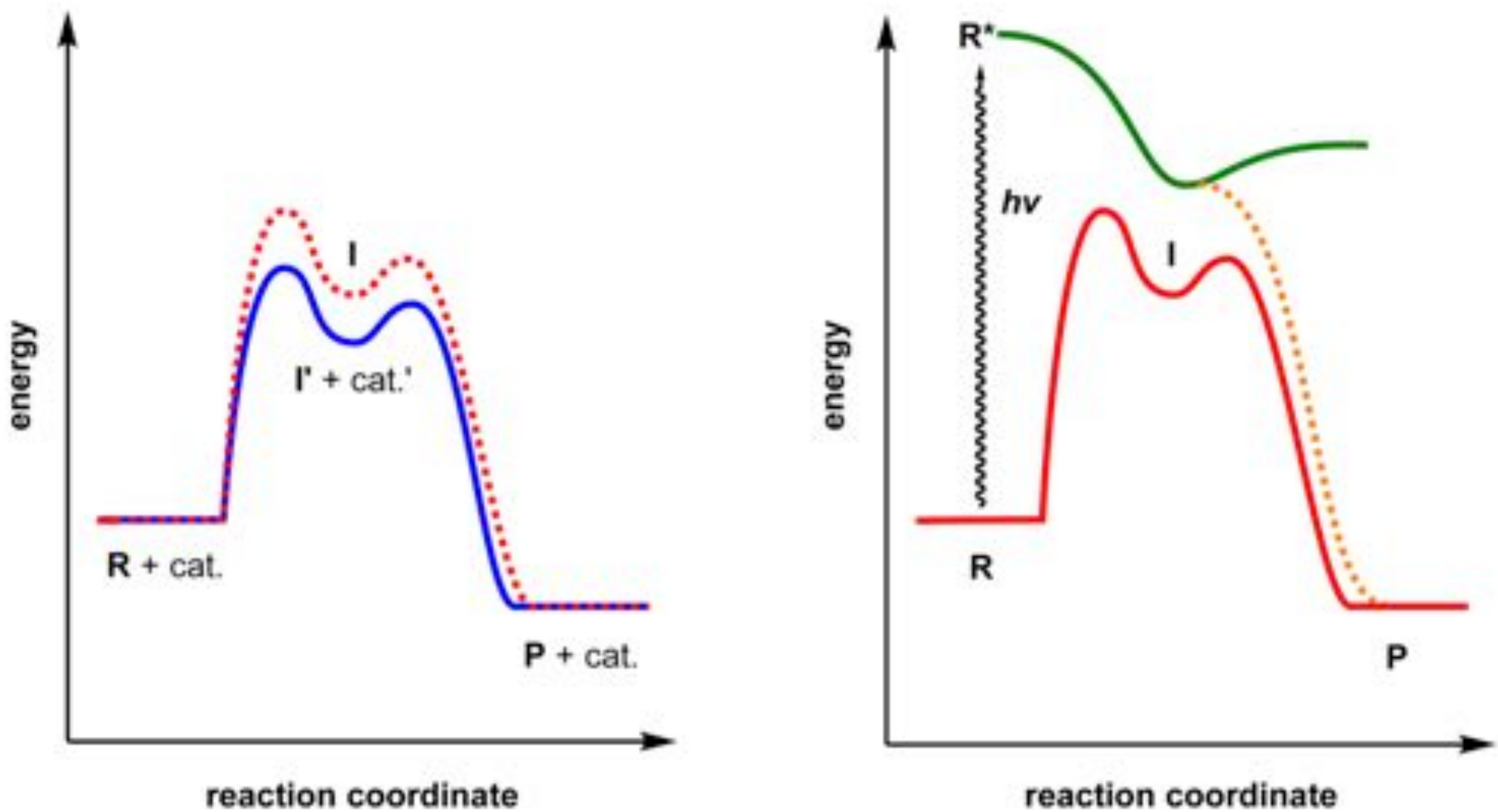
2) In the excited state antibonding orbitals are occupied, which allow for reactions to occur that are not possible in the ground state

3) Photochemical reactions have the potentail to be Green as they only consume photons

Complex Molecule Synthesis Enabled by Photochemistry

Thermal vs photochemical topography

- Reactant (R) goes through intermediate (I) to form product (P)



Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

typical absorption range of organic compounds

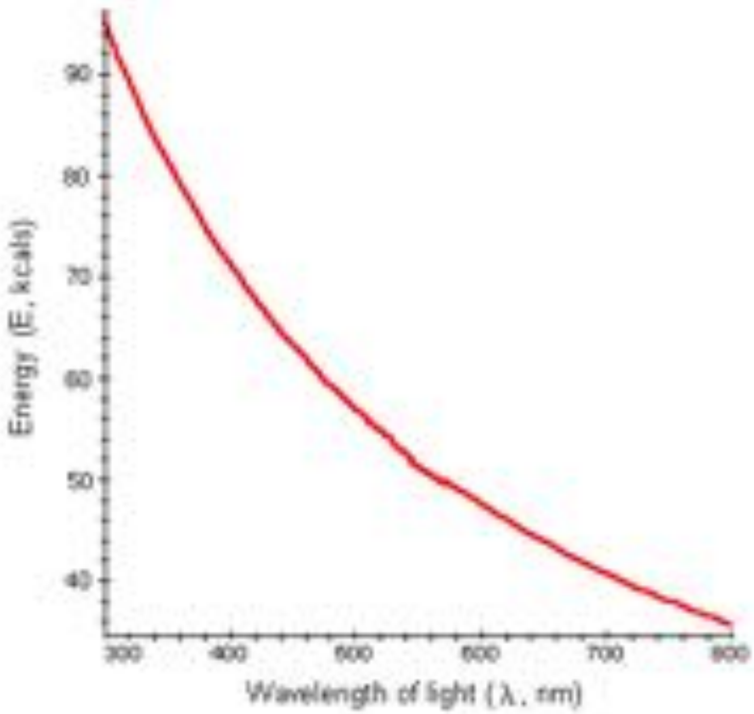
- Most organic molecules absorb light in the UV-region

Simple alkenes	190 - 200 nm	Ultra Violet (UV)
Acyclic diene	220 - 250 nm	Ultra Violet (UV)
Cyclic diene	250- 270 nm	Ultra Violet (UV)
Styrene	270 - 300 nm	Ultra Violet (UV)
Saturated ketones	270 - 280 nm	Ultra Violet (UV)
α,β-Unsaturated ketones	280 - 300 nm	Ultra Violet (UV)
Aromatic compounds	250 - 280 nm	Ultra Violet (UV)
Common photocatalysts	350 - 440 nm	Visible

Complex Molecule Synthesis Enabled by Photochemistry

Energy absorbed from light

- Energy as a function of wavelength is hyperbolic



$$E = \frac{\mathrm{N}\, h\, \mathrm{c}}{\lambda}$$

$$E = energy\ in\ a\ mol\ of\ photons\ (cal)$$
$$N = Avagadro'number\ (per\ mol)$$
$$h = Plank's\ constant\ (cal \cdot \mathrm{sec})$$
$$c = velocity\ of\ light\ (nm/sec)$$
$$\lambda = wavelength\ (nm)$$

A molecule absorbing blue light, with a wavelength of 400 nm, absorbs about 71 kcal of energy

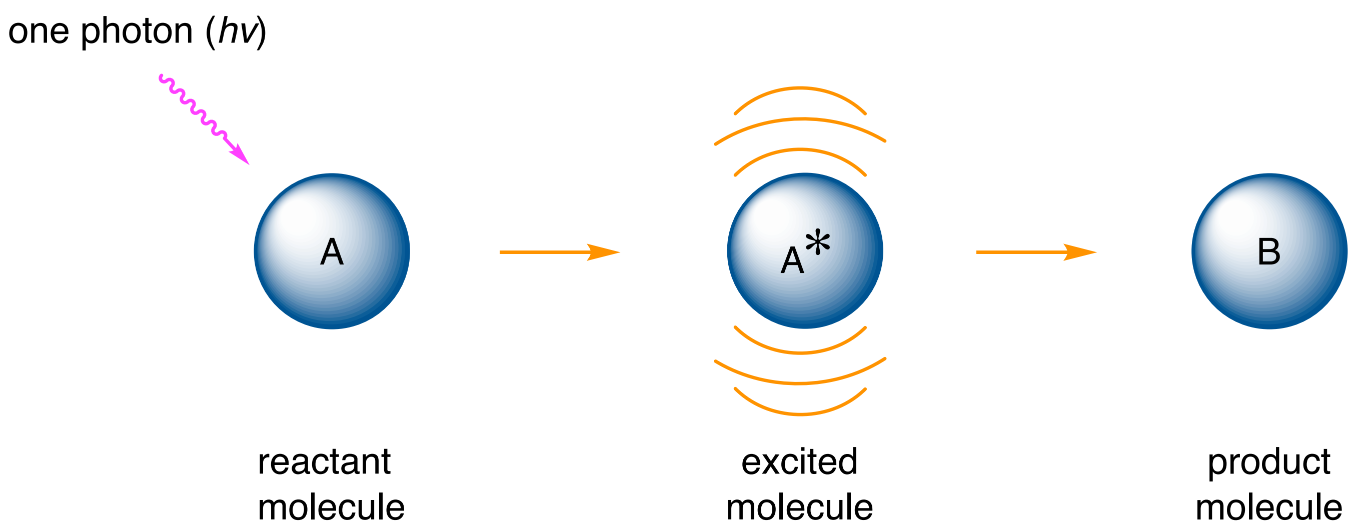
Purves, W. K., G. H. Orians, H. C. Heller, and D. Sadava. **1998**. Life: *The Science of Biology* (Fifth Edition). Sinauer Associates, Sunderland, MA.

Complex Molecule Synthesis Enabled by Photochemistry

2 basic laws governing photochemical reactions

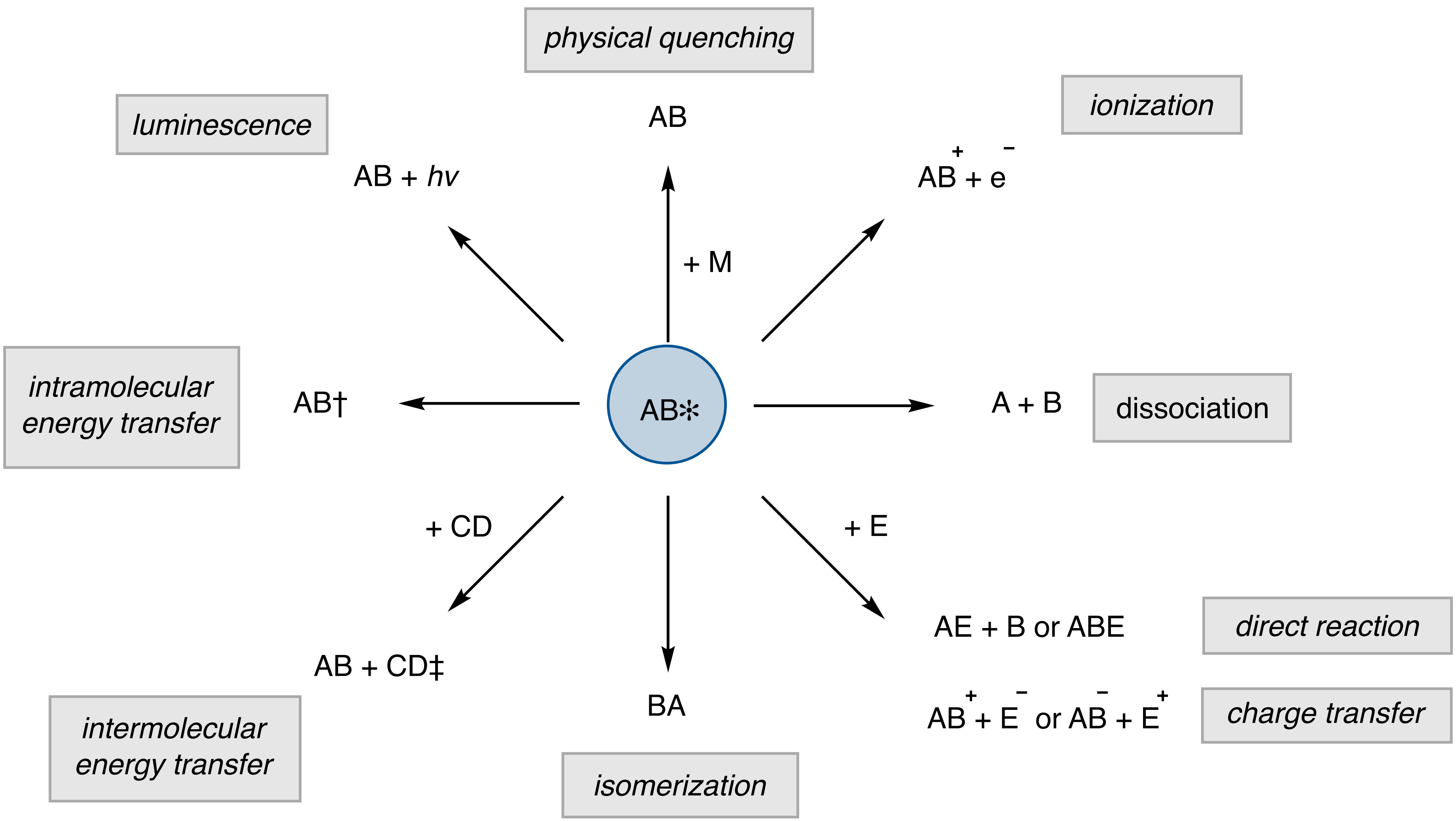
- Grotthus-Draper law (Principle of Photochemical Activation): Only the light which is absorbed by a system can bring about chemical change

- Stark-Einstein law (Law of Photochemical Equivalence): Each reactant molecule absorbs a single photon to provide an activated species to form products



Complex Molecule Synthesis Enabled by Photochemistry

reactivity of excited state intermediates



For more physics details see: *Physical Organic Photochemistry* - Scott Simonovich Group Meeting (2011)

Complex Molecule Synthesis Enabled by Photochemistry

Outline

- General outline

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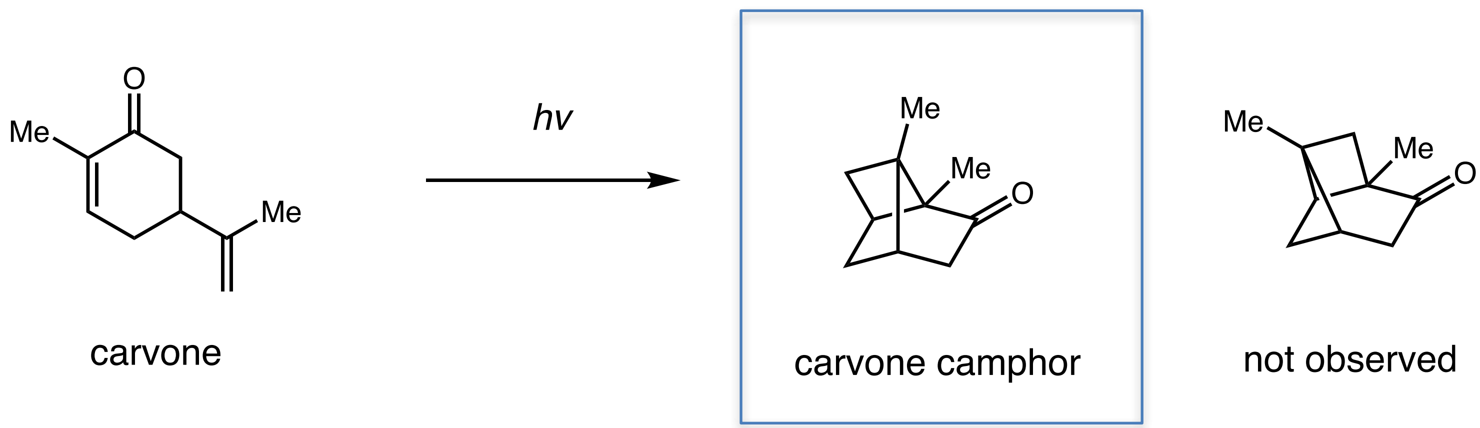
Complex Molecule Synthesis Enabled by Photochemistry

first report on the [2 + 2] photocycloaddition

- In 1908 Ciamician and Silber observed carvone camphor formation from carvone when exposed to sunlight for one year

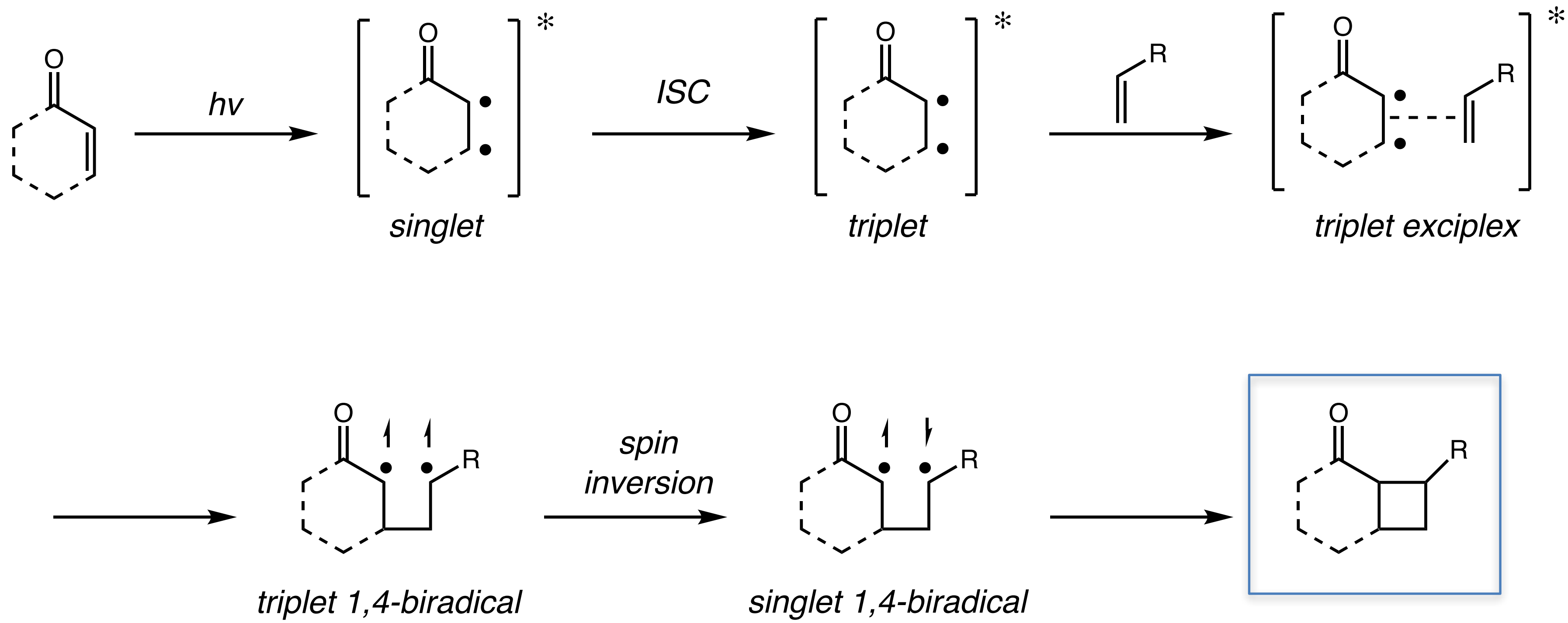


Ciamician, G.; Silber, P. Chemische Lichwirkungen. *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1928.

Complex Molecule Synthesis Enabled by Photochemistry

photoexcitation of enones

- α,β-unsaturated carbonyl compounds are often employed due to ease of excitability

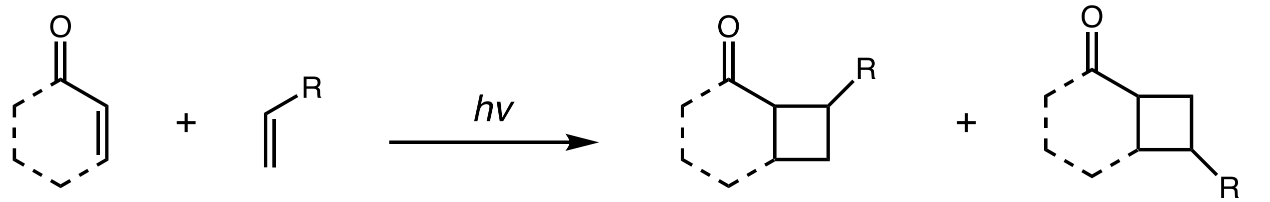


Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297.

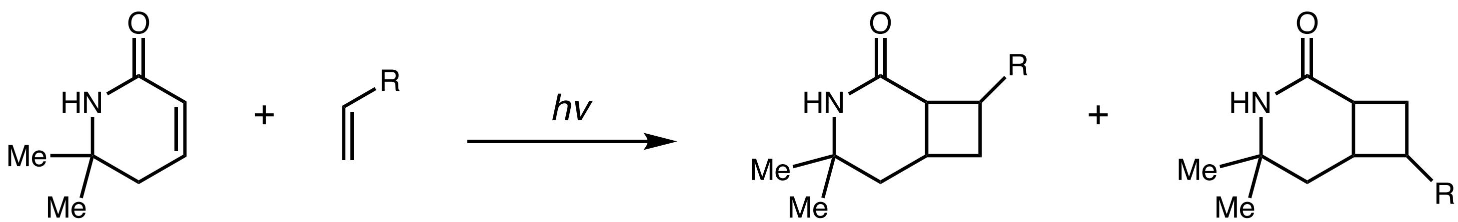
Complex Molecule Synthesis Enabled by Photochemistry

photoexcitation of enones

Regioselectivity in [2 + 2] photocycloadditions



head-to-head *head-to-tail*



head-to-head **A** *head-to-tail* **B**

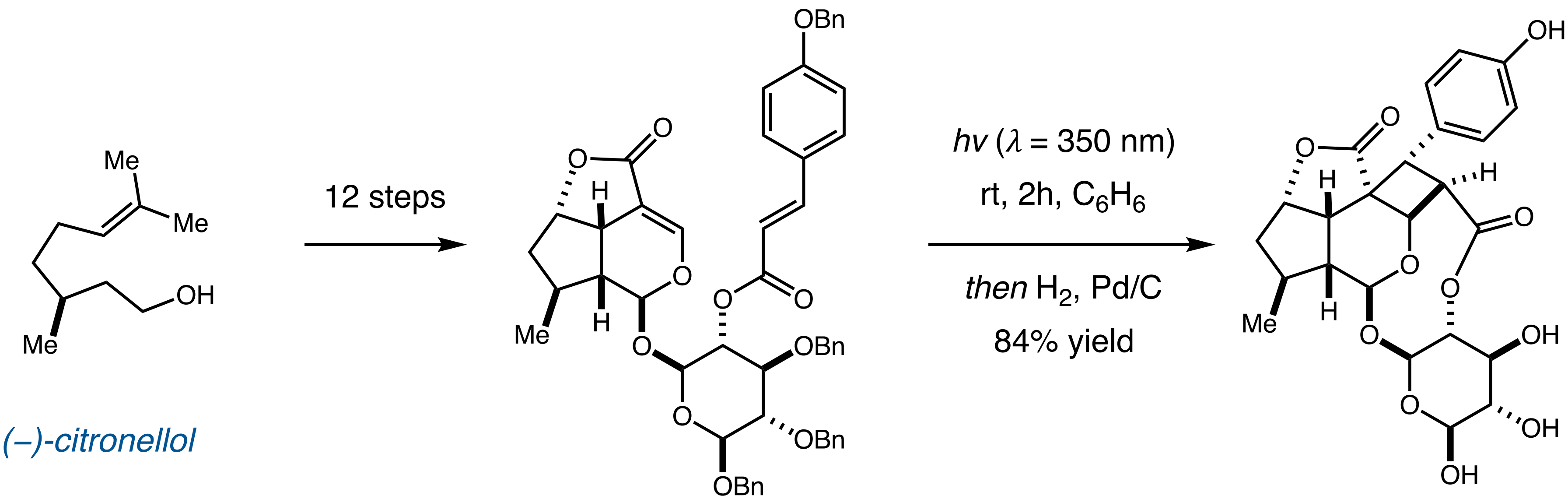
R	rr (**A**: **B**)
OEt	5:95
CN	82:18

Crimmins, M. T.; Reinhold, T. L. *Org. React.* **1993**, *44*, 297.

Complex Molecule Synthesis Enabled by Photochemistry

Total synthesis of (–)-littoralisone

- [2 + 2] photocycloaddition enables the the total sysnthesis of (–)-littoralisone



(–)-citronellol

(–)-littoralisone

13 steps

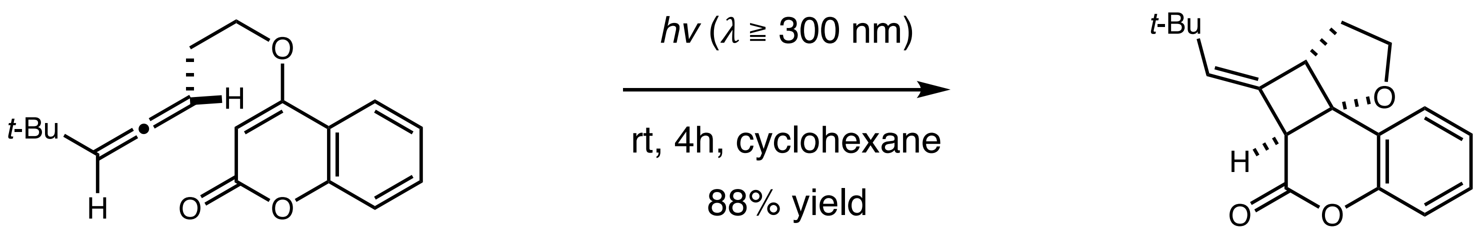
13% yield overall

Mangion, I. K.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 3696.

Complex Molecule Synthesis Enabled by Photochemistry

[2 + 2] cycloadditions using allenes

- Optically active allenes can be employed with retention of steroechemisitry



92% ee

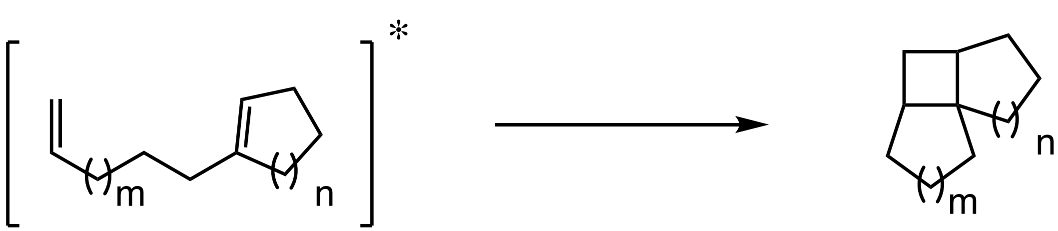
92% ee

Carreira, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc.* **1994**, *116*, 6622.

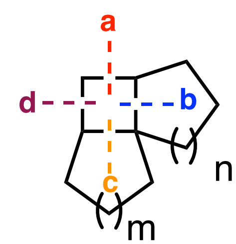
Complex Molecule Synthesis Enabled by Photochemistry

[2 + 2] photocycloaddition, followed by ring-opening

- Exploiting the inherent ring strain found in cyclobutanes to access medium-sized rings



photoexcited olefin *cyclobutane*



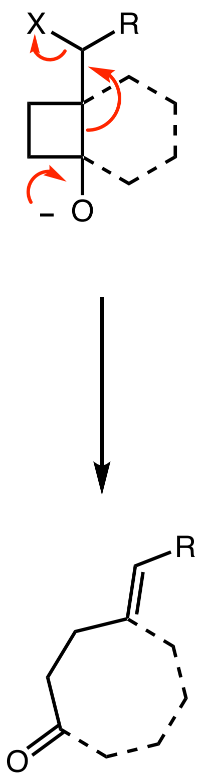
ring-opening at positions a-d give rise to different size rings

Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

[2 + 2] photocycloaddition, followed by ring-opening

■ Three common stratagies for cyclobutane ring opening



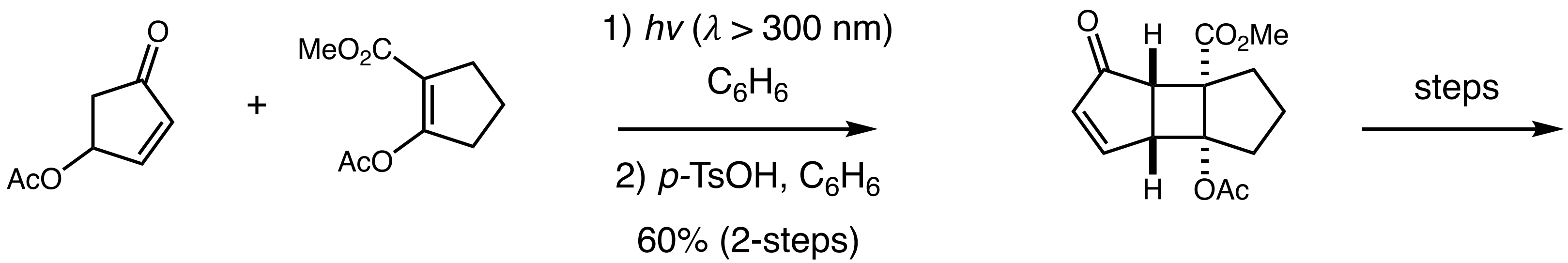
Grob fragmentation

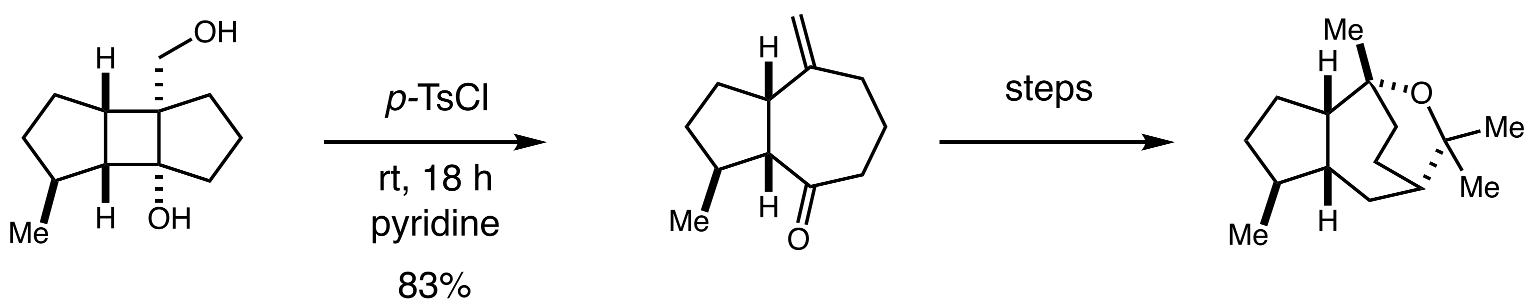
Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

Synthesis of (±)-epikessane

- A [2 + 2] cycloaddition followed by Grob fragmentaion enables the synthesis of (±)-epikessane





(±)-epikessane

Grob fragmentation

Liu, H.-J.; Lee, S. P. *Tetrahedron Lett.* **1977**, 3699

Complex Molecule Synthesis Enabled by Photochemistry

[2 + 2] photocycloaddition, followed by ring-opening

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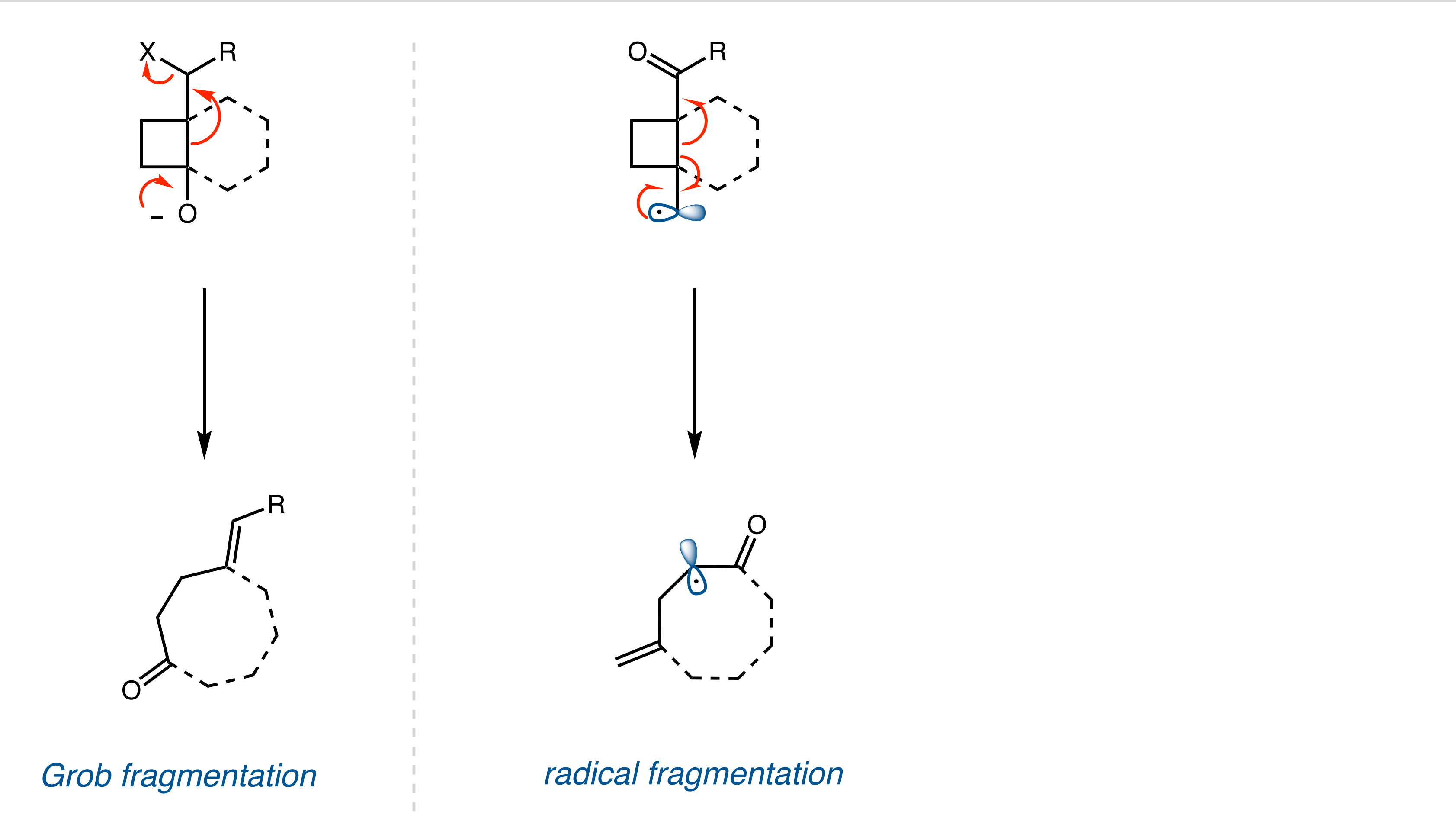
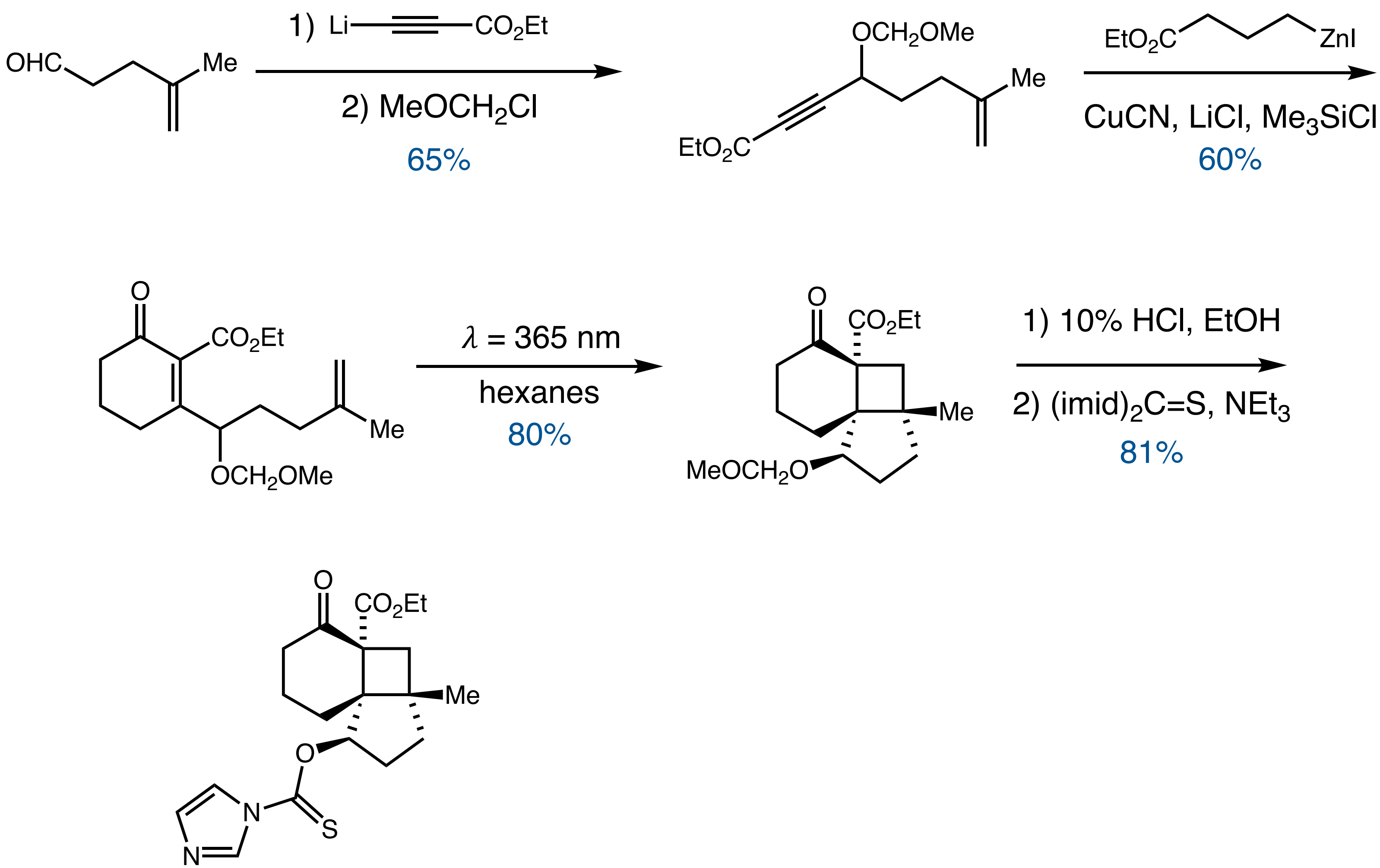


Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

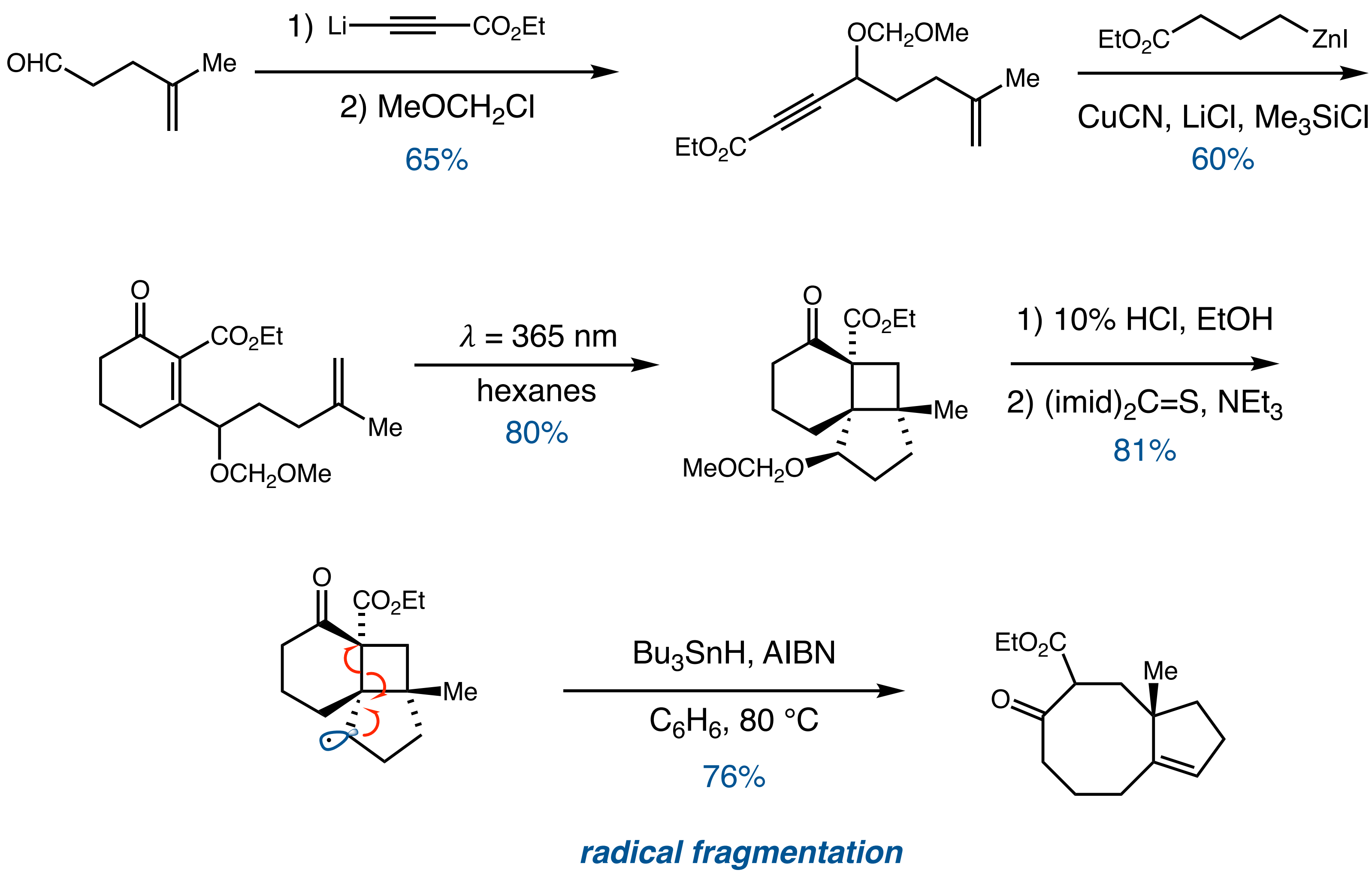
radical fragmentation



Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519.

Complex Molecule Synthesis Enabled by Photochemistry

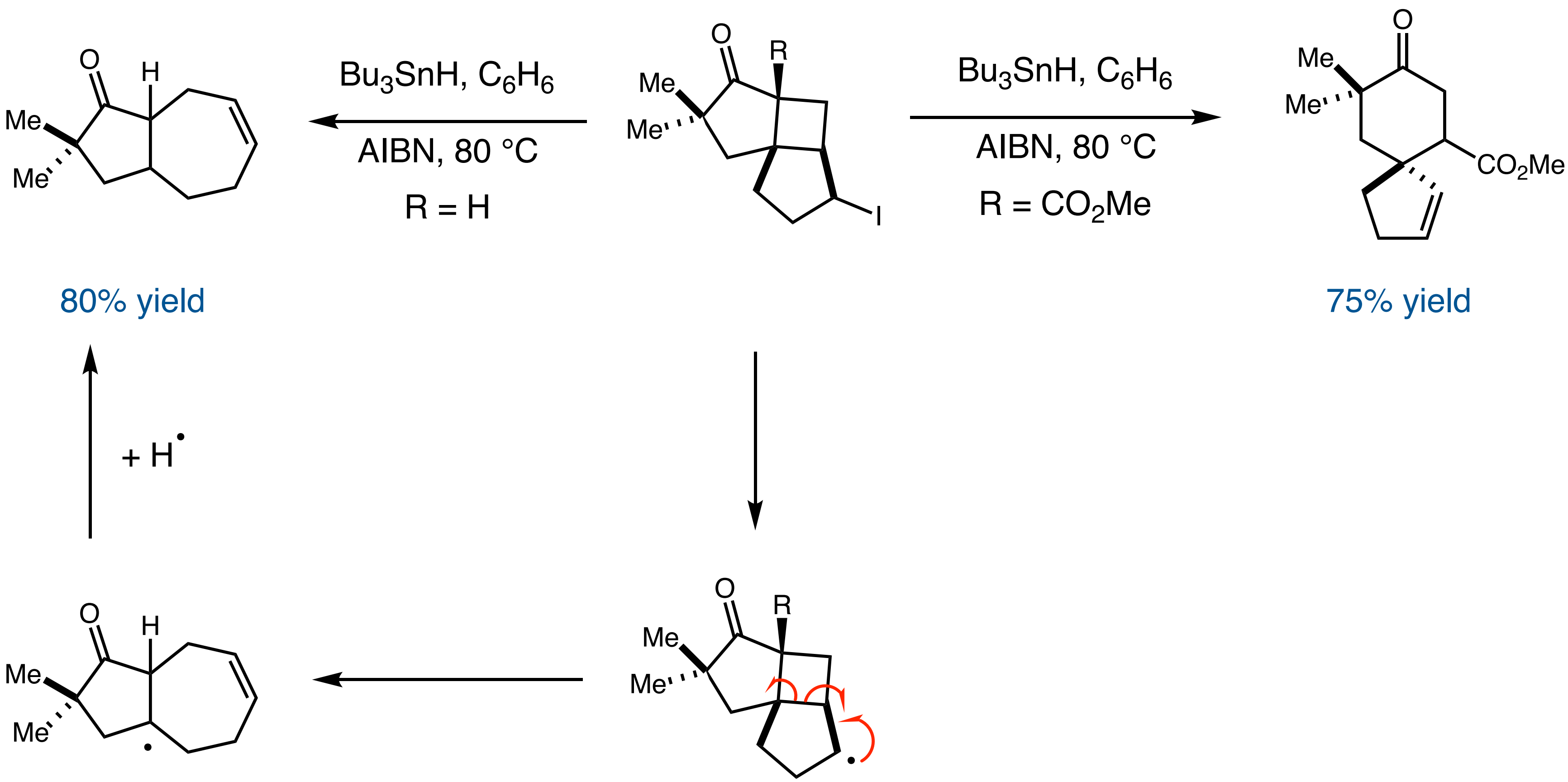
radical fragmentation



Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519.

Complex Molecule Synthesis Enabled by Photochemistry

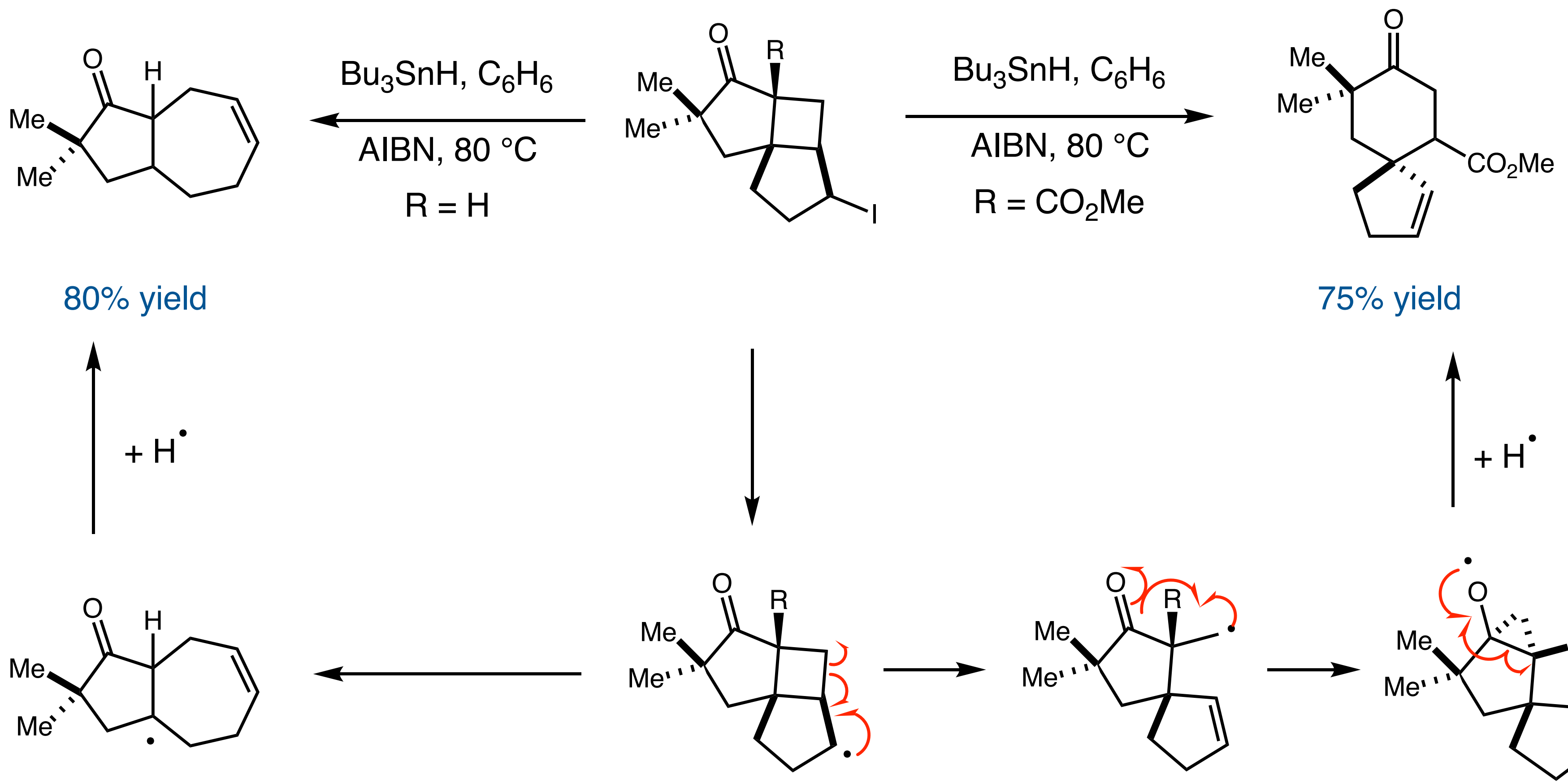
radical fragmentation



Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519.

Complex Molecule Synthesis Enabled by Photochemistry

radical fragmentation



Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519.

Complex Molecule Synthesis Enabled by Photochemistry

[2 + 2] photocycloaddition, followed by ring-opening

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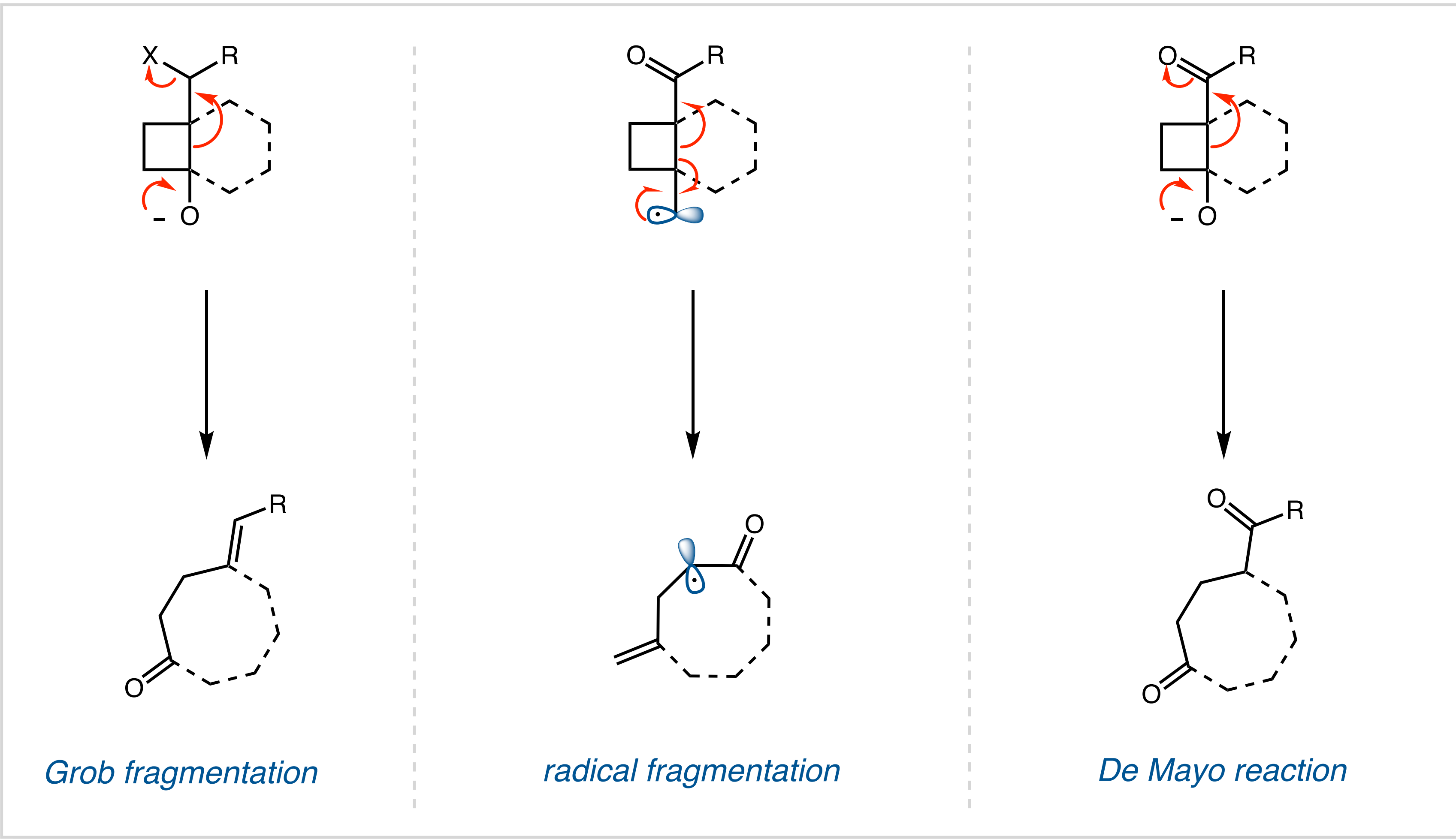
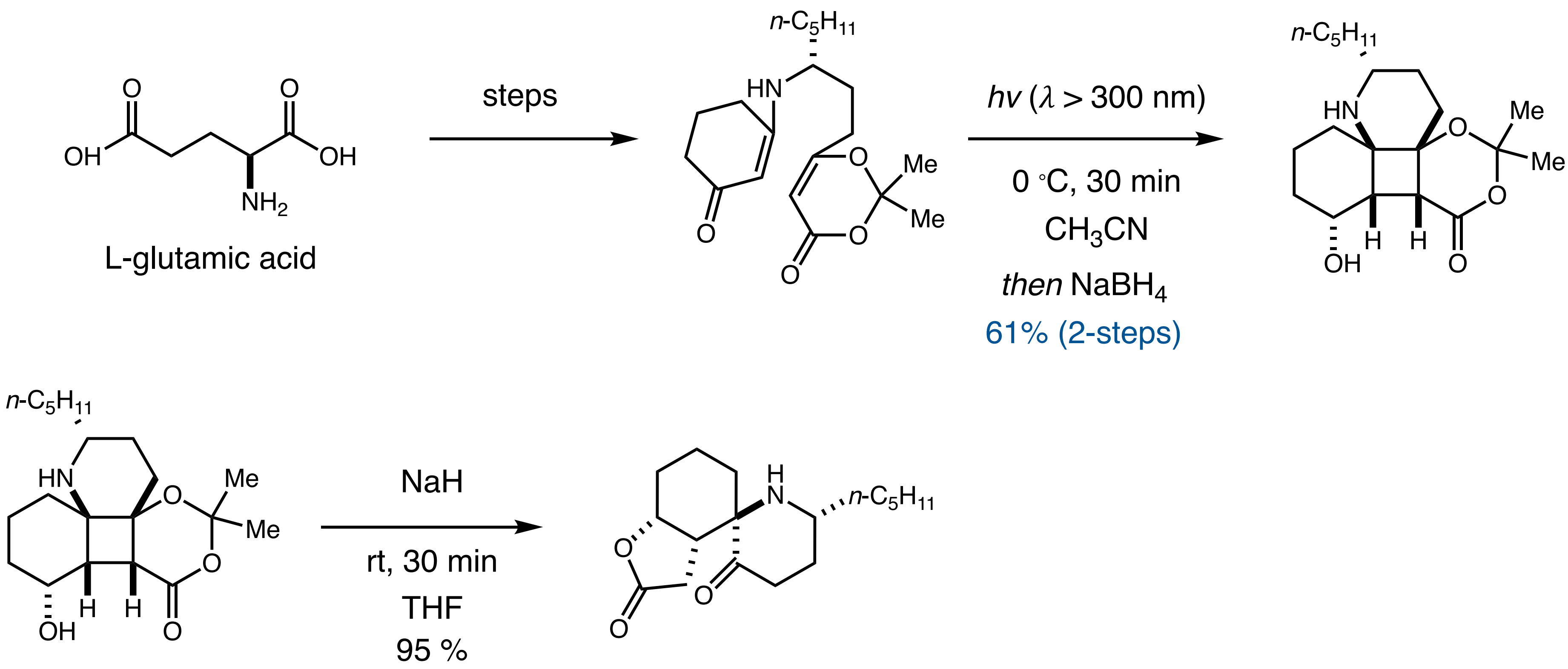


Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

Synthesis of (–)-perhydrohistrionicotoxin

- De Mayo fragmentaion enables the synthesis of (–)-perhydrohistrionicotoxin



De Mayo reaction

Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.

Complex Molecule Synthesis Enabled by Photochemistry

Synthesis of (–)-perhydrohistrionicotoxin

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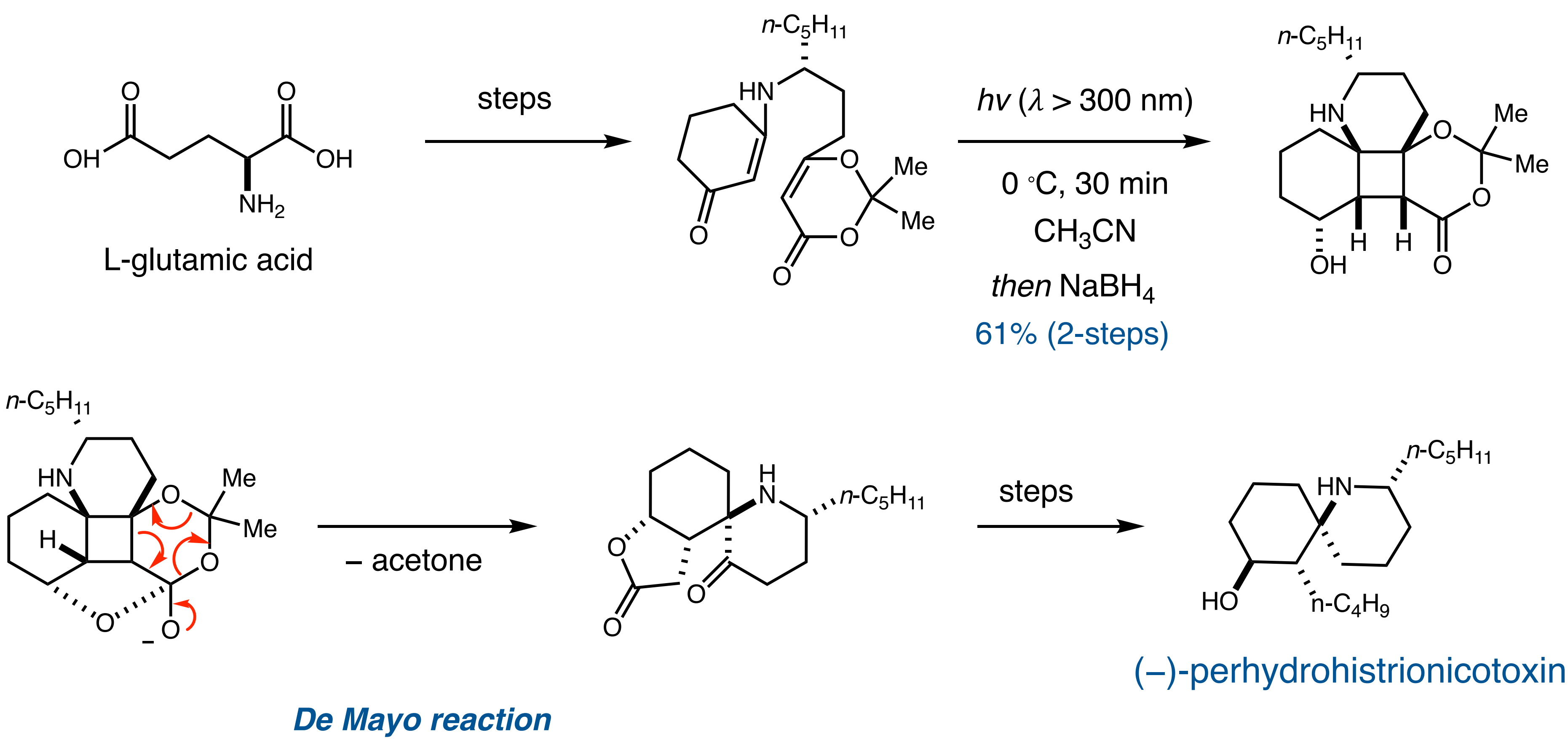
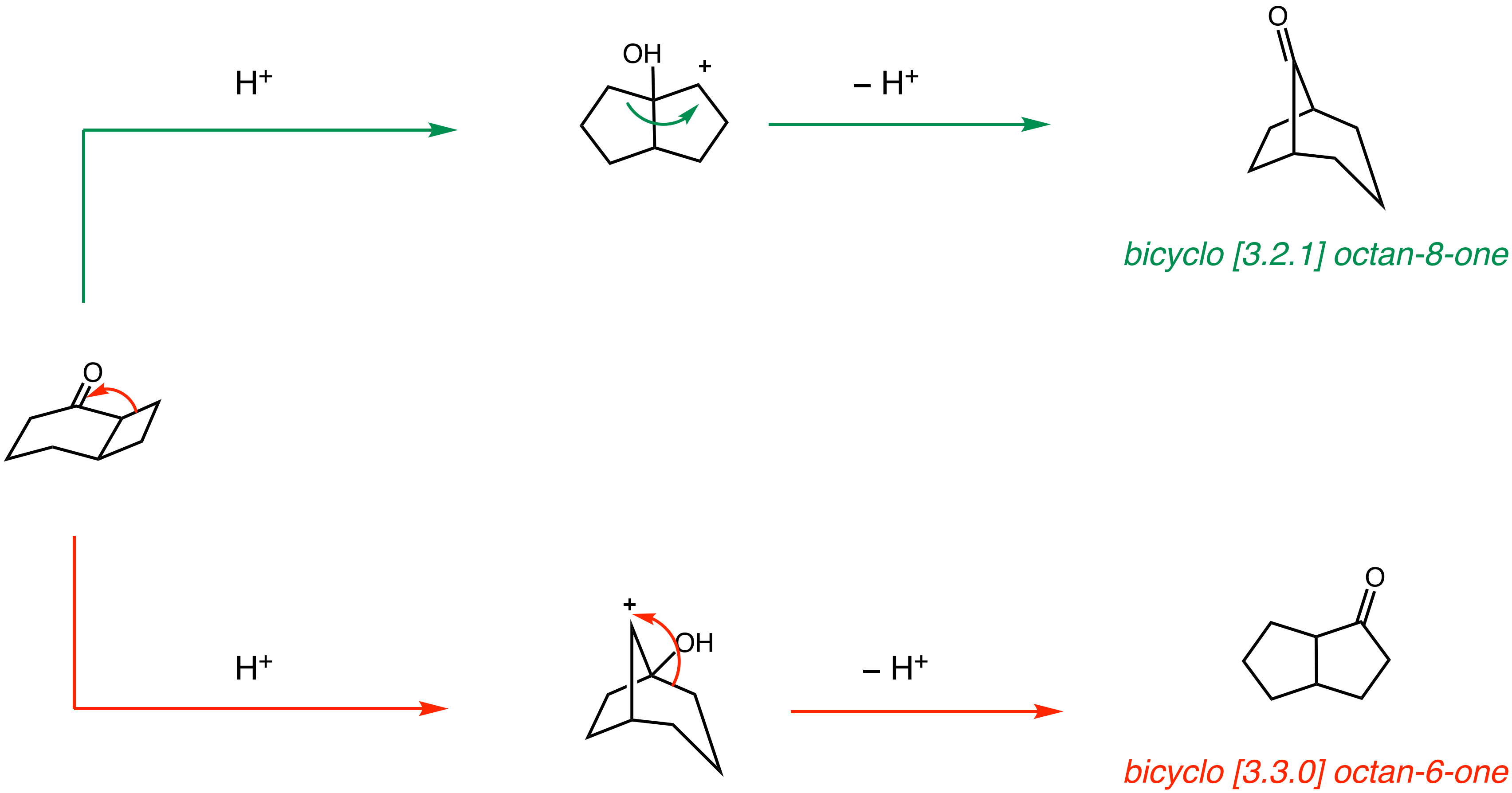


Winkler, J. D.; Hershberger, P. M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.

Complex Molecule Synthesis Enabled by Photochemistry

Cargill rearrangement

- Ring expansion of cyclobutanes via the Cargill rearrangement

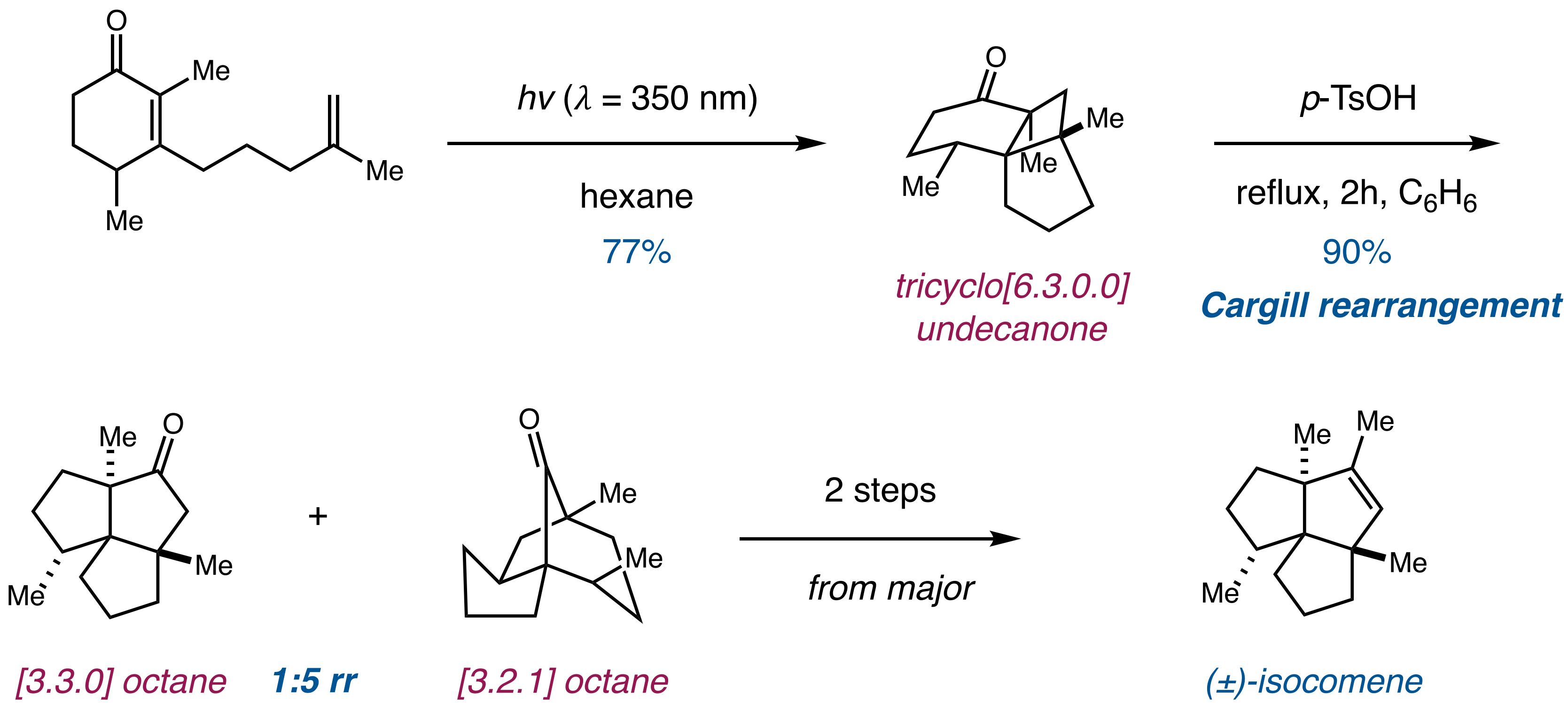


Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

Cargill rearrangement

- Pirrung's synthesis of (±)-isocomene using the Cargill rearrangment

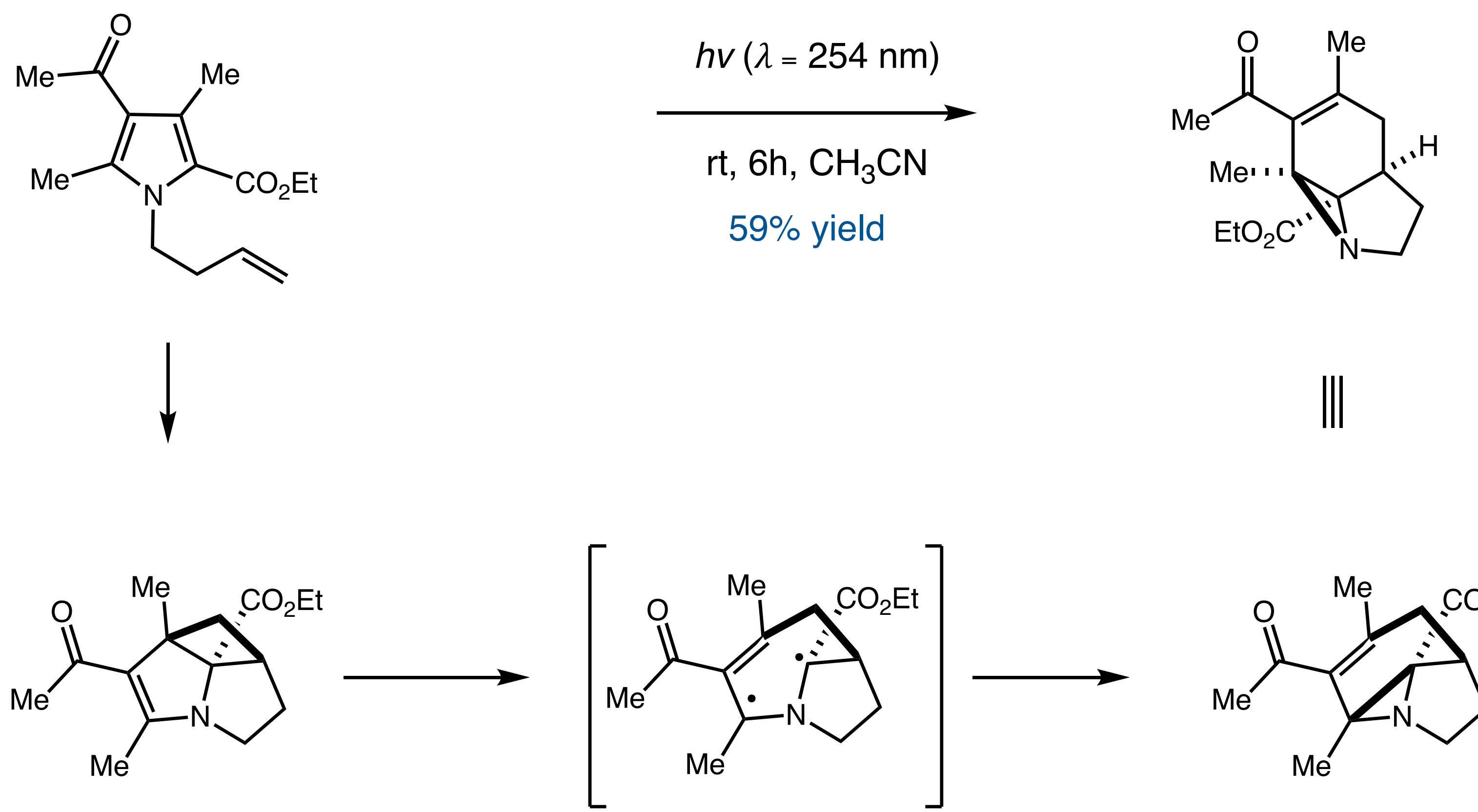


Pirrung, M. C. *J. Am. Chem. Soc.* **1979**, *101*, 7130.

Complex Molecule Synthesis Enabled by Photochemistry

tricyclic aziridines from pyrroles

- [2 + 2] photocycloaddition/rearrangement of pyrroles to form aziridines



Flow:
12 mM in CH_3CN
@9.5 mL/min
1 h, 0.91 g, 51%
(22 g/day)

Maskill, K. G.; Knowles, J. P.; Elliott, L. D.; Alder, R. W.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2013**, *52*, 1499.

Complex Molecule Synthesis Enabled by Photochemistry

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General outline

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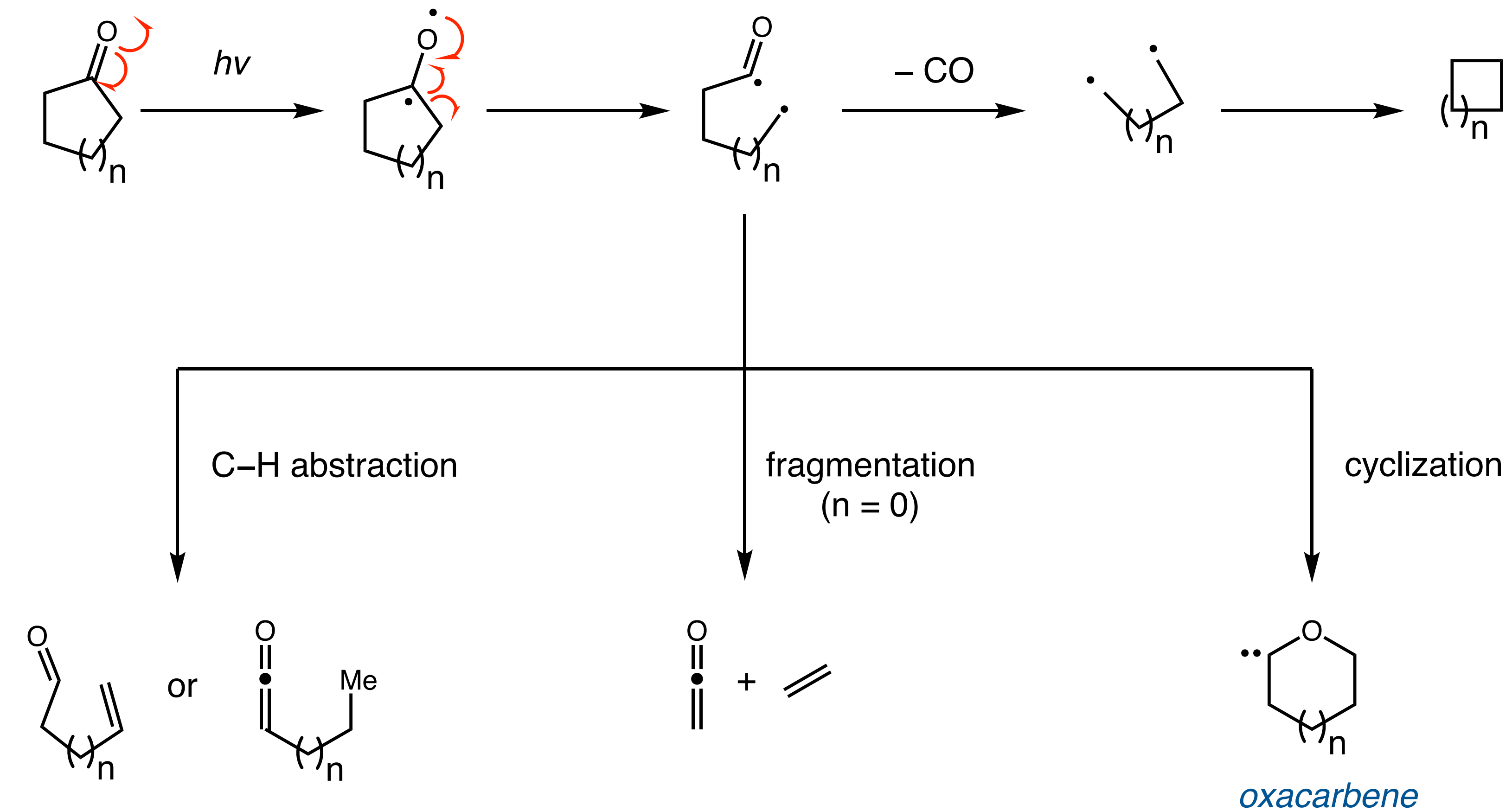
Complex Molecule Synthesis Enabled by Photochemistry

Norrish type I reaction

■ Possible products generated by Norrish type I cleavage



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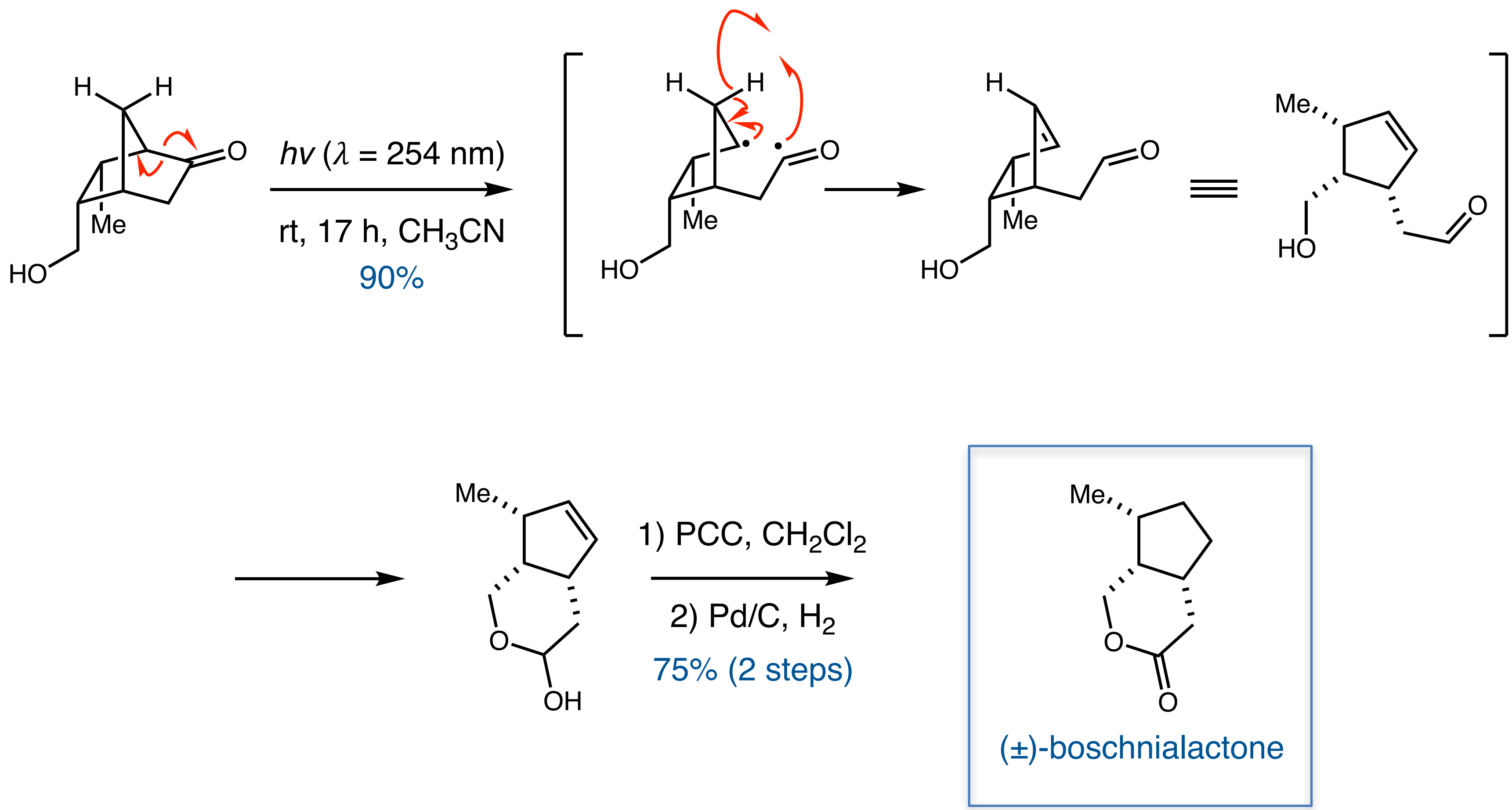
Complex Molecule Synthesis Enabled by Photochemistry

Norrish type I reaction

- Norrish type I cleavage followed by HAT for the synthesis of (±)-boschnialactone

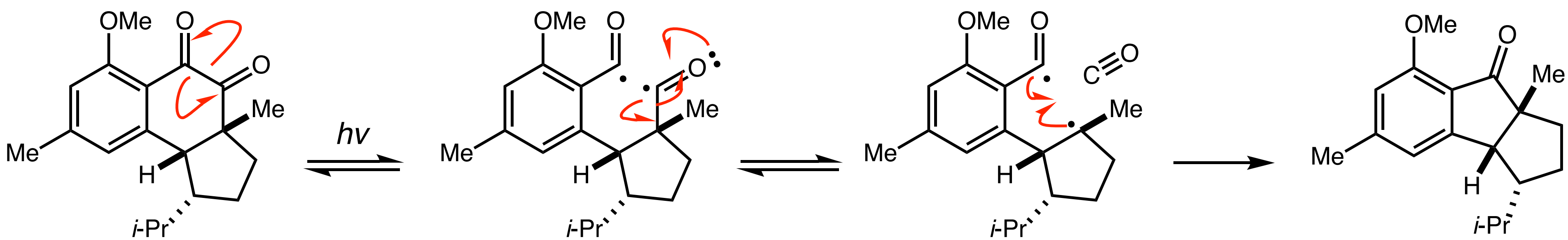


Callant, P.; Storme, P.; Van der Eycken, E.; Vandewalle, M. *Tetrahedron Lett.* **1983**, *24*, 5797.

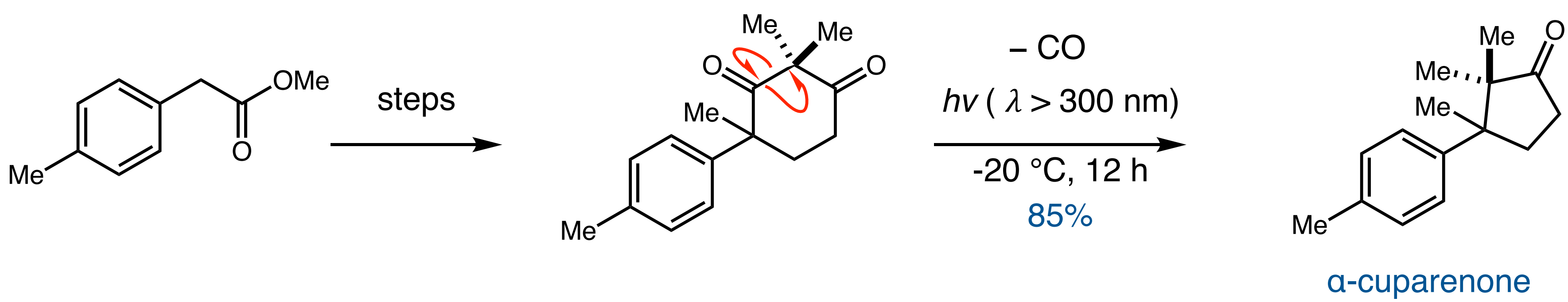
Complex Molecule Synthesis Enabled by Photochemistry

Norrish type I reaction

■ Norrish type I excision of carbon monoxide observed in the synthesis of the hamigerans



■ Norrish type I excision of carbon monoxide for the synthesis of α-cuparenone



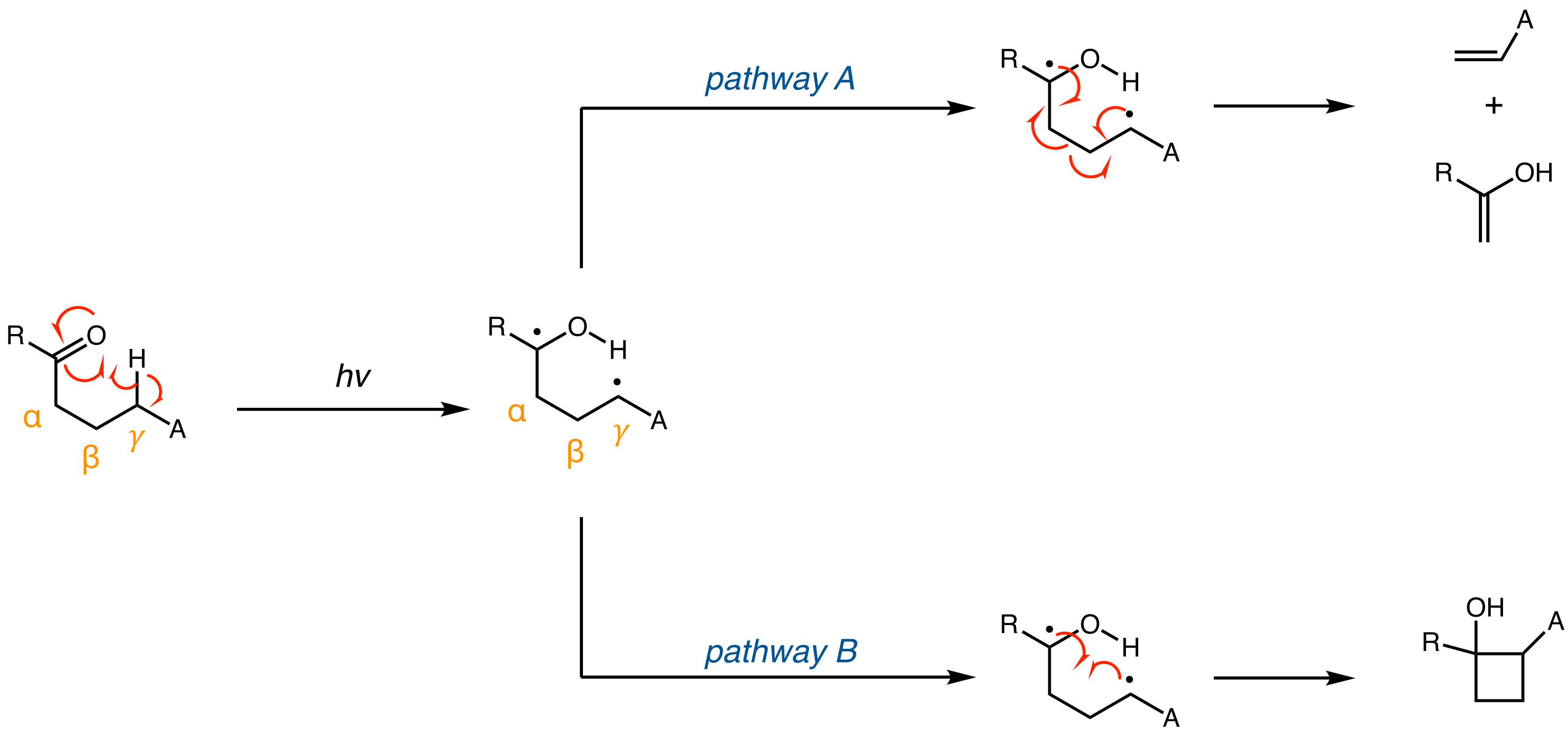
Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613.

Ng, D.; Yang, Z.; Garcia-Garibay, M. A. *Org. Lett.* **2004**, *6*, 645.

Complex Molecule Synthesis Enabled by Photochemistry

Norrish type II reaction

Possible products generated by Norrish type II cleavage

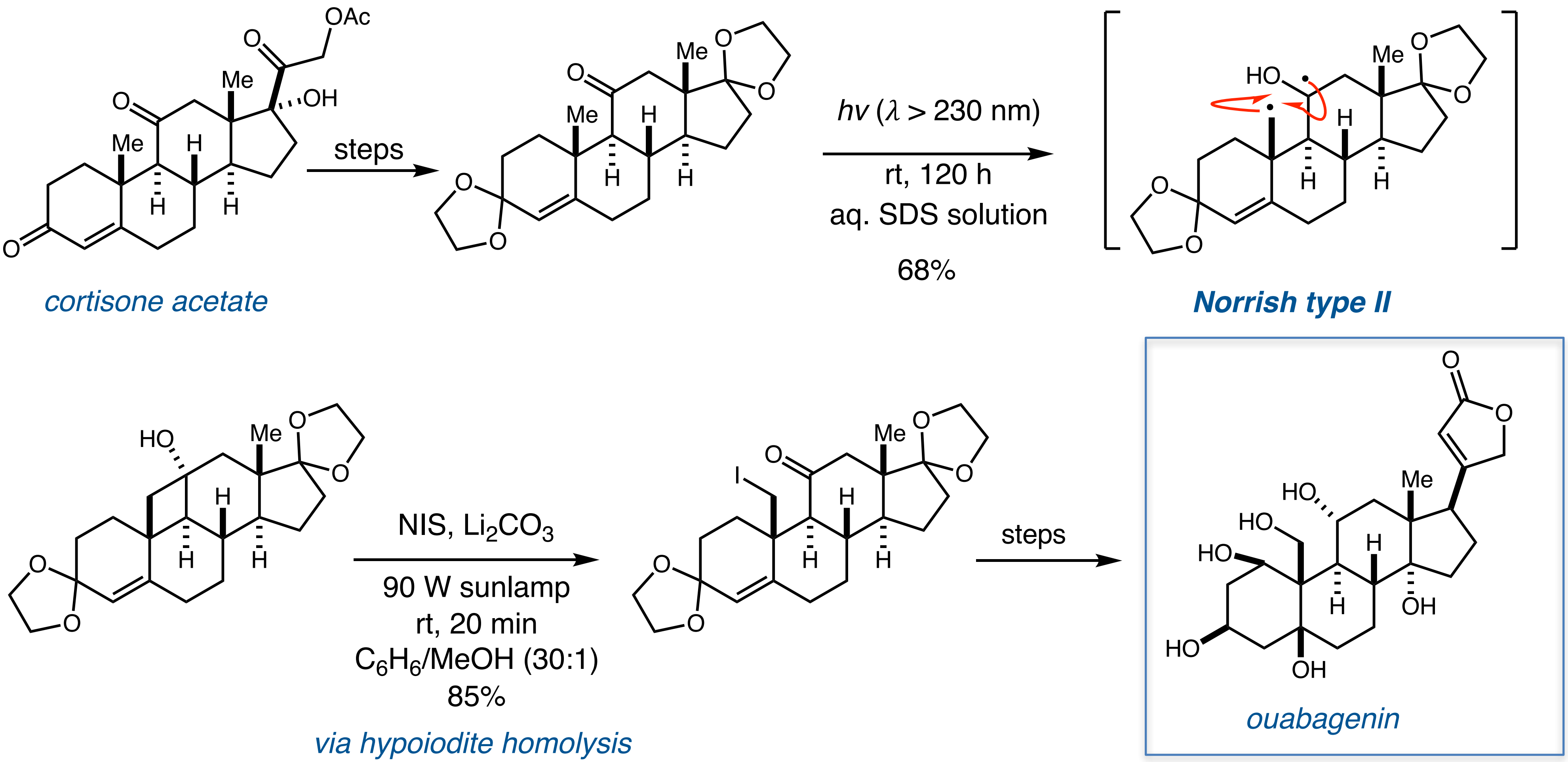


Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

Synthesis of ouabagenin

- Norrish type II cyclization in a semisynthesis of ouabagenin



Renata, H.; Zhou, Q.; Baran, P. S. *Science* **2013**, *339*, 59.

Complex Molecule Synthesis Enabled by Photochemistry

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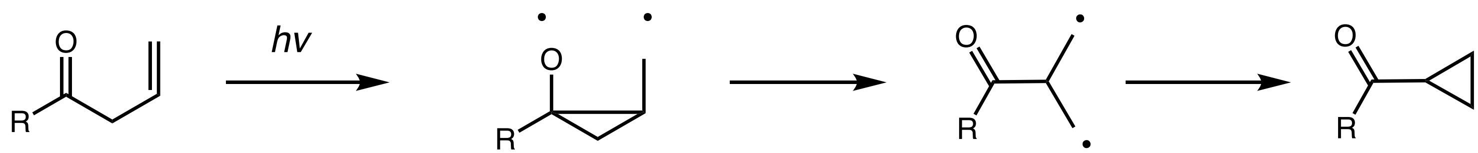
Complex Molecule Synthesis Enabled by Photochemistry

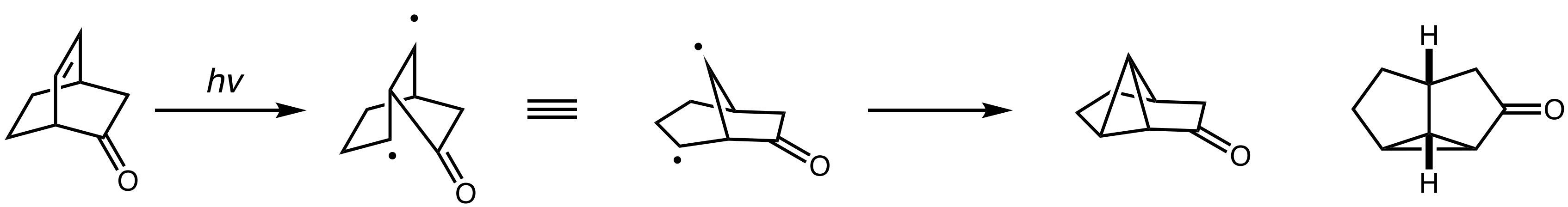
Oxa-di-π-methane rearrangement

■ General reacativity of the oxa-di-π-methane rearrangement

acyclic substrates



cyclic substrates

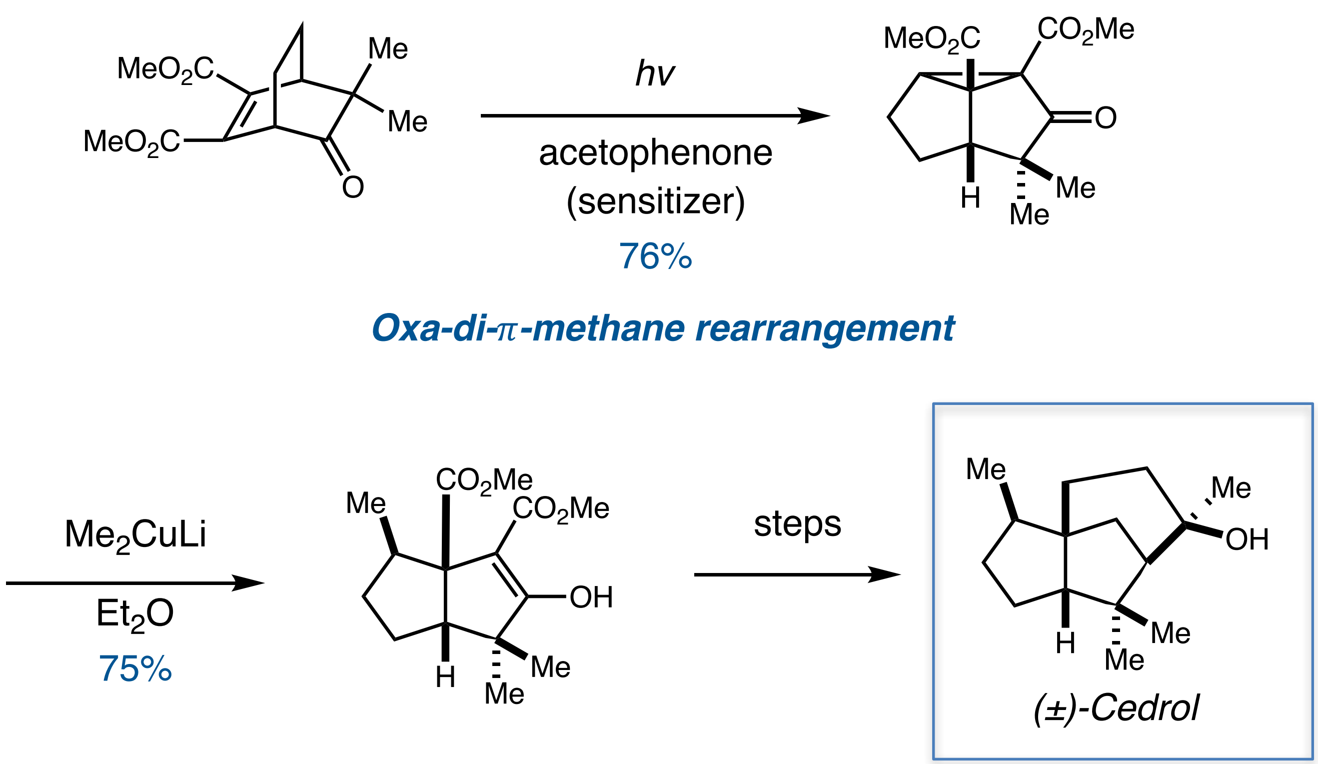


Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

Oxa-di-π-methane rearrangement

■ Use of the *Oxa-di-π-methane rearrangement in the formal total synthesis of (±)-Cedrol*

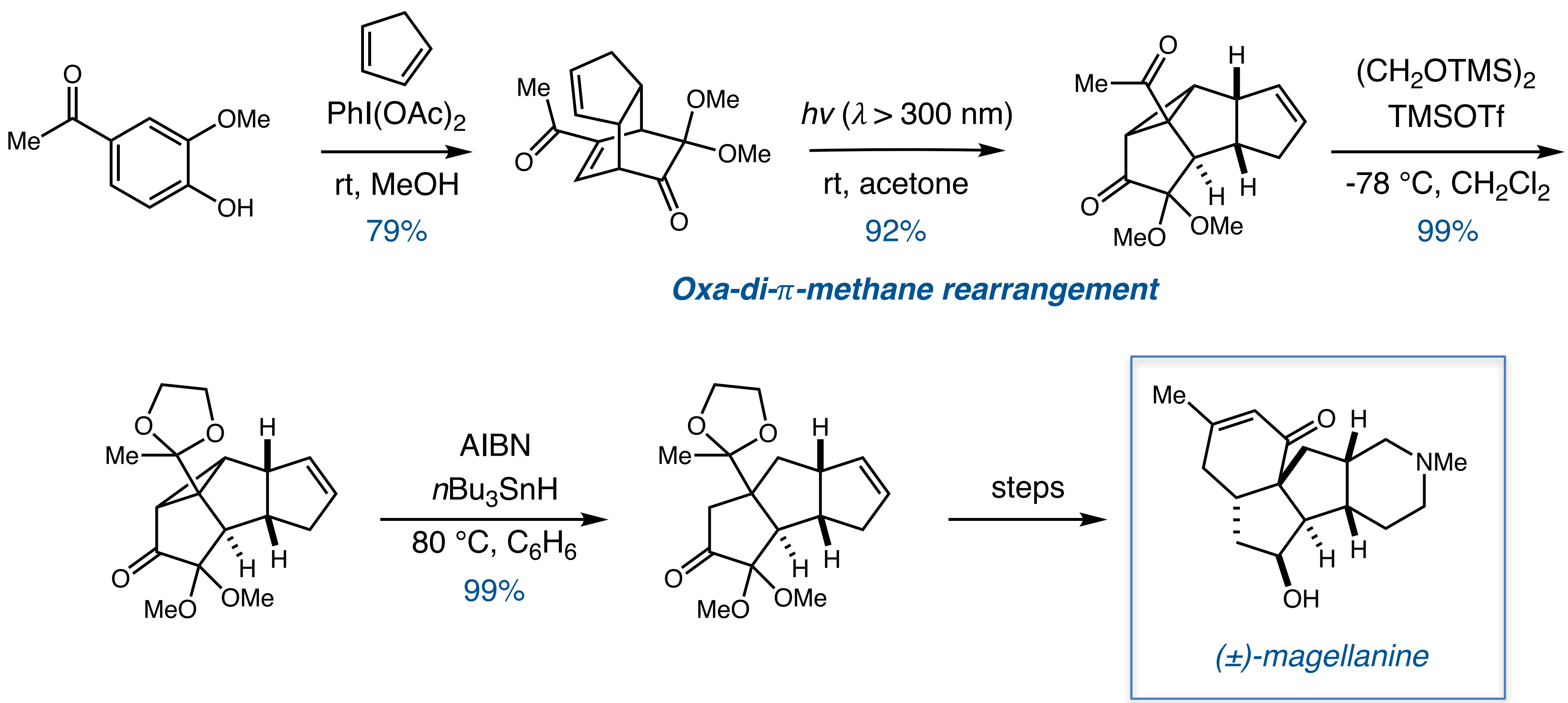


Stork, G.; Clarke, F. H., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 1072.
Zimmerman, H. E.; Armesto, D. *Chem. Rev.* **1996**, *96*, 3065.

Complex Molecule Synthesis Enabled by Photochemistry

Oxa-di-π-methane rearrangement

- Use of the *Oxa-di-π-methane rearrangement in the total synthesis of (±)-magellanine*

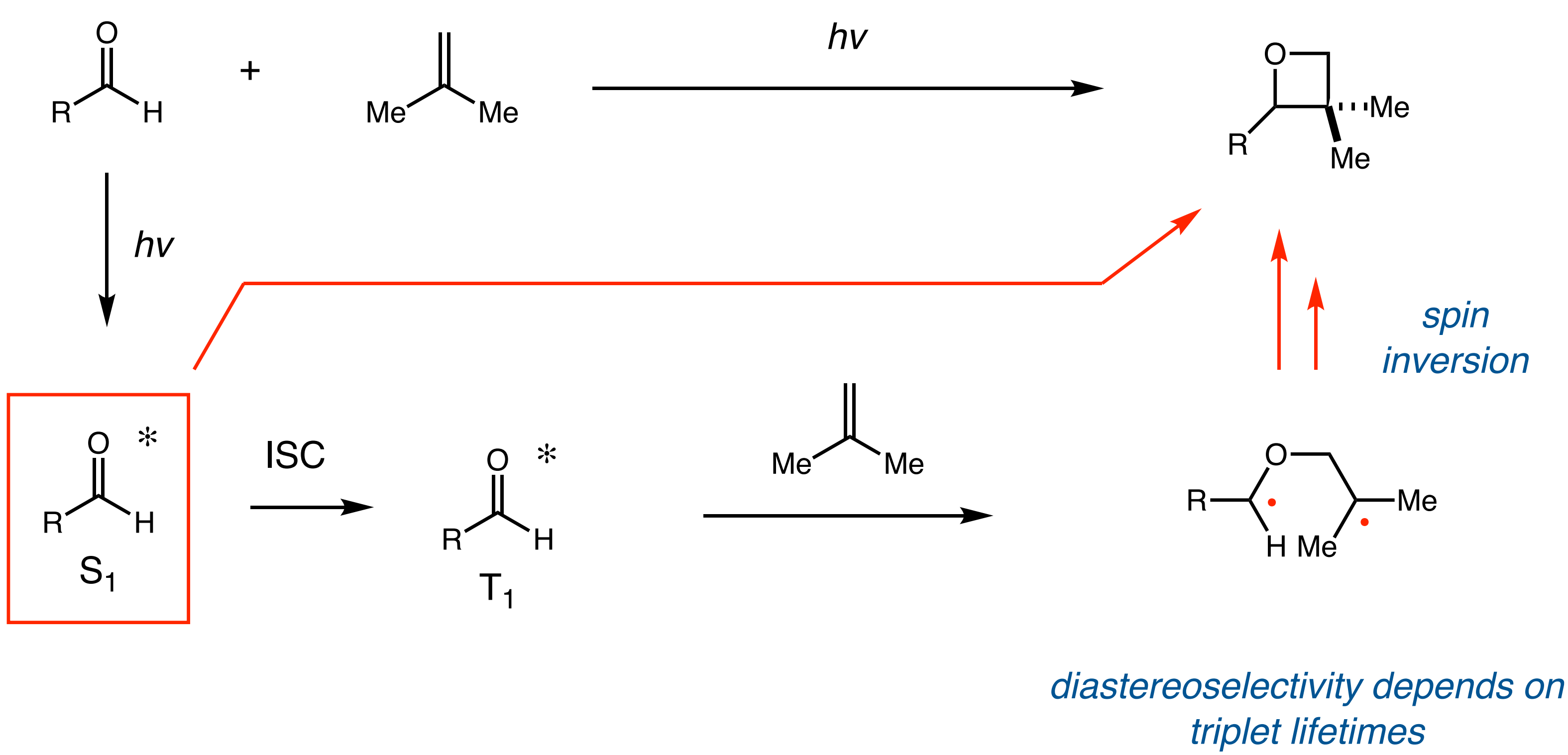


Yen, C.-F.; Liao, C.-C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4090.

Complex Molecule Synthesis Enabled by Photochemistry

Paternò–Büchi reaction

- [2 + 2] photocycloaddition of carbonyl compounds with alkenes– the *Paternò–Büchi reaction*

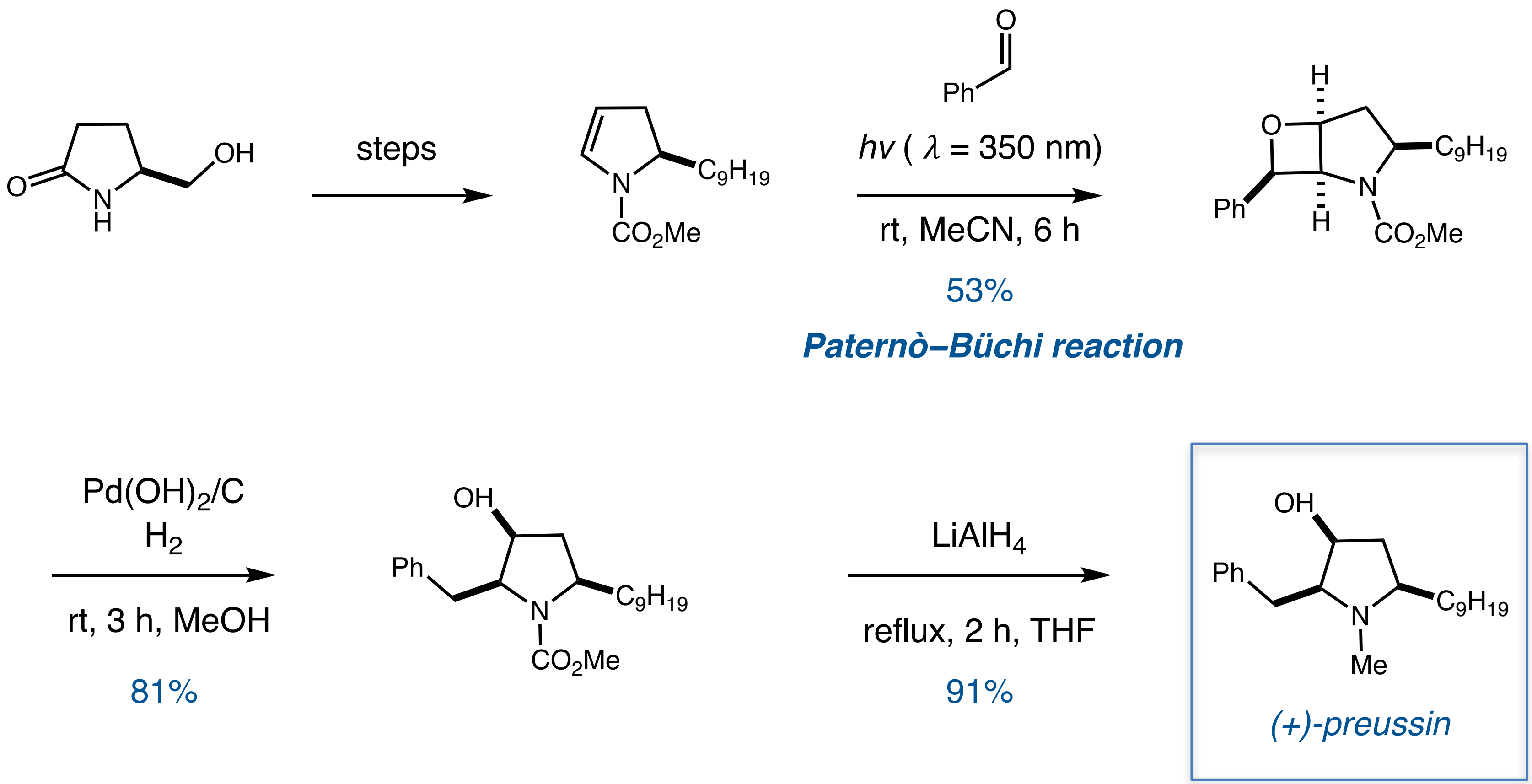


Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

Paternò–Büchi reaction

- Total synthesis of the pyrrolindinol alkaloid (+)-preussin

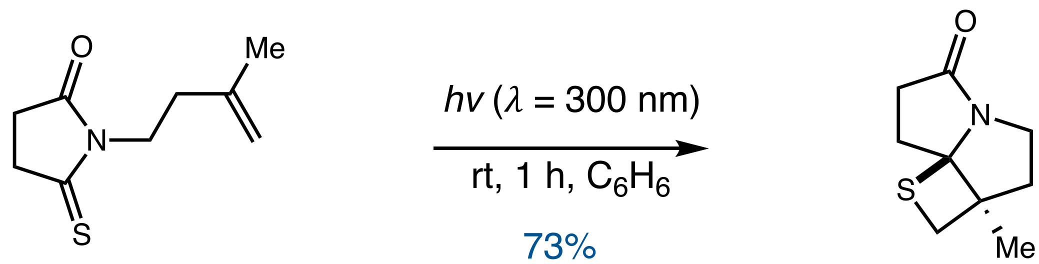


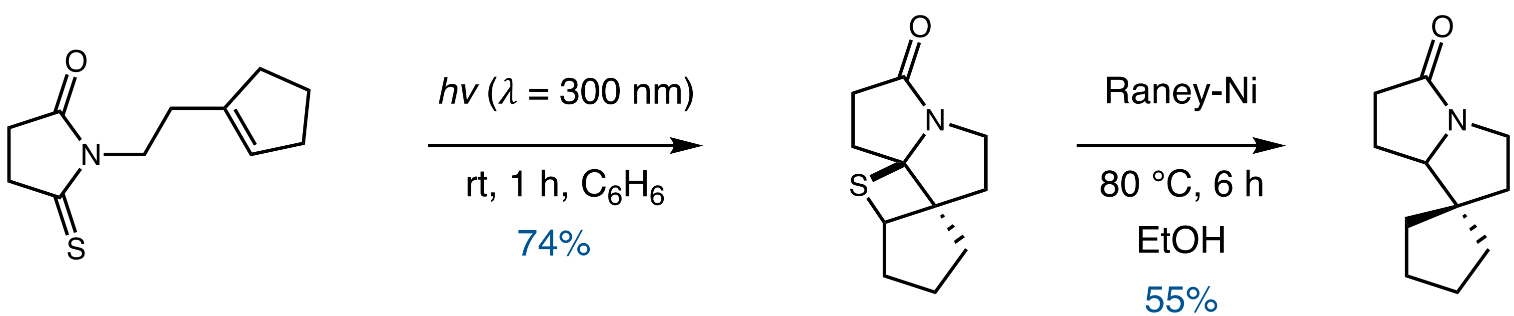
Bach, T.; Brummerhop, H.; Harms, K. *Chem. - Eur. J.* **2000**, *6*, 3838.

Complex Molecule Synthesis Enabled by Photochemistry

Paternò–Büchi reaction

■ Intramolecular *Paternò–Büchi reaction of thiocarbonyl compounds*



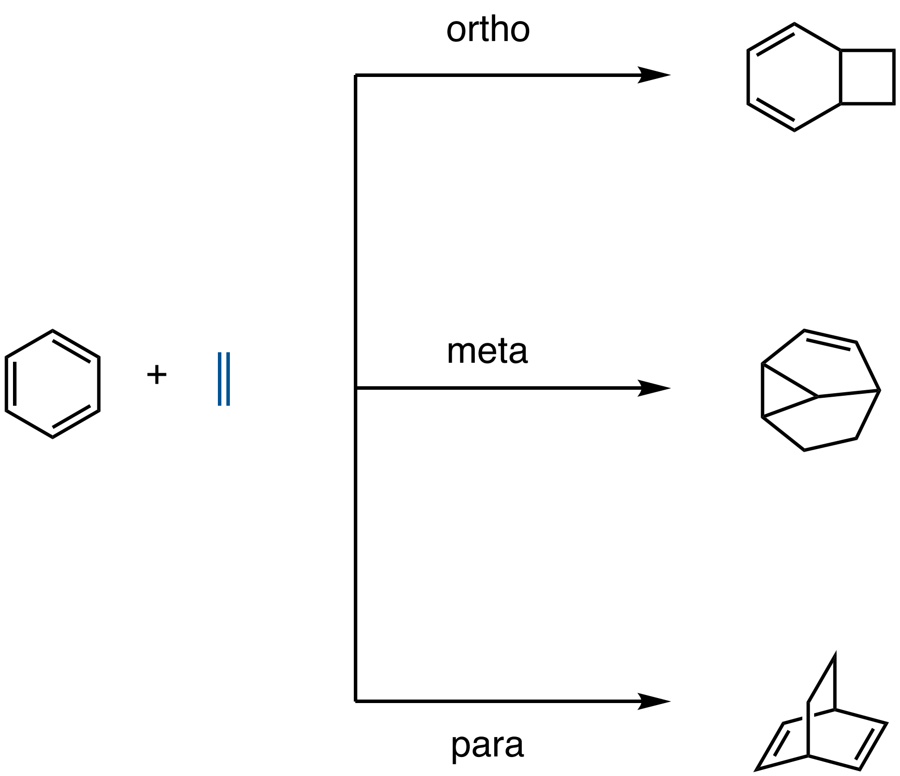


Padwa, A.; Jacquez, M. N.; Schmidt, A. *J. Org. Chem.* **2004**, *69*, 33.

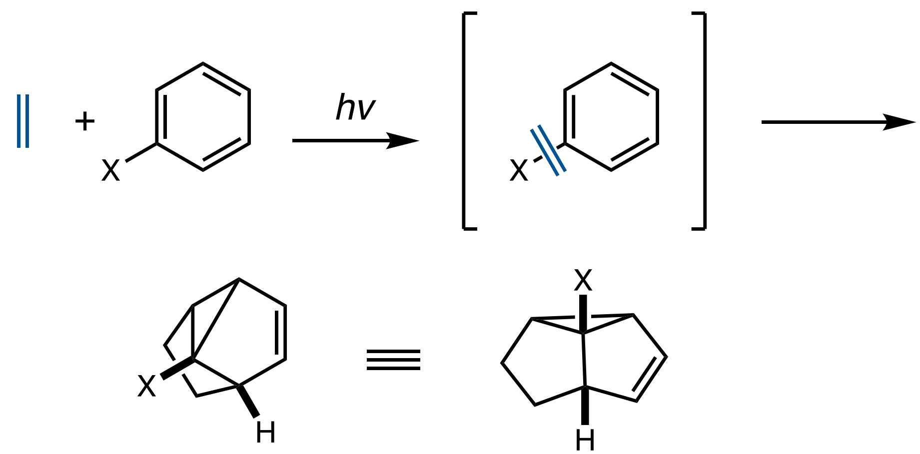
Complex Molecule Synthesis Enabled by Photochemistry

meta-photocycloaddition

■ Three modes of photocycloaddition of alkenes to benzene rings



meta-photocycloaddtion pathway



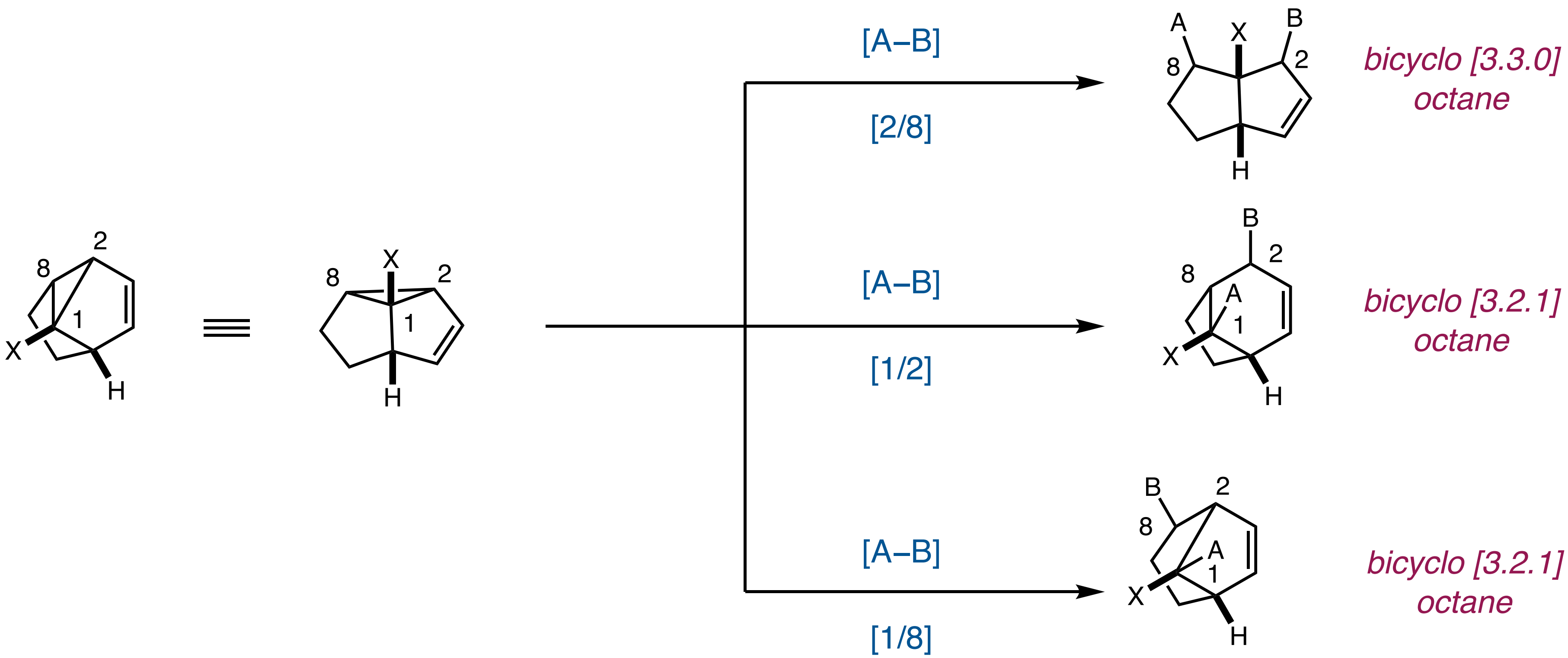
- first reported in 1966 by Wilzbach and Kaplen
- meta-photocycloadditions are most common
- formation of three σ-bonds and up to six stereocenters in one step
- tricyclic product can fragment in several ways

Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

meta-photocycloaddition

■ Fragmentation of the meta-photocycloaddition adduct to form complex architectures



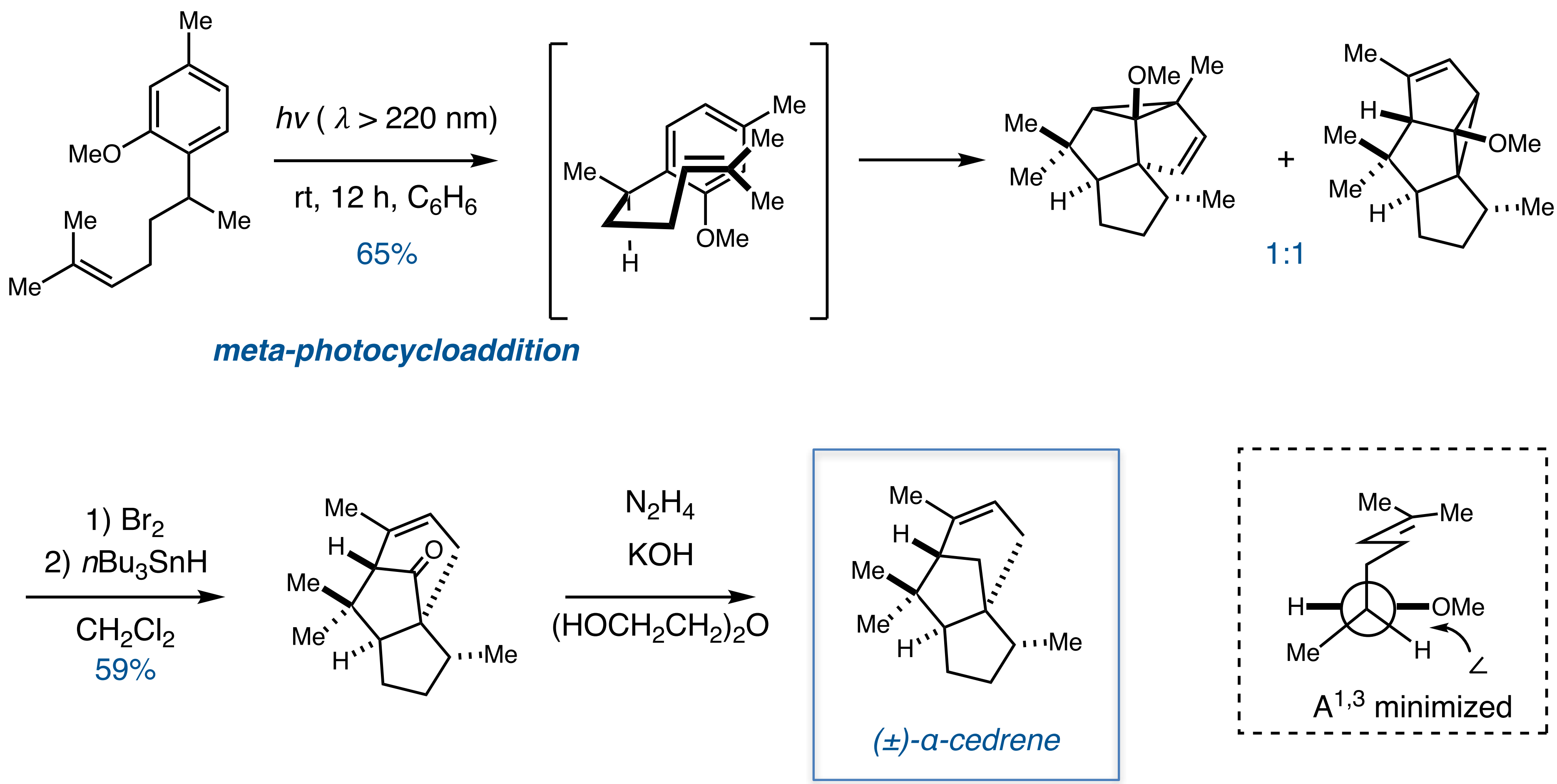
Powerful method for generating molecular complexity in one step!

Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Complex Molecule Synthesis Enabled by Photochemistry

meta-photocycloaddition

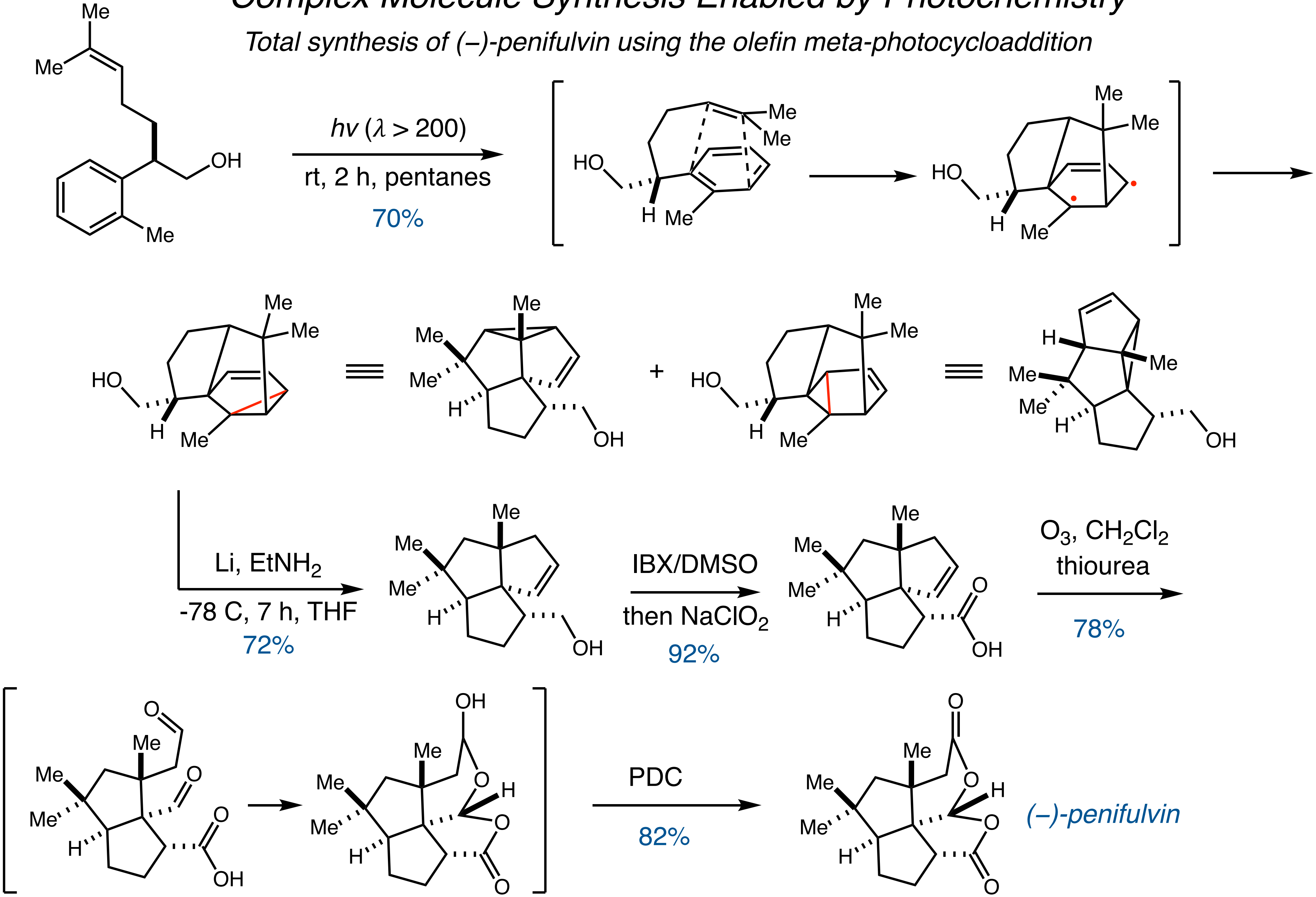
Wender's total synthesis of (±)-α-cedrene



Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688.

Complex Molecule Synthesis Enabled by Photochemistry

Total synthesis of (–)-penifulvin using the olefin meta-photocycloaddition



Gaich, T.; Mulzer, J. *J. Am. Chem. Soc.* **2009**, *131*, 452.

Complex Molecule Synthesis Enabled by Photochemistry

Outline

General outline

1) Why are photochemical reactions interesting?

2) 2+2 cycloaddtions and cyclobutane ring-opening reactions

3) Norrish type I and II applications to complex architectures

4) Oxa-di-π-methane rearrangement

5) Paternò–Büchi reaction

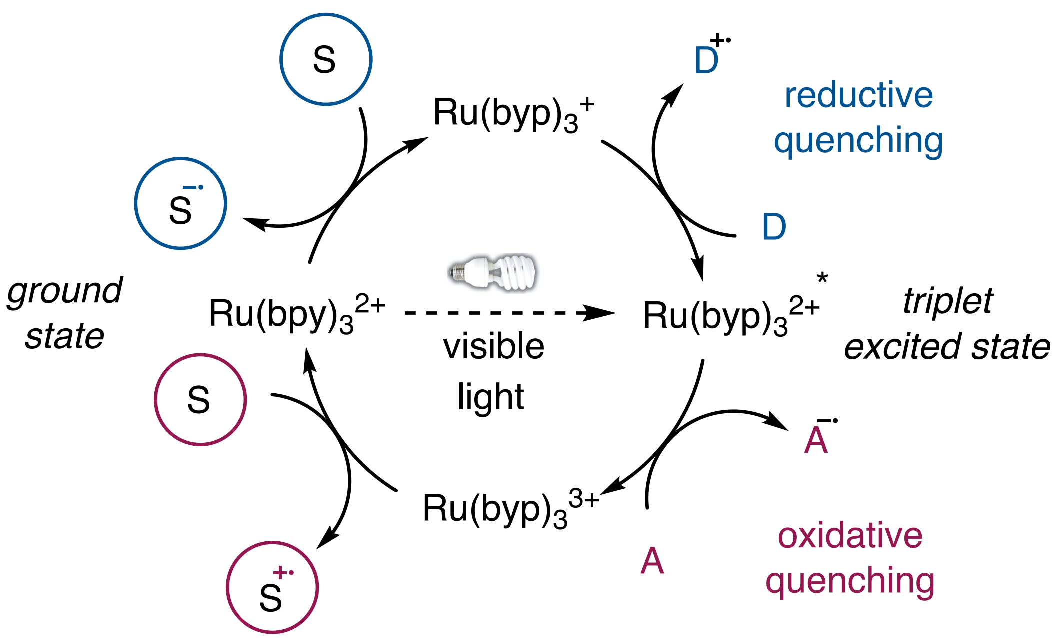
6) meta-photocycloaddition reaction in total synthesis

7) Photoredox applications to complex molecule synthesis

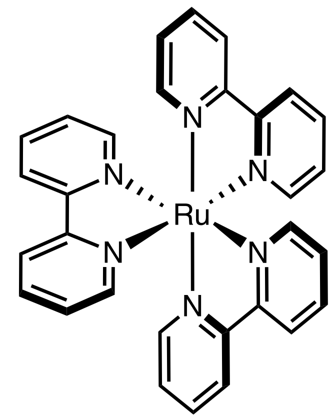
Complex Molecule Synthesis Enabled by Photochemistry

Photoredox catalysis

- Use the use of visible light to enable single-electron transfer between photoexcitable catalysts and organic or organometallic molecules



A = acepter, D = doner, S = substate



$Ru(bpy)_3^{2+}$

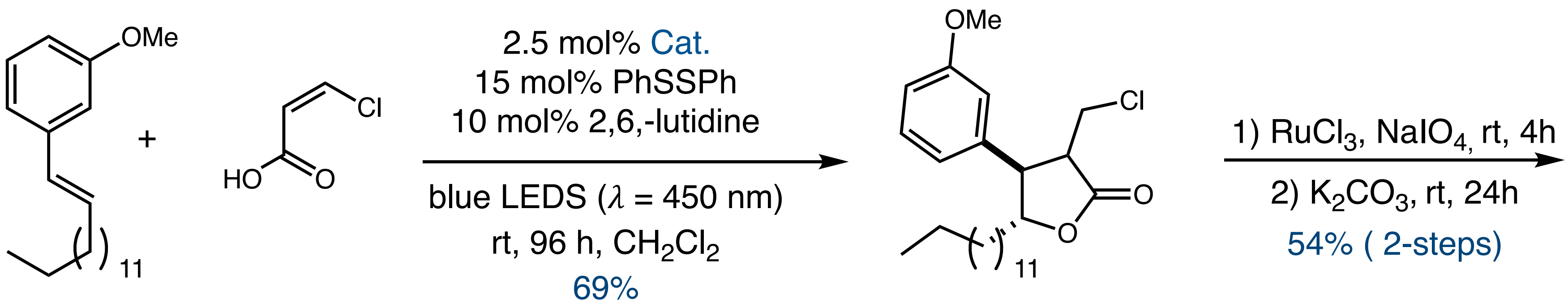
Strong visible light absorption
High quantum yield ($\Phi \approx 1$)
Long-lived excited state (τ = 900 ns)
Easy tuning of physical properties

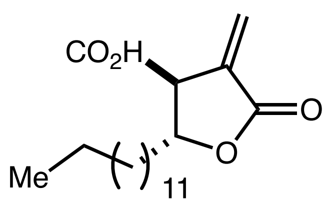
Prier, C. K.; Rankic, D. A.; MacMillan, D. W. C. *Chem. Rev.* **2013**, *113*, 5322.

Complex Molecule Synthesis Enabled by Photochemistry

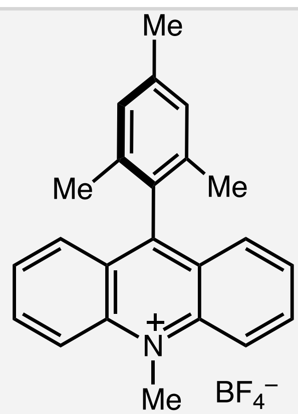
Photoredox catalysis

- Polar radical crossover cycloaddition (PRCC) for the synthesis of protolichestrenic acid





(±)-protolichesterinic acid



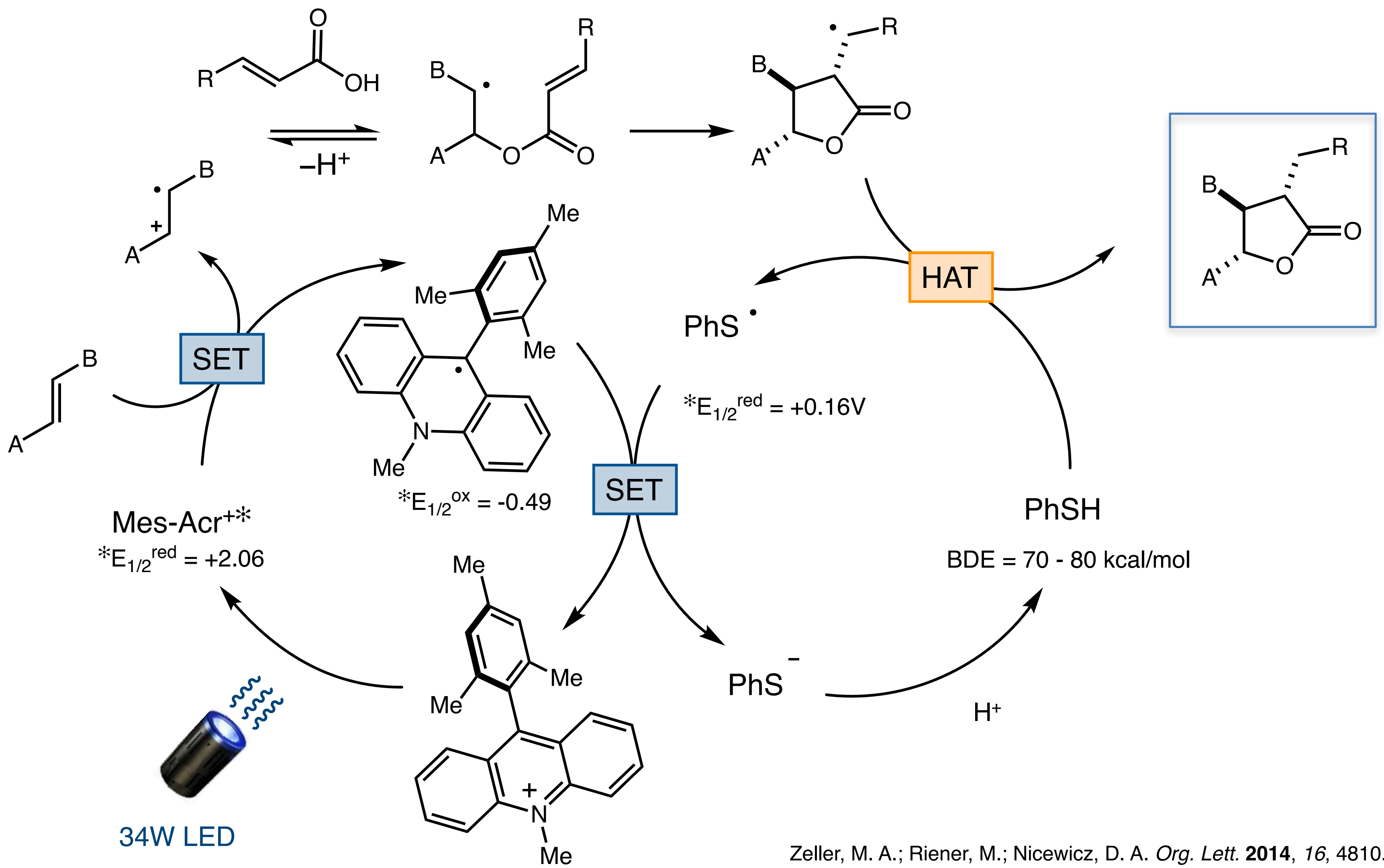
Mes-Acr$^+$

Zeller, M. A.; Riener, M.; Nicewicz, D. A. *Org. Lett.* **2014**, *16*, 4810.

Complex Molecule Synthesis Enabled by Photochemistry

Photoredox catalysis

■ Proposed mechanism for the polar radical crossover cycloaddition

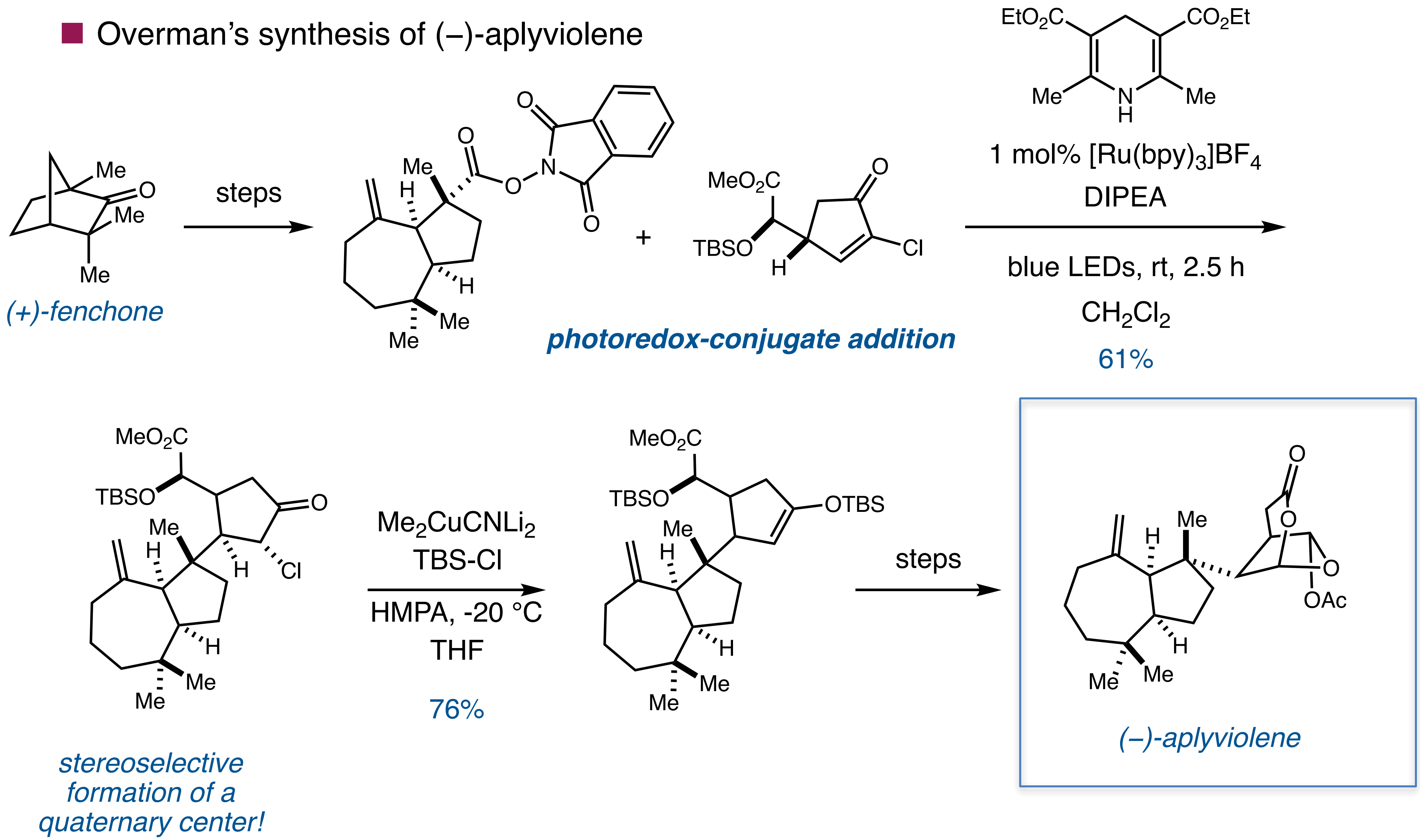


Zeller, M. A.; Riener, M.; Nicewicz, D. A. *Org. Lett.* **2014**, *16*, 4810.

Complex Molecule Synthesis Enabled by Photochemistry

Photoredox catalysis

- Overman's synthesis of (–)-aplyviolene

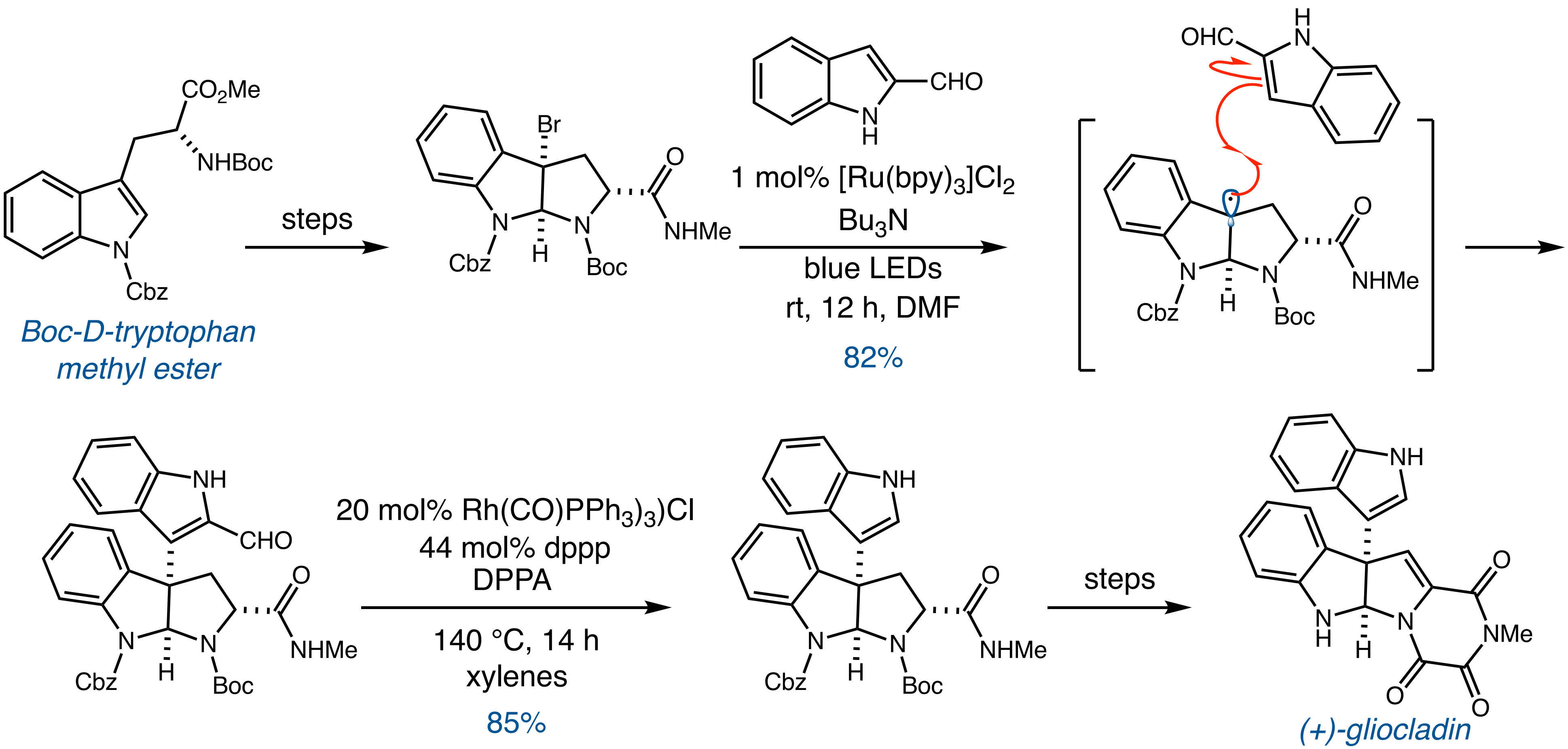


Schnermann, M. J.; Overman, L. E. *Angew. Chem., Int. Ed.* **2012**, *51*, 9576.

Complex Molecule Synthesis Enabled by Photochemistry

Photoredox catalysis

- Photoredox-enabled synthesis of the pyrroloindoline (+)-gliocladin



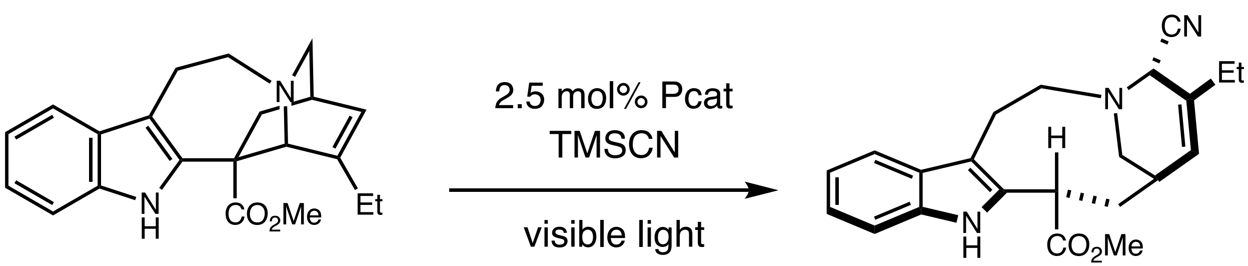
DPPA = diphenylphosphoryl azide
dppp = 1,3-bis (diphenylphosphino) propane

Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 9655.

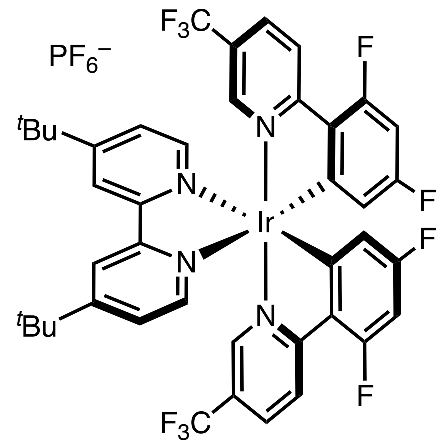
Complex Molecule Synthesis Enabled by Photochemistry

Photoredox catalysis

■ Photoredox-enabled fragmentation of (+)-catharanthine



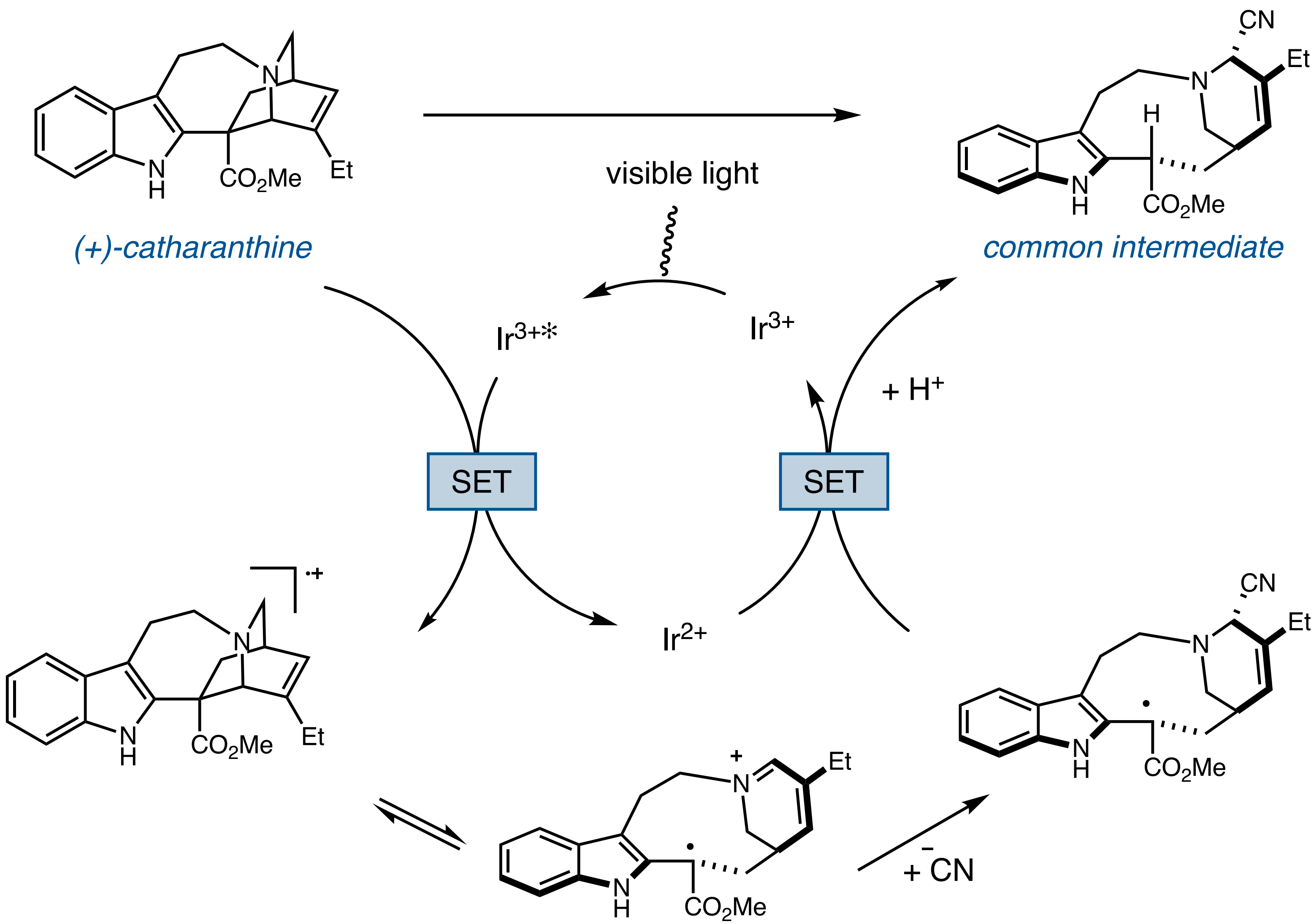
(+)-catharanthine *common intermediate*



Beatty, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 10270.

Complex Molecule Synthesis Enabled by Photochemistry

Catalytic cycle for fragmentation

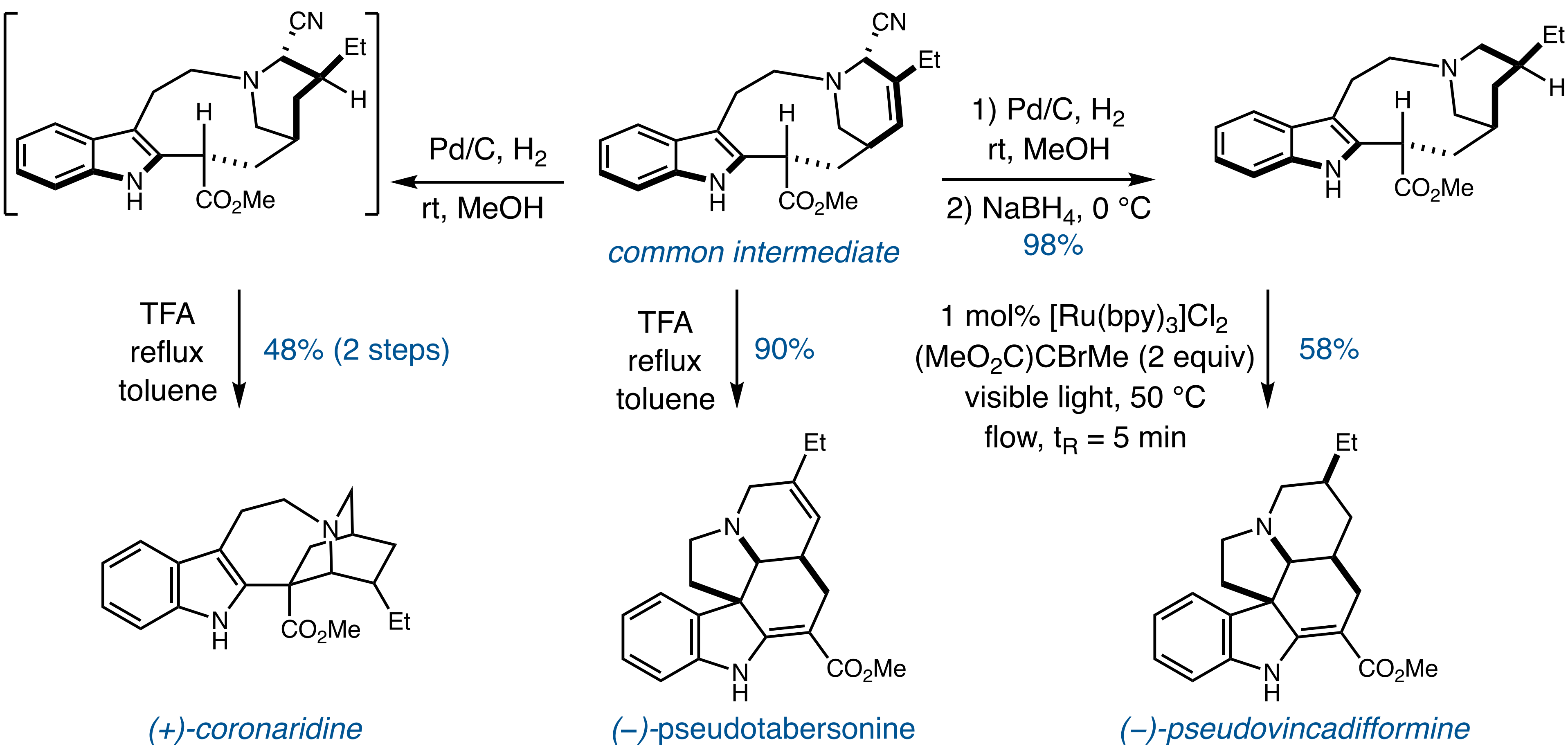


Beatty, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 10270.

Complex Molecule Synthesis Enabled by Photochemistry

Photoredox catalysis

- Photoredox-enabled synthesis of (–)-pseudotabersonine, (–)-pseudovincadifformine, and (+)-coronaridine via a common intermediate



Beatty, J. W.; Stephenson, C. R. J. *J. Am. Chem. Soc.* **2014**, *136*, 10270.

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7) Photoredox applications to complex molecule synthesis

8) Summary

Complex Molecule Synthesis Enabled by Photochemistry

Summary

Why are photochemical reactions interesting?

Advantages:

Photochemical reactions enable transformations not possible by thermal conditions

Highly stained adducts can leveraged to form medium rings with rich functionality

Photochemical reactions are “green” as they only consume photons

Disadvantages:

Requirement for high energy UV-light

In general, hard to control absolute stereochemistry

Good reviews if you want to learn more:

Karkas, M. D.; Porco, J. A.; Stephenson, C. R. J. *Chem. Rev.* **2016**, *116*, 9683.

Nicholls, T. P.; Leonori, D.; Bissember, A. C. *Nat. Prod. Rep.* **2016**, *33*, 1248.

Douglas, J. J.; Sevrin, M. J.; Stephenson, C. R. J. *Org. Process Res. Dev.* **2016**, *20*, 1134.

Bach, T.; Hehn, J. P. *Angew. Chem., Int. Ed.* **2011**, *50*, 1000.