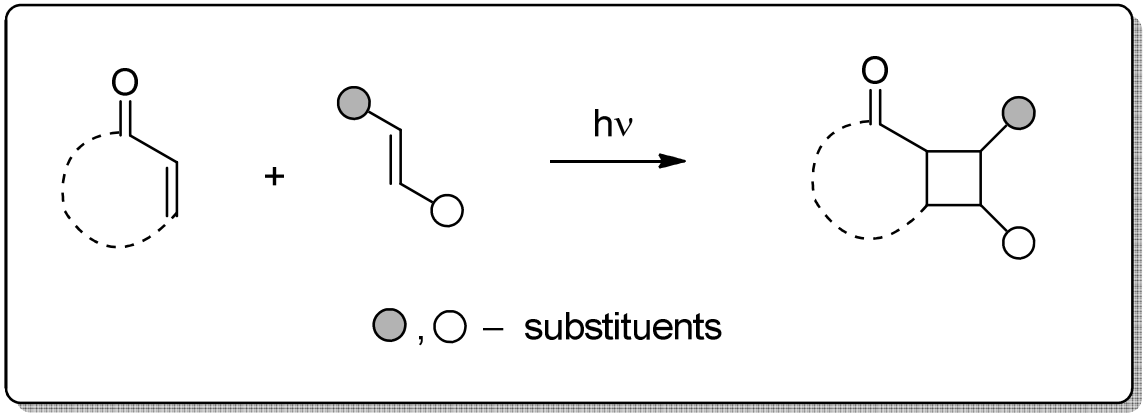
Chirality and Light:
Enantioselective Catalysis of Photochemical Reactions

Ischia Advanced School of Chemistry Ischia, September 27, 2016

[2+2] Photocycloaddition



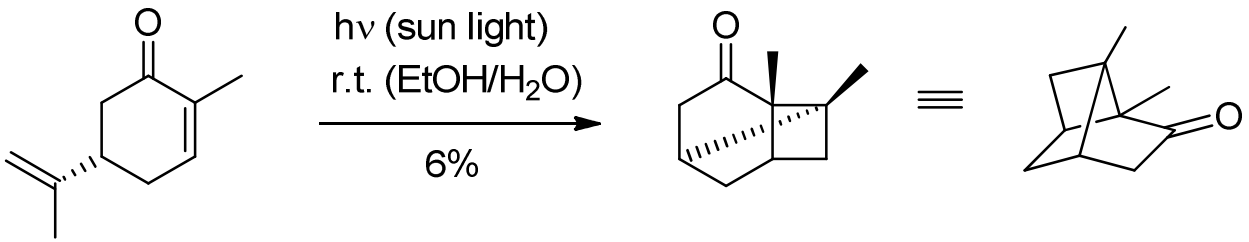
– Creation of up to four stereogenic centers in a single reaction

– Performed either intra- or intermolecularly

– Most useful with one reaction component being an α,β-unsaturated carbonyl compound

S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, DOI: 10.1021/acs.chemrev.5b00723

[2+2] Photocycloaddition: Initial Discovery

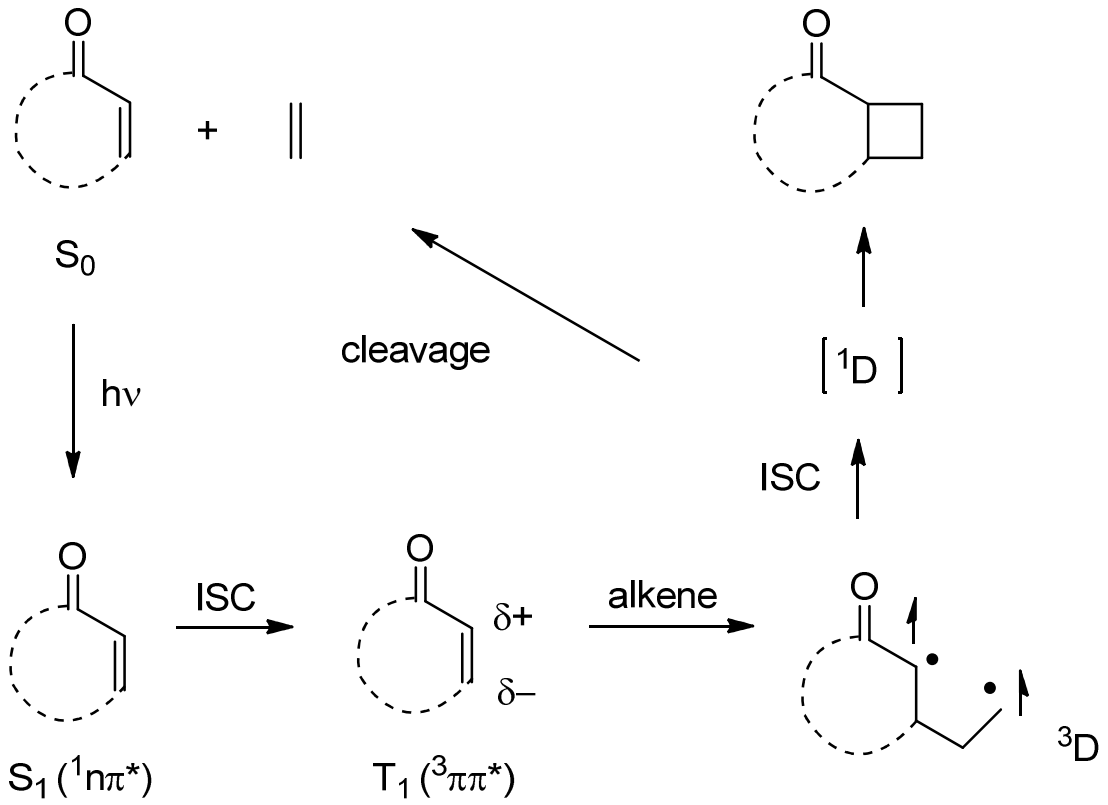


G. Ciamician, P. Silber, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 1928-1935

Seminal Publications in the 1950s and 1960s:

G. Büchi, I. M. Goldman,	*J. Am. Chem. Soc.* **1957**, *79*, 4741-4748
P. De Mayo, H. Takeshita, A. B. M. A. Sattar,	*Proc. Chem. Soc.* **1962**, 119
G. O. Schenck, W. Hartmann, S.-P. Mannsfeld, W. Metzner, C. H. Krauch,	*Chem. Ber.* **1962**, *95*, 1642-1647
P. E. Eaton,	*J. Am. Chem. Soc.* **1962**, *84*, 2454-2455
E. J. Corey, R. B. Mitra, H. Uda,	*J. Am. Chem. Soc.* **1963**, *85*, 362-363

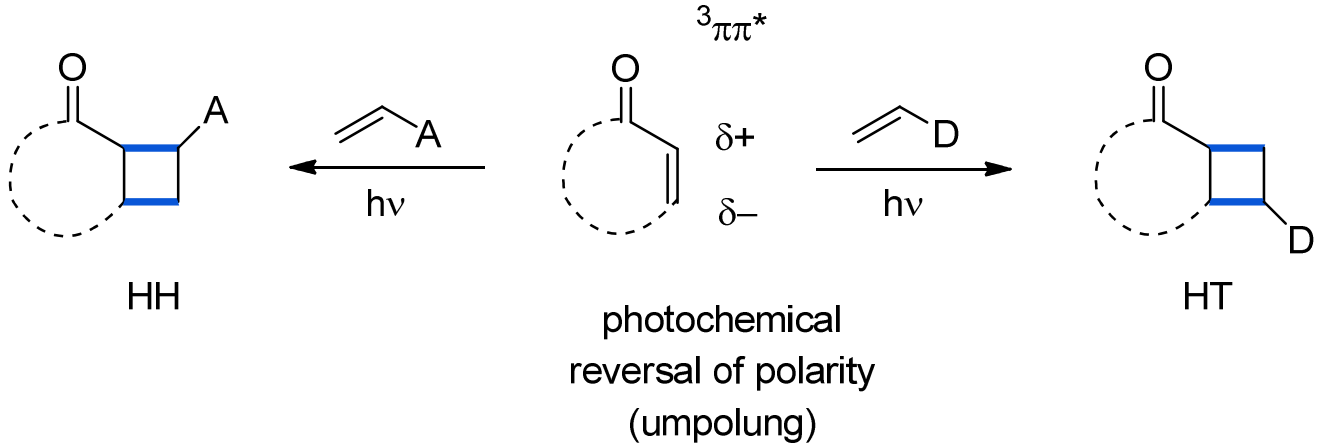
[2+2] Photocycloaddition: Mechanism



S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, DOI: 10.1021/acs.chemrev.5b00723

[2+2] Photocycloaddition: Regioselectivity I

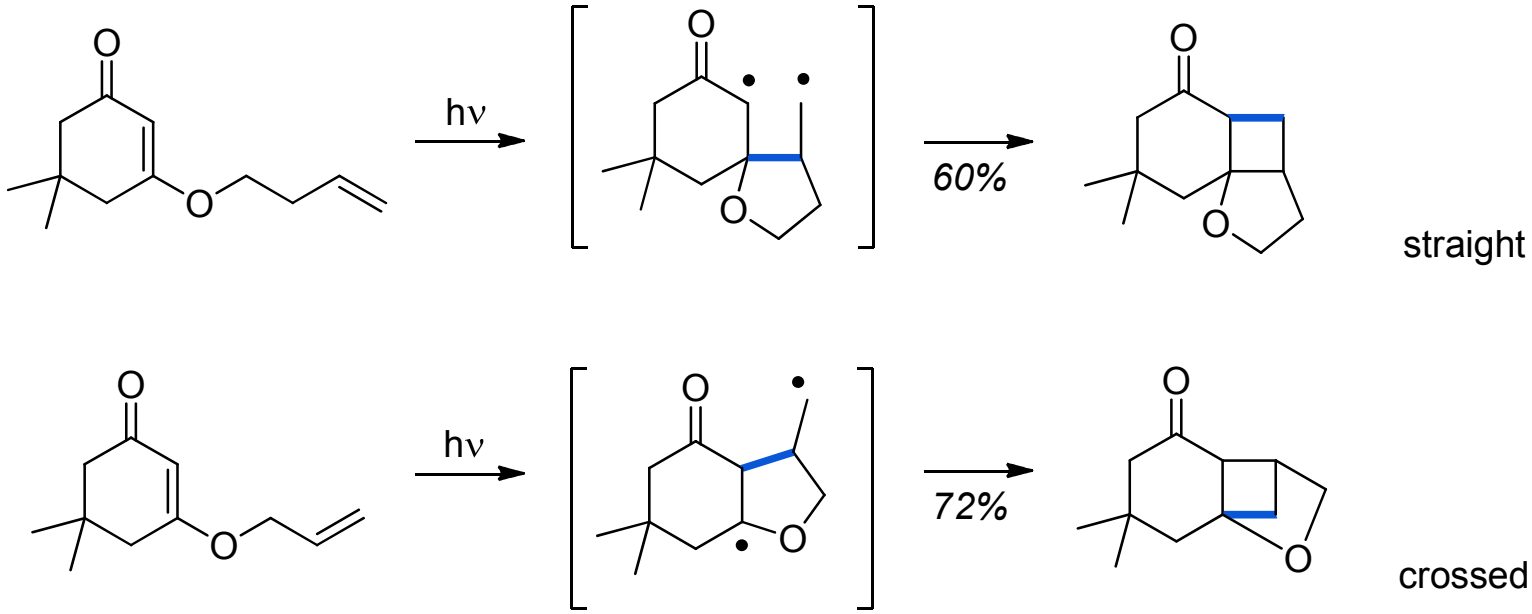
Rule of thumb: With acceptor (A) substituted olefins, the major product is the so called head-to-head (HH) product. With donor (D) substituted olefins, the head-to-tail (HT) product prevails. 1,4-Diradical stability!



S. Poplata, A. Tröster, Y.-Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, DOI: 10.1021/acs.chemrev.5b00723

[2+2] Photocycloaddition: Regioselectivity II

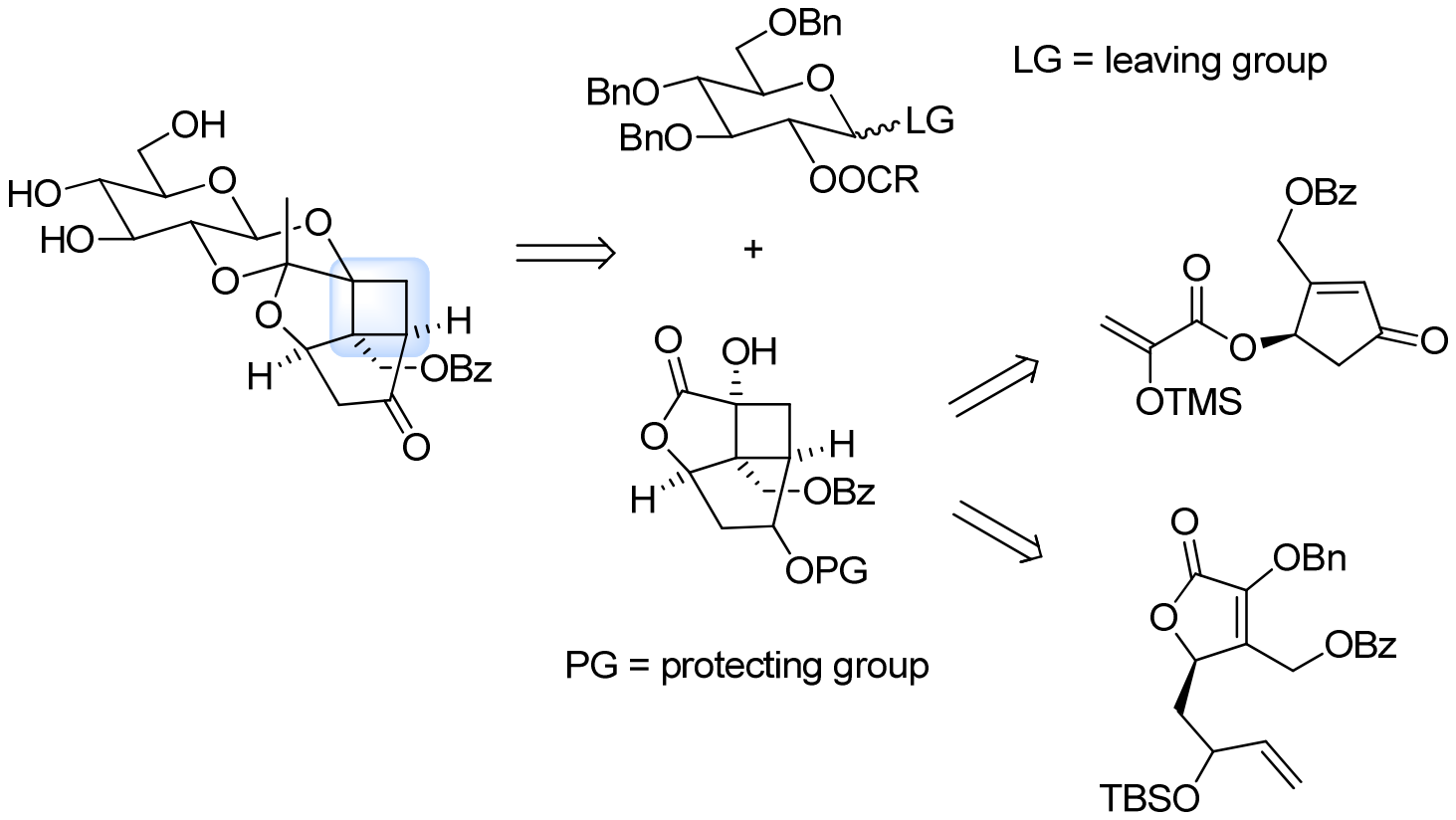
Rule of thumb: If possible, a five-membered ring is formed in the first reaction step (C-C bond formation).



R. Srinivasan, K. H. Carlough, *J. Am. Chem. Soc.* **1967**, *89*, 4932-4936

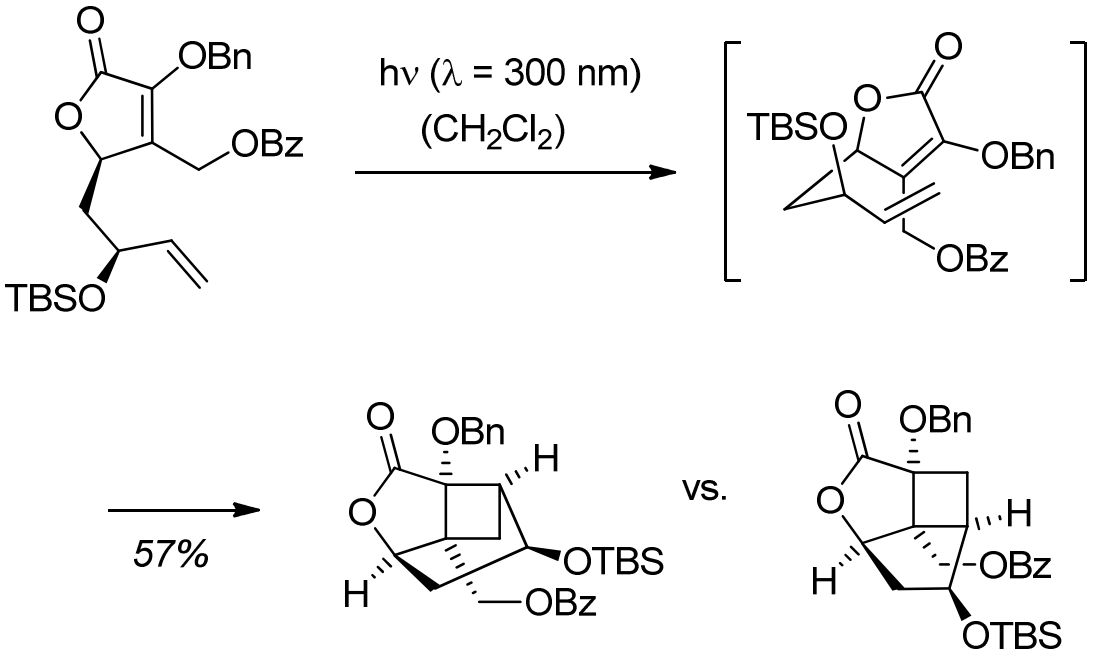
R. S. H. Liu, G. S. Hammond, *J. Am. Chem. Soc.* **1967**, *89*, 4936-4944

Lactiflorin – Retrosynthetic Concept



P. Lu, E. Herdtweck, T. Bach, *Chem. Asian J.* **2012**, *7*, 1947-1958

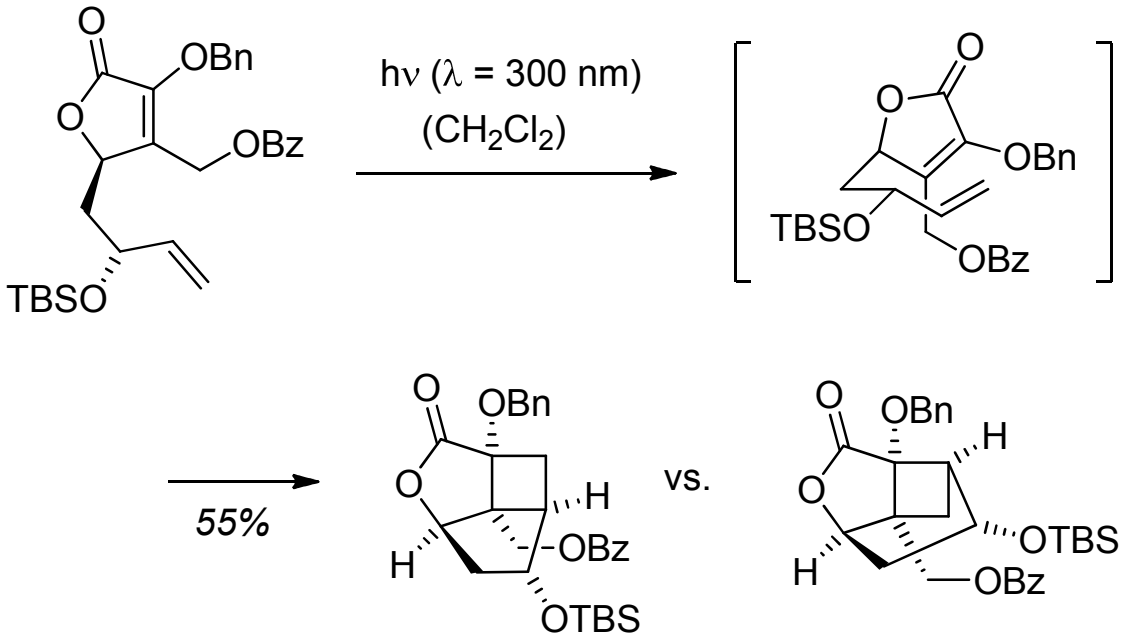
Intramolecular [2+2]-Photocycloaddition I



r.r. = 53/47

P. Lu, E. Herdtweck, T. Bach, *Chem. Asian J.* **2012**, *7*, 1947-1958

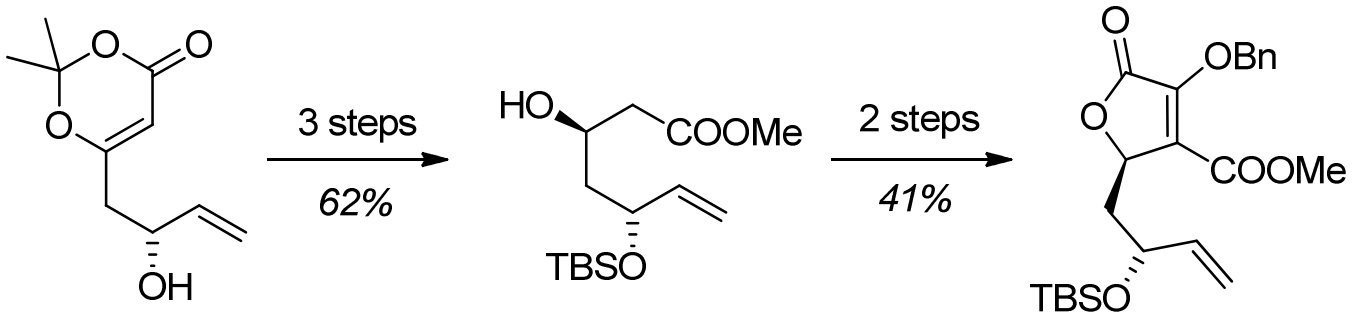
Intramolecular [2+2]-Photocycloaddition II



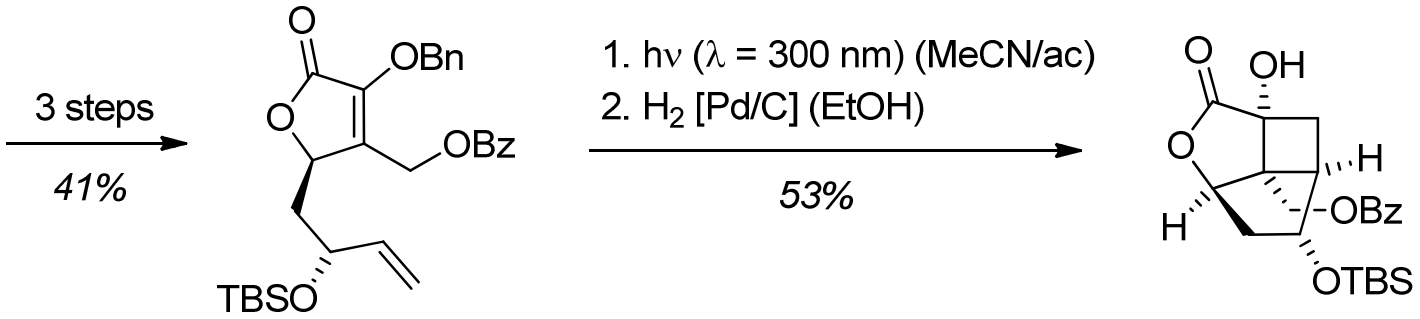
r.r. = 73/27

P. Lu, T. Bach, *Angew. Chem. Int. Ed.* **2012**, *51*, 1261-1264

Synthesis of the Photocycloaddition Precursor

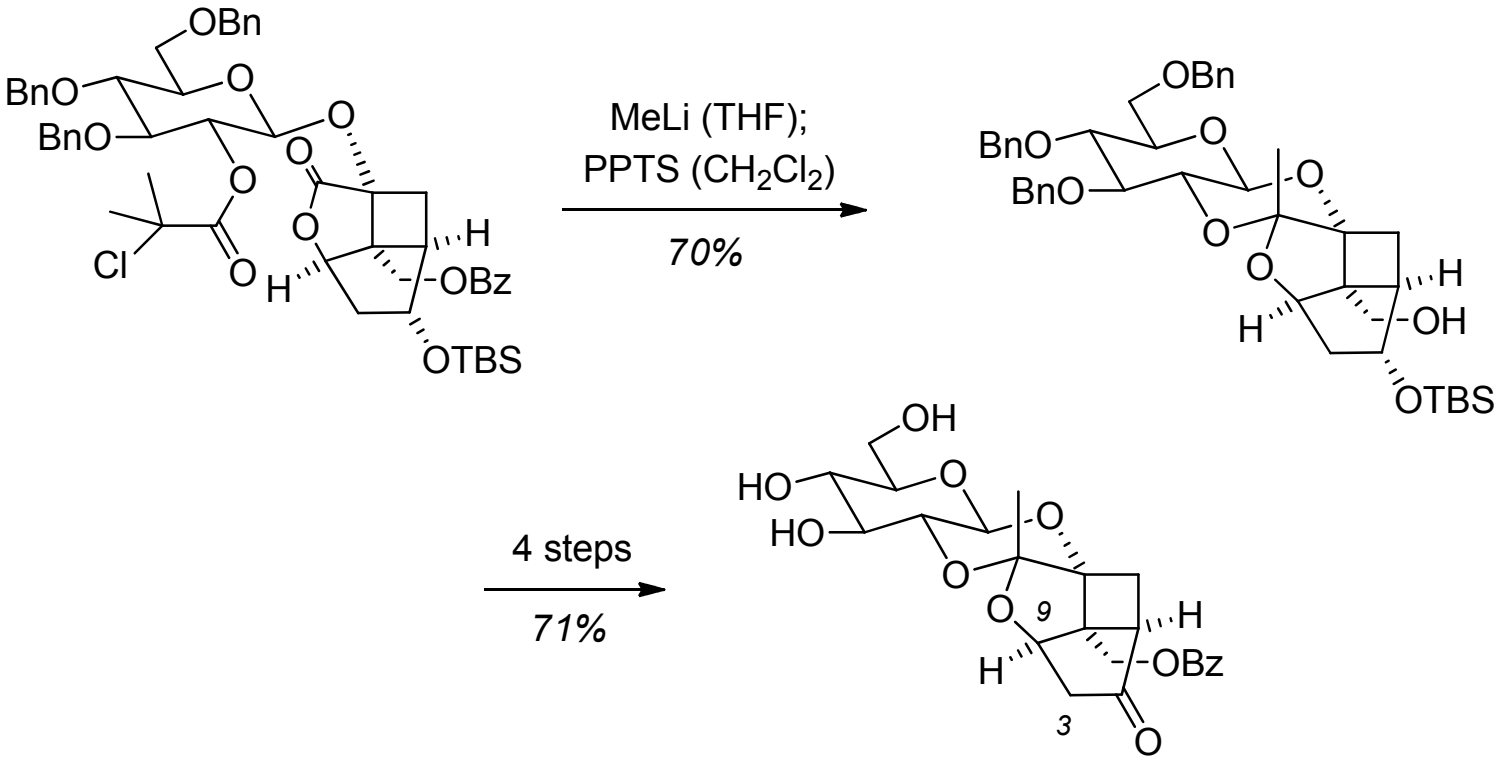


see: R. A. Singer, E. M. Carreira,
J. Am. Chem. Soc. **1995**, *117*, 12360-12361



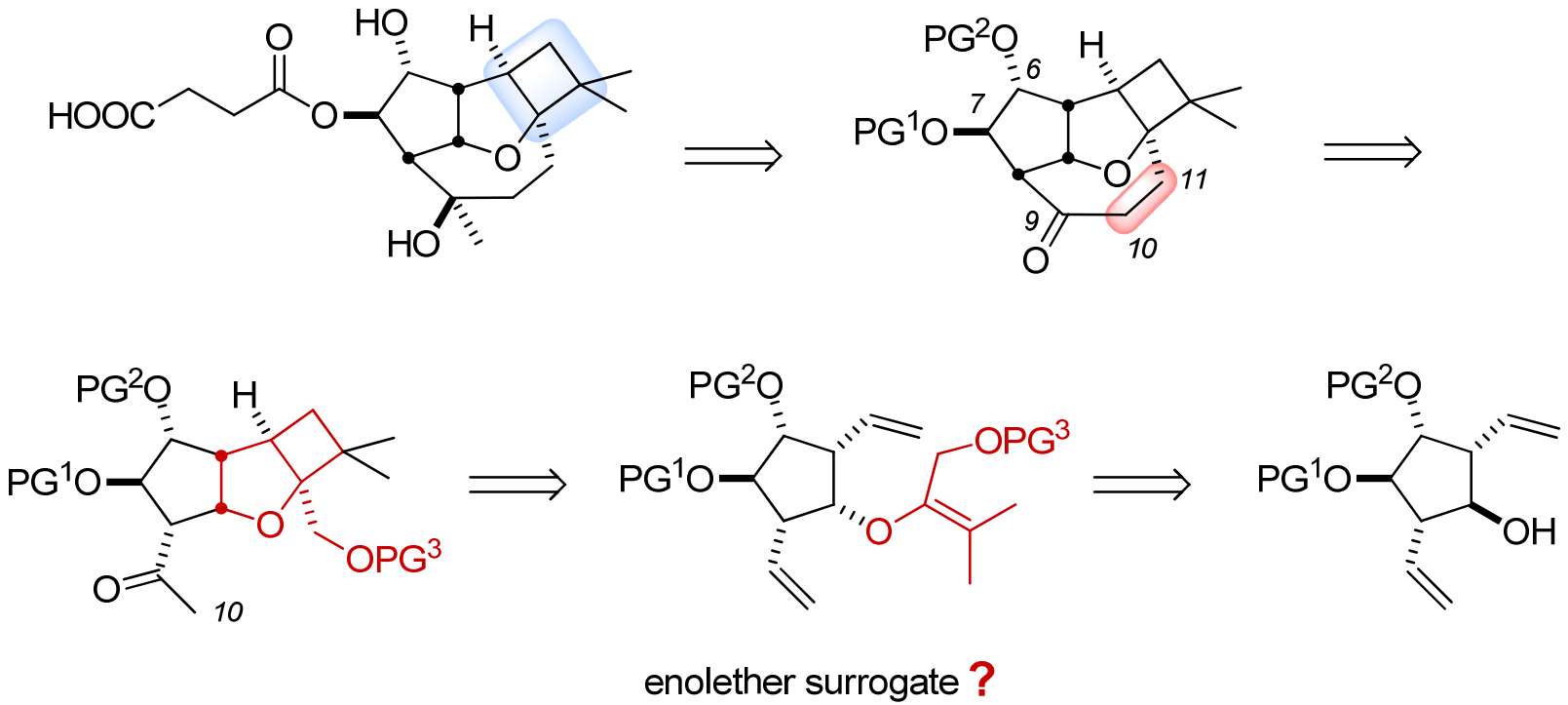
P. Lu, T. Bach, *Angew. Chem. Int. Ed.* **2012**, *51*, 1261-1264

Completion of the Synthesis



P. Lu, T. Bach, *Angew. Chem. Int. Ed.* **2012**, *51*, 1261-1264

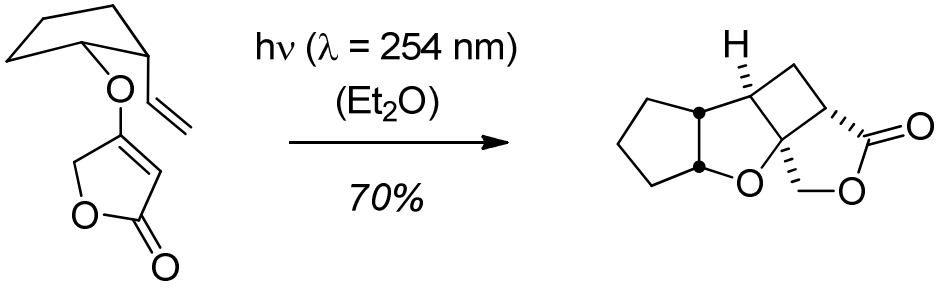
Punctaporonin C – Retrosynthetic Concept



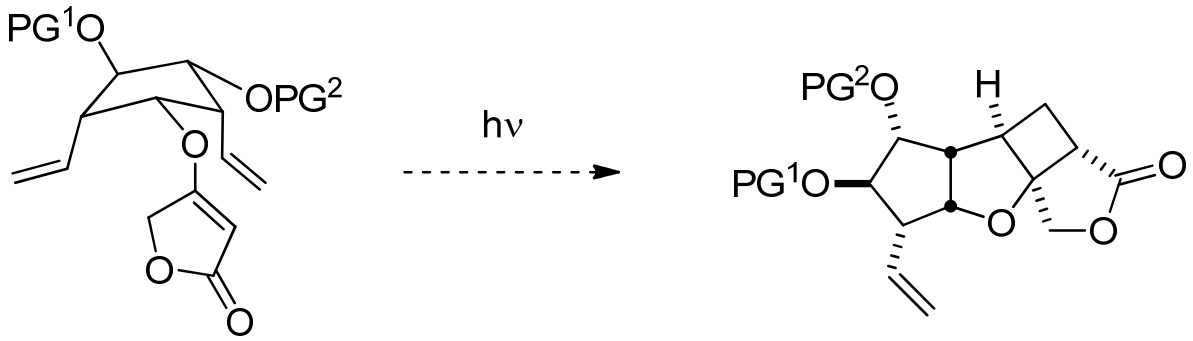
enolether surrogate ?

M. Fleck, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47*, 6189-6191

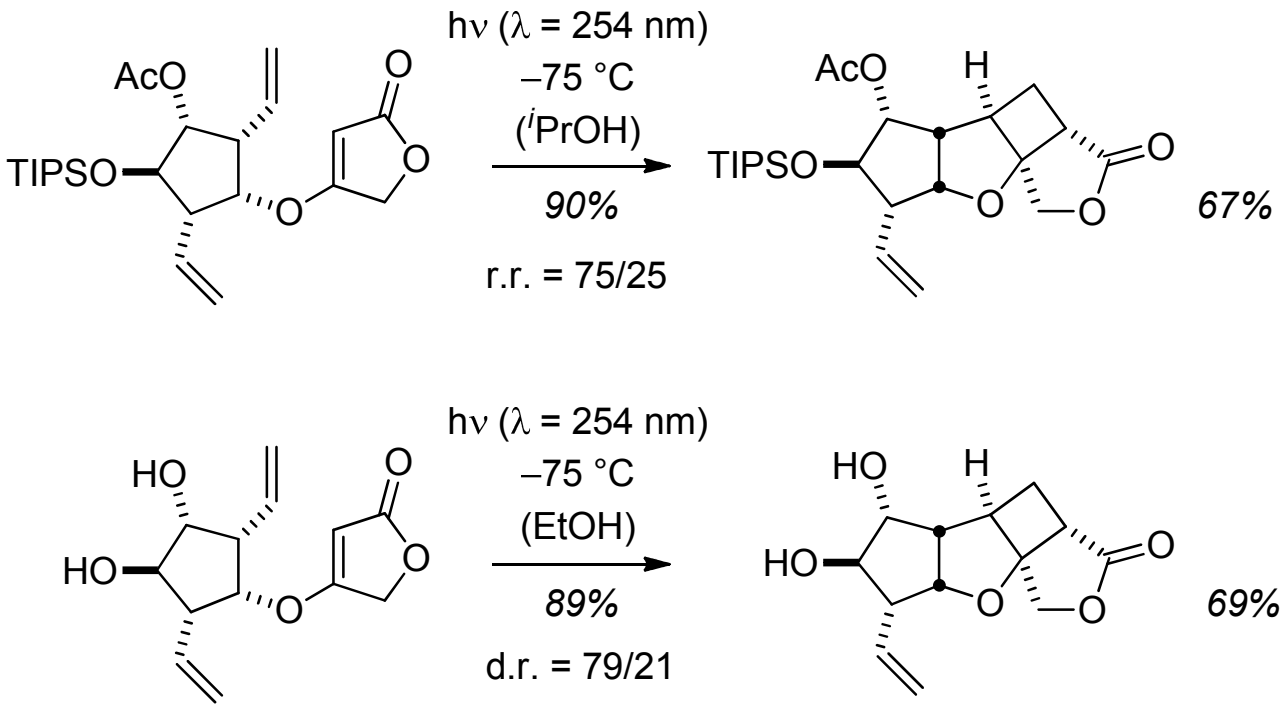
Conformation Preference of Tetronate?



M. Kemmler, T. Bach, *Angew. Chem. Int. Ed.* **2003**, *42*, 4824-4826

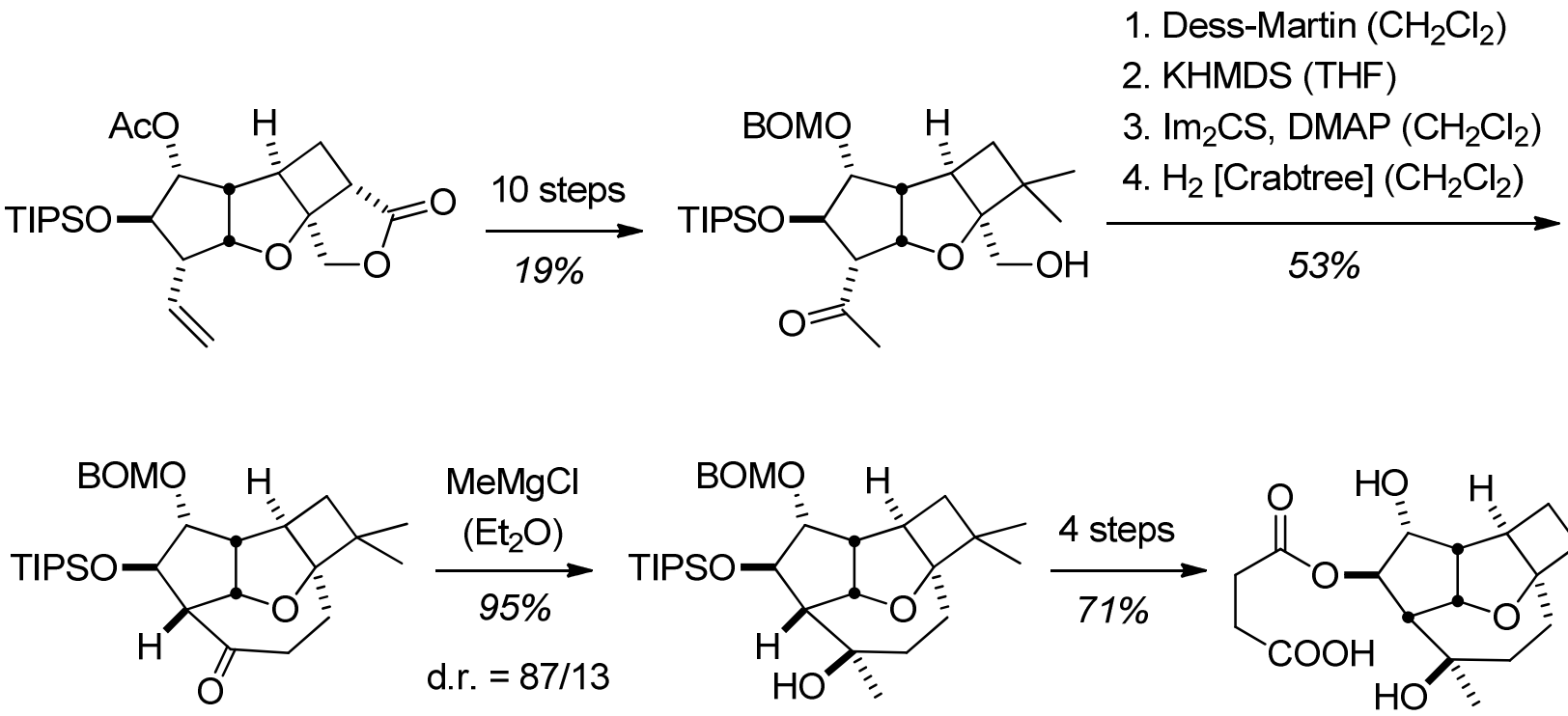


Successful Double Bond Differentiation



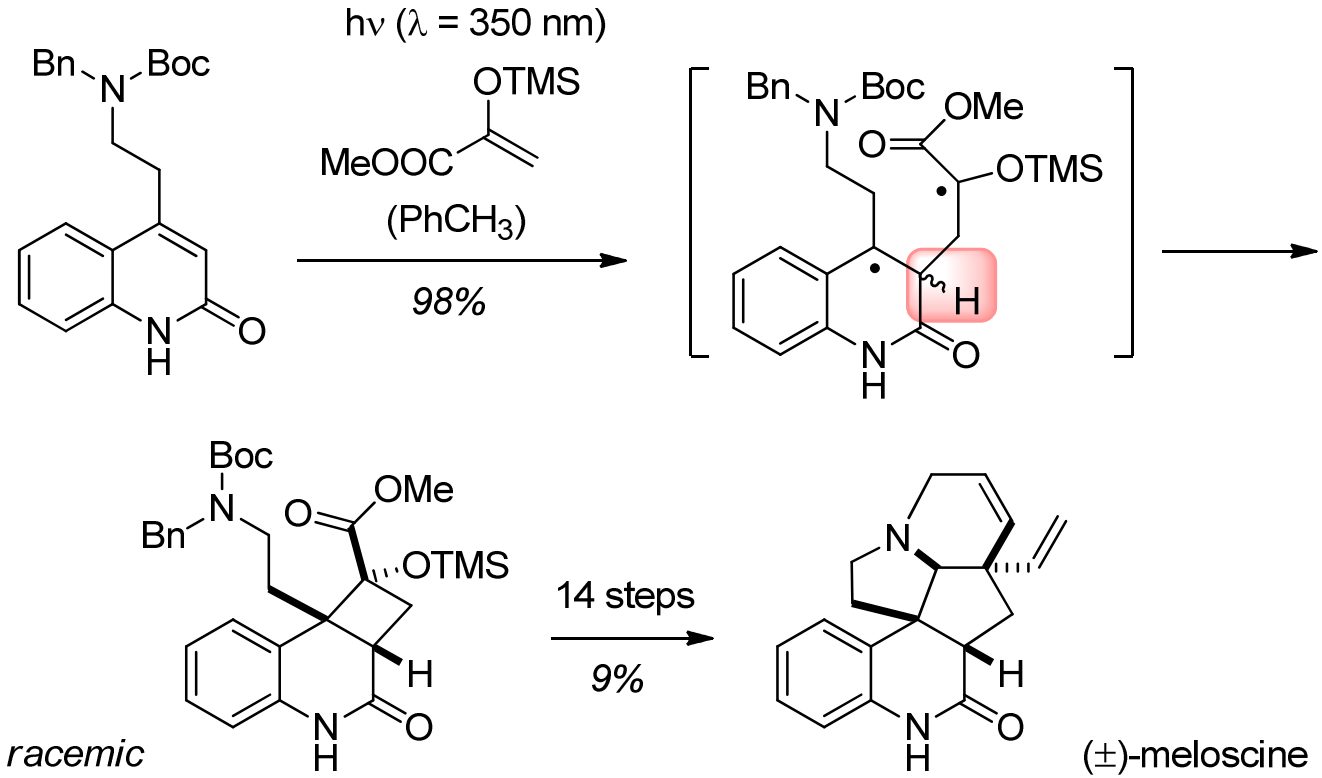
M. Fleck, T. Bach, *Chem. Eur. J.* **2010**, *16*, 6015-6032

Completion of the Synthesis



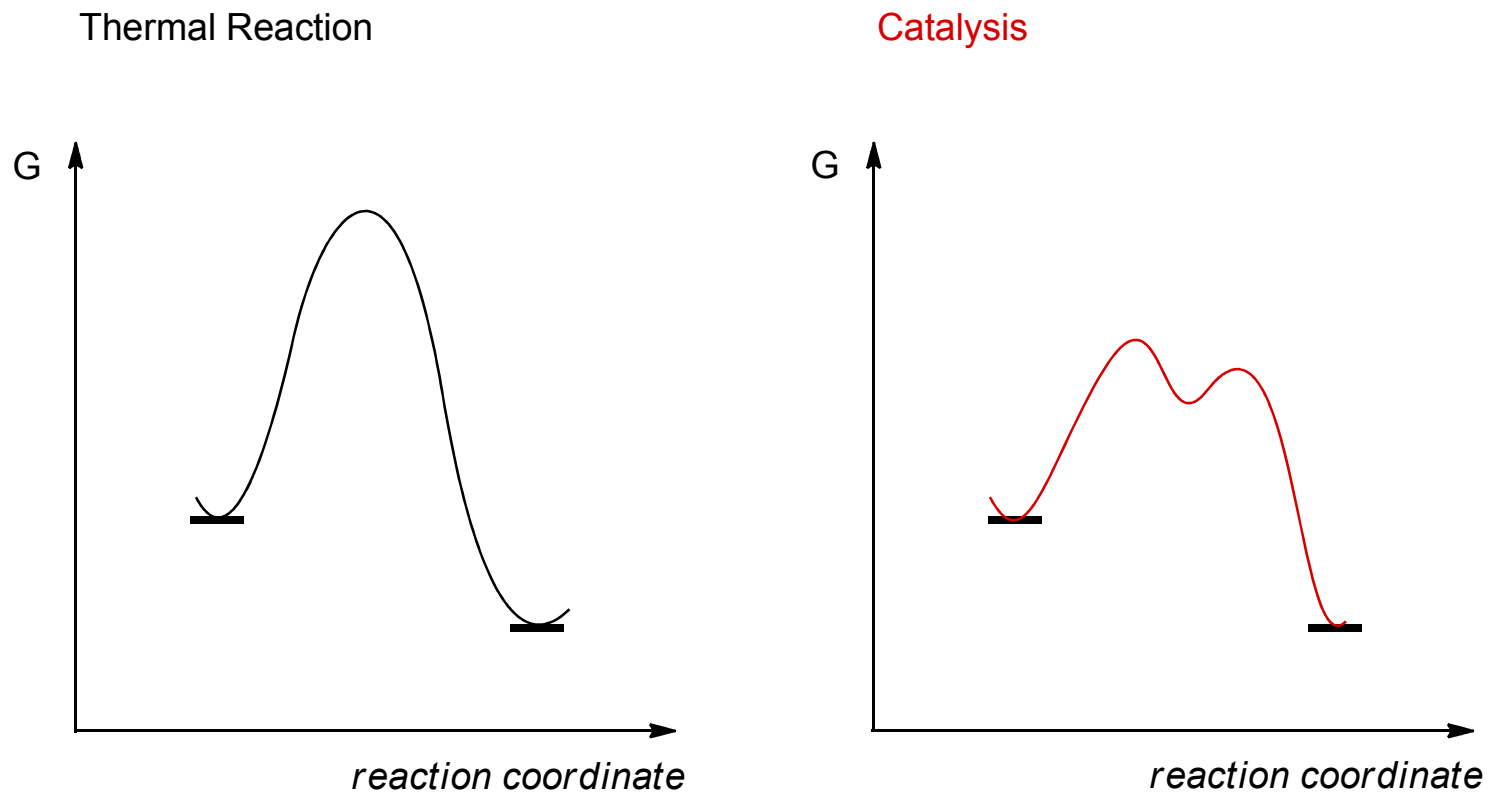
M. Fleck, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47*, 6189-6191

Enantioselectivity – Relevance II



P. Selig, T. Bach, *Angew. Chem. Int. Ed.* **2008**, *47,* 5082-5084

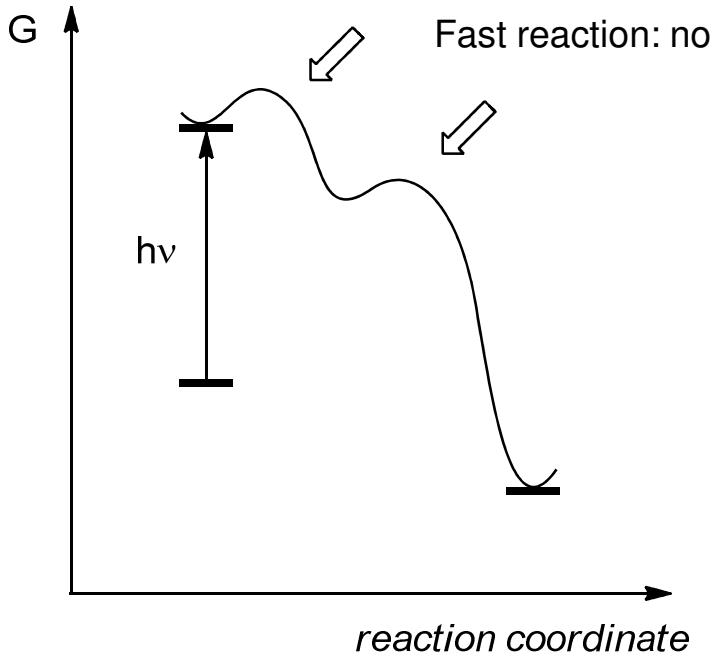
Conventional Mode of Catalysis



R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *47,* 3872-3890

Intrinsic Difficulties

Photochemical Reaction (diabatic)



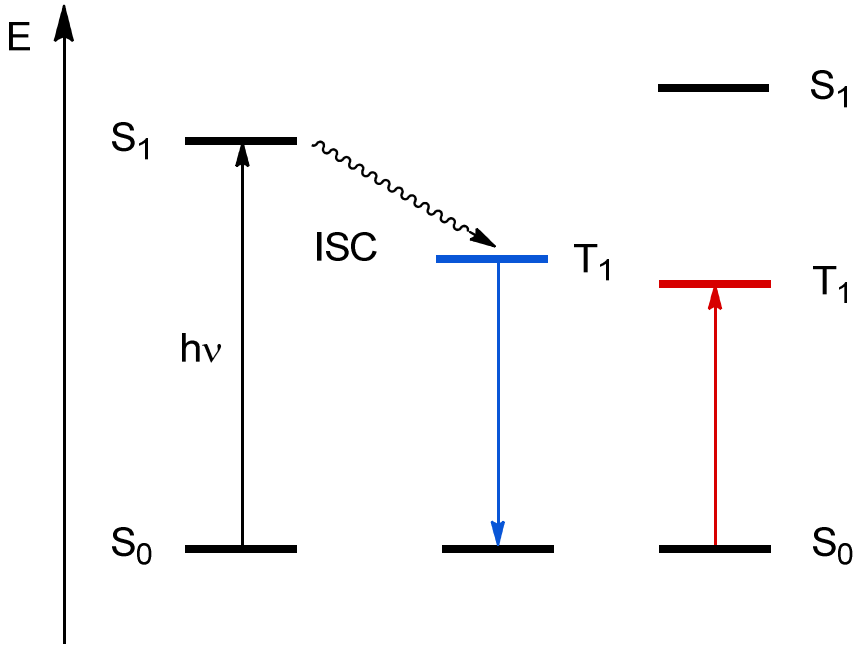
Fast reaction: no significant rate increase by a catalyst

KEY QUESTION:

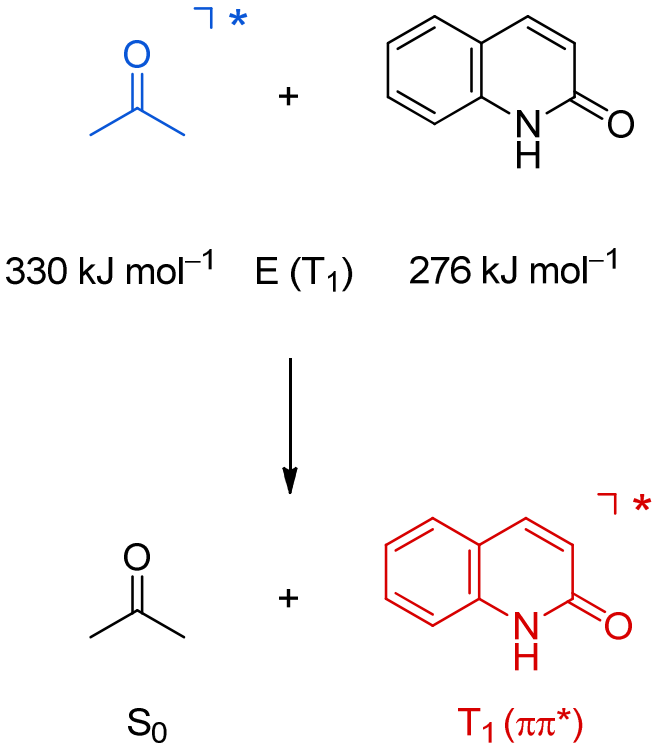
How can chiral information be imposed on the photochemical substrate upon excitation?

R. Brimioulle, D. Lenhart, M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2015**, *47,* 3872-3890

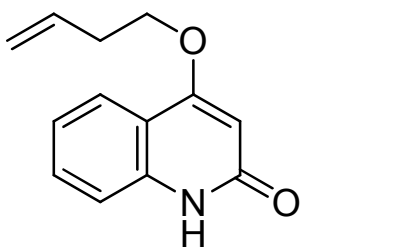
Sensitization by Triplet Energy Transfer



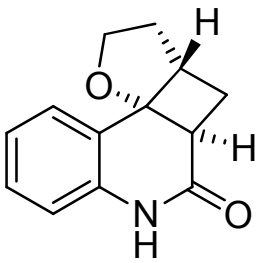
Example:

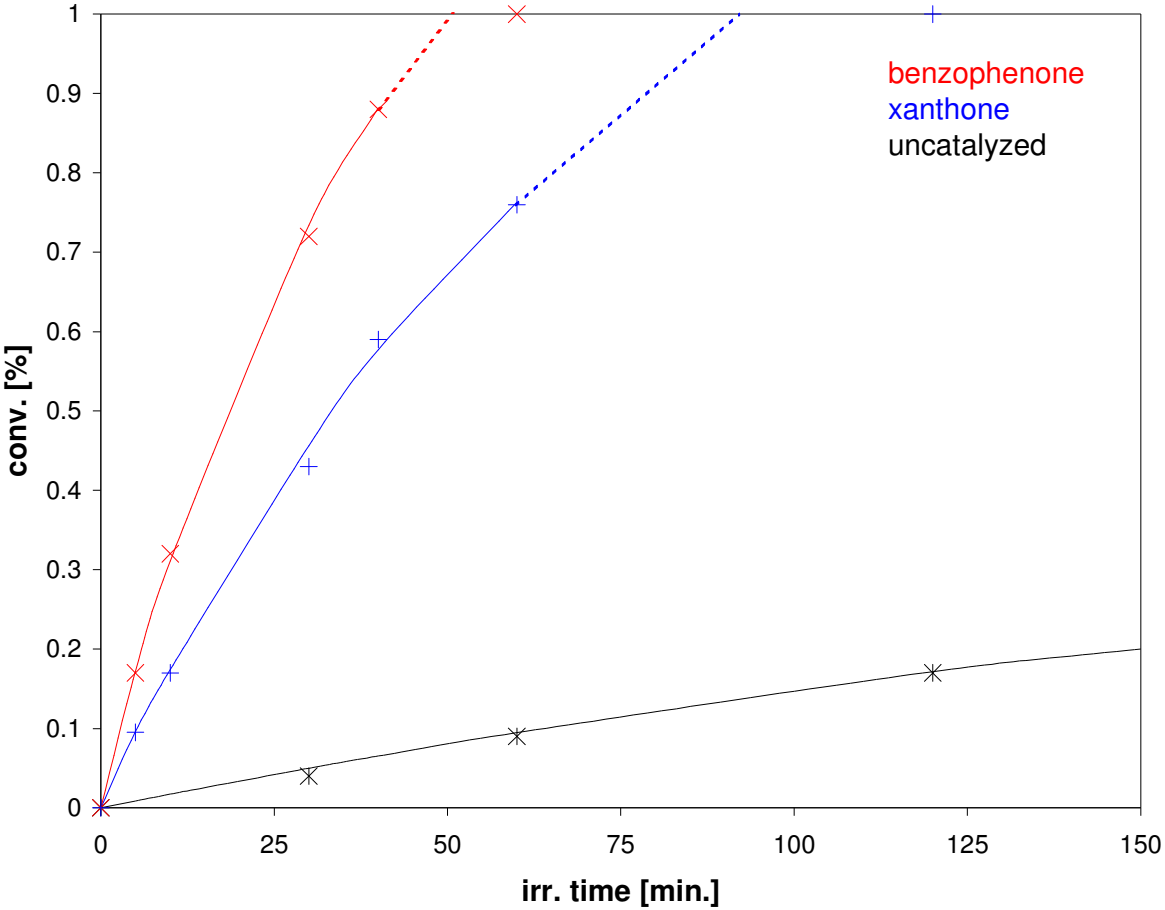


Rate Acceleration of [2+2] Photocycloaddition



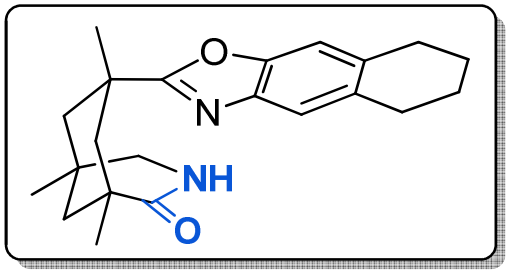
hν (λ = 366 nm)
–25 °C ($PhCF_3$)
r.r. = 91/9

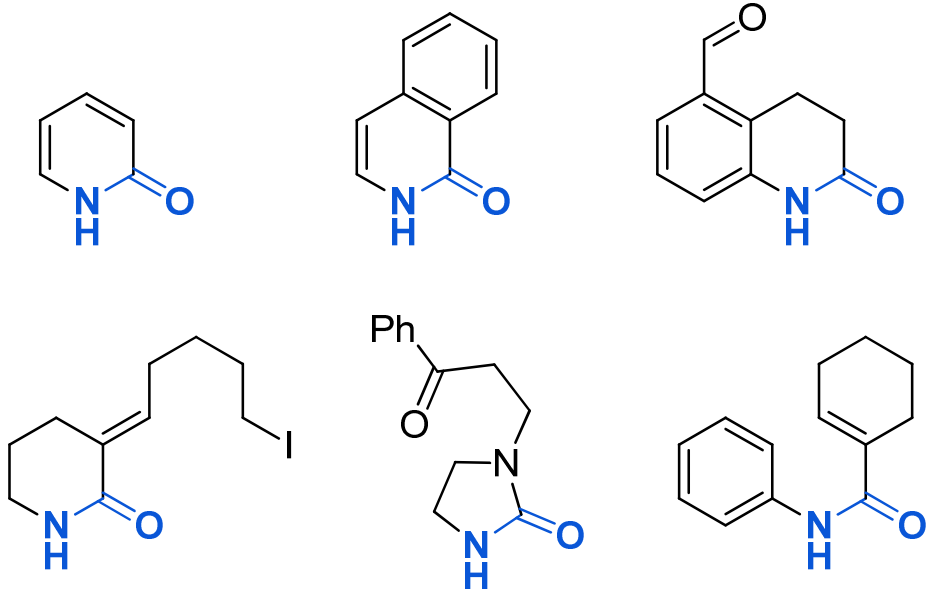




C. Müller, A. Bauer, T. Bach, *unpublished results*

Stoichiometric Use of Chiral Template

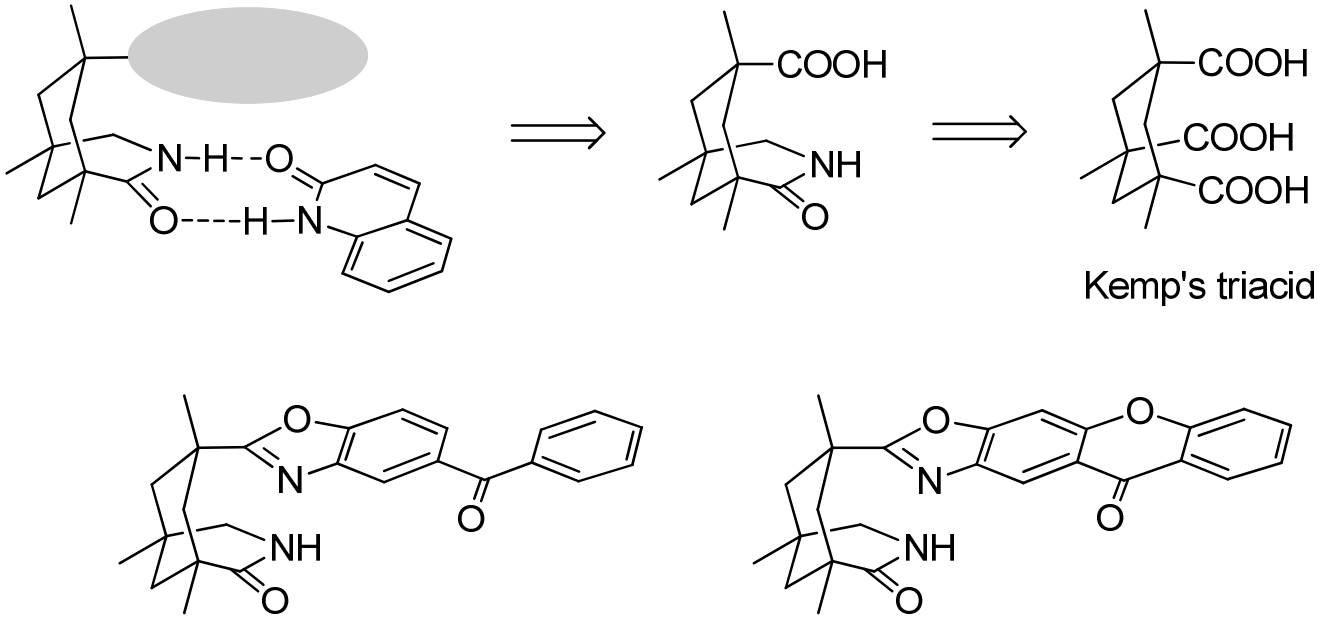




H. Bergmann, B. Grosch
T. Aechtner, M. Dressel
D. Albrecht, K. A. B. Austin

Angew. Chem. Int. Ed. **2000**, *39*, 2302-2304
J. Am. Chem. Soc. **2002**, *124*, 7982-7990
Angew. Chem. Int. Ed. **2003**, *42*, 3693-3696
Angew. Chem. Int. Ed. **2008**, *47*, 5082-5084
Angew. Chem. Int. Ed. **2011**, *50*, 8416-8419
J. Am. Chem. Soc. **2013**, *135*, 14948-14951

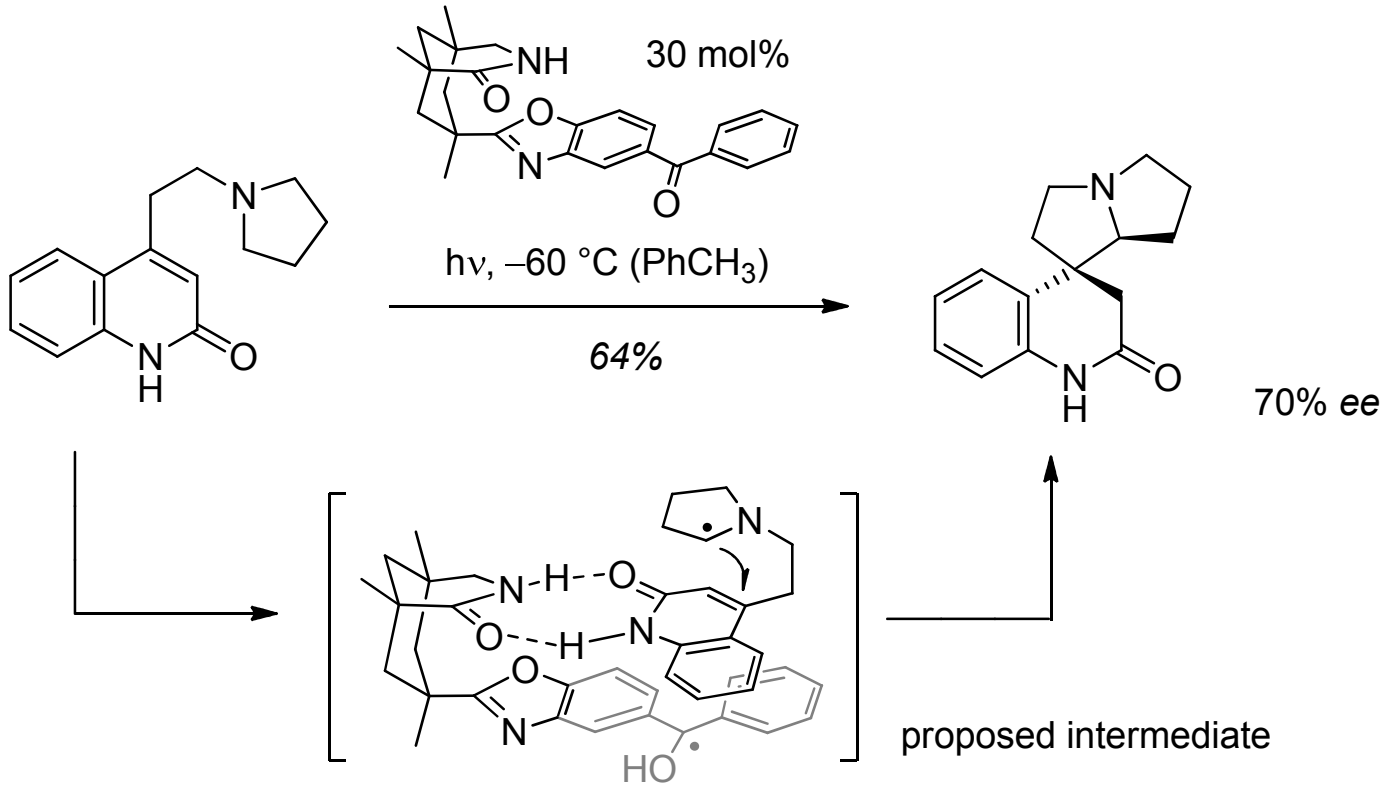
Potential Sensitizers



A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139-1140

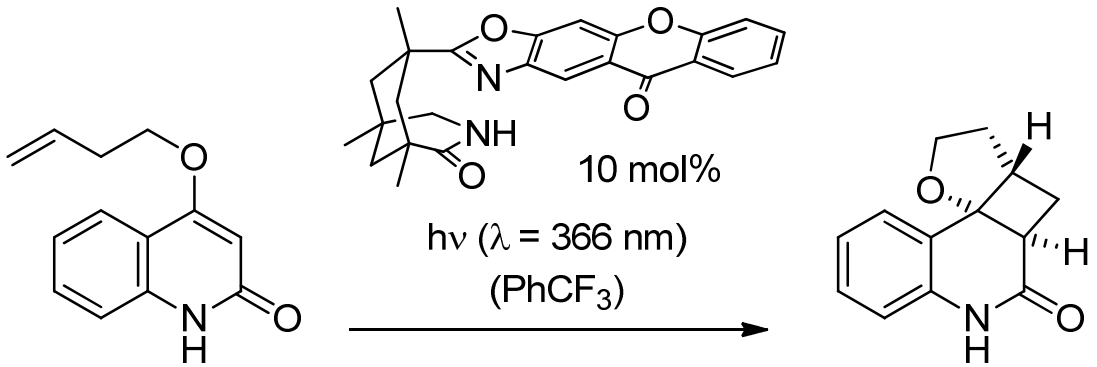
C. Müller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.* **2009**, *48,* 6640-6642

Hint at Catalytic Activity



A. Bauer, F. Westkämper, S. Grimme, T. Bach, *Nature* **2005**, *436*, 1139-1140

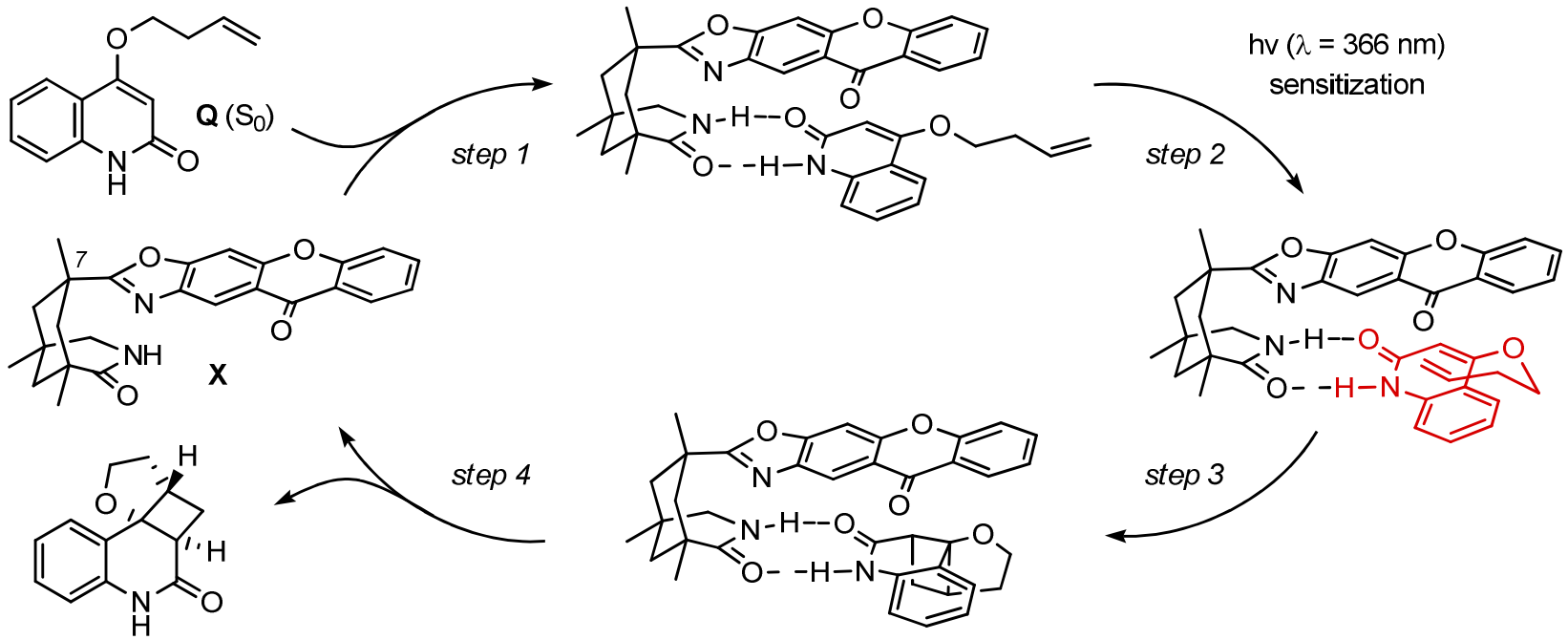
High Enantioselectivity even at Room Temperature



–25 °C	*90%*	r.r. = 78/22	92% *ee*
0 °C	*84%*	r.r. = 76/24	91% *ee*
r.t.	*82%*	r.r. = 81/19	88% *ee*

M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.* **2013**, *19*, 7461-7472

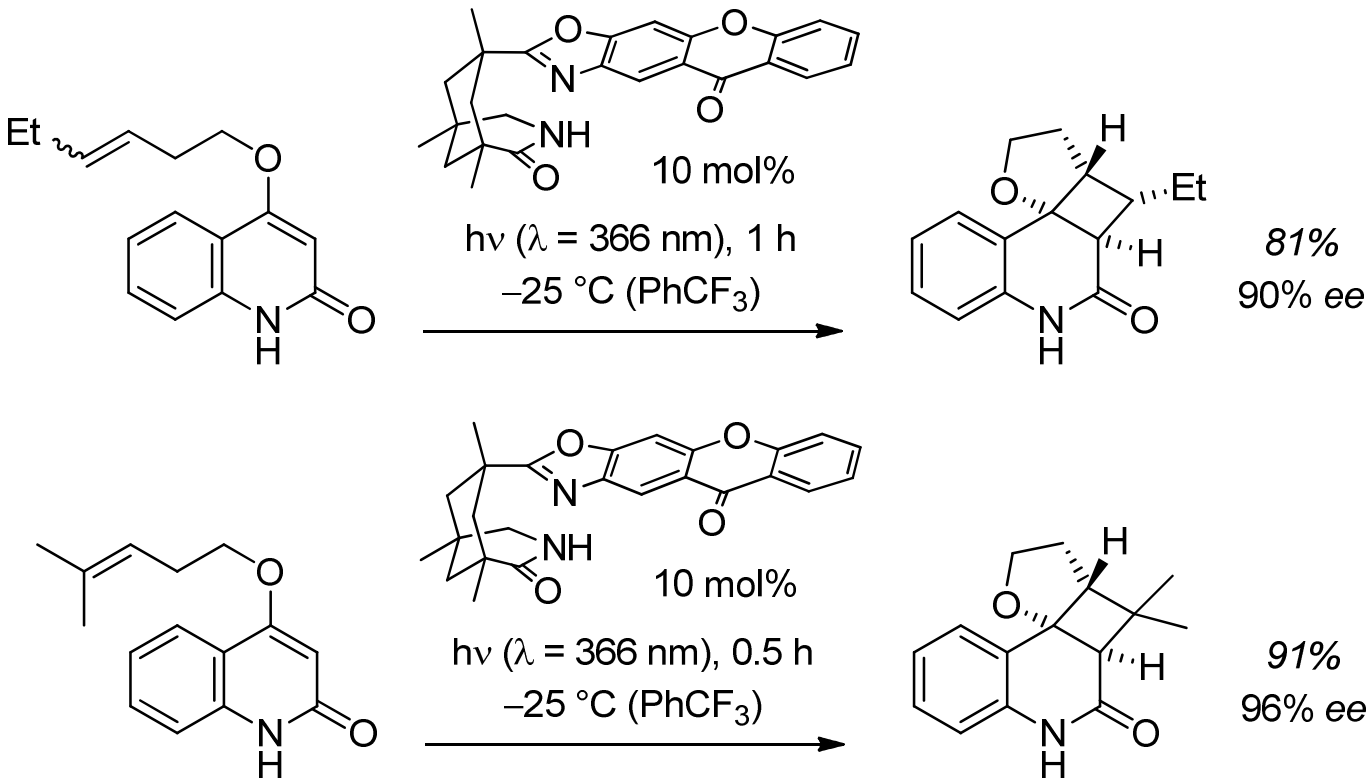
Catalytic Cycle



C. Müller, A. Bauer, T. Bach, *Angew. Chem. Int. Ed.* **2009**, *48,* 6640-6642

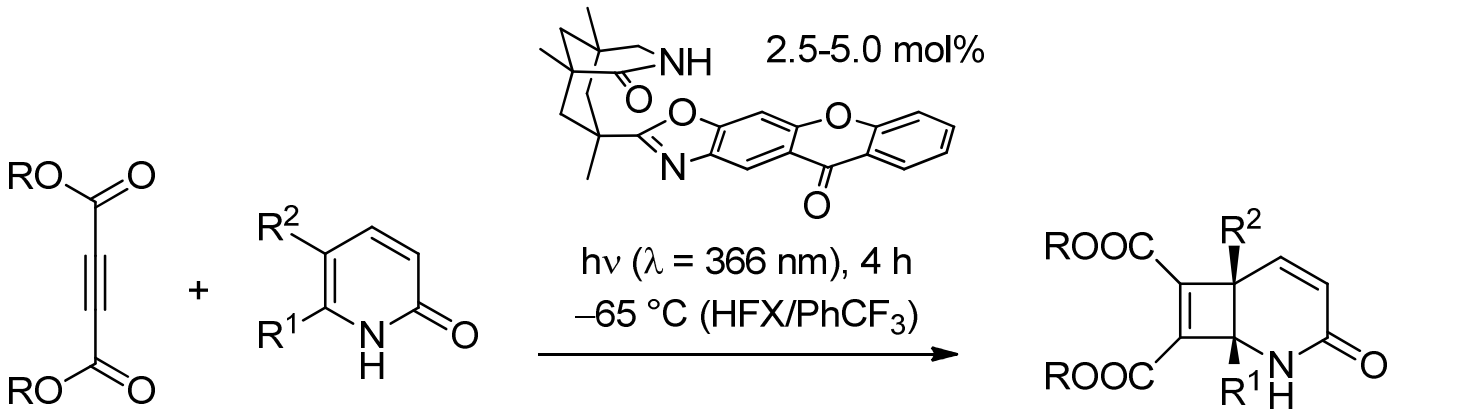
C. Müller, **A. Bauer,** M. M. Maturi, M. C. Cuquerella, M. A. Miranda, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 16689-16697

Multiply Substituted Alkenes

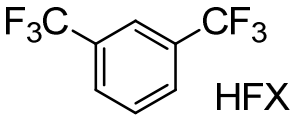


M. M. Maturi, M. Wenninger, R. Alonso, A. Bauer, A. Pöthig, E. Riedle, T. Bach, *Chem. Eur. J.* **2013**, *19*, 7461-7472

Intermolecular [2+2] Photocycloaddition



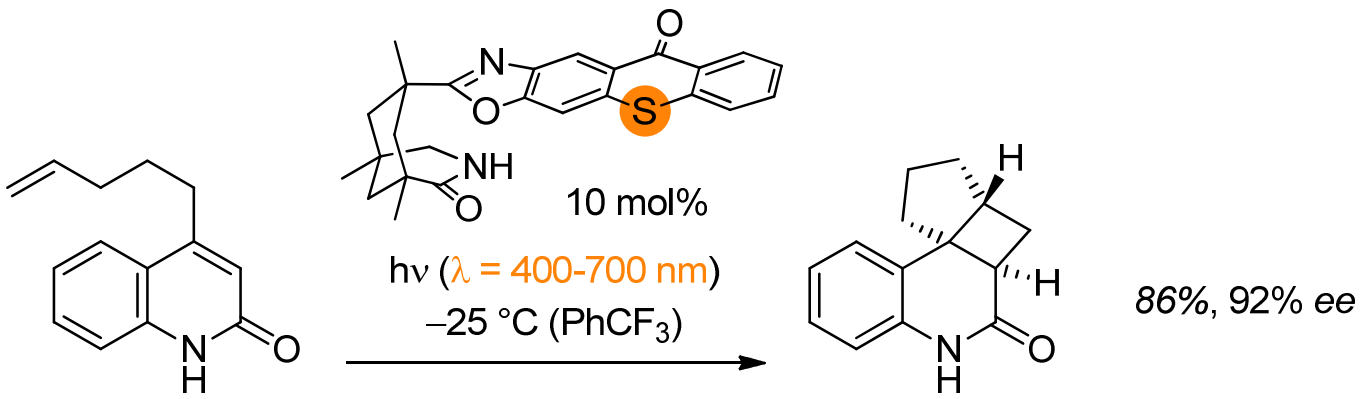
R = *t* Bu	R^1 = H	R^2 = H	*64%*	64% *ee*
R = Et	R^1 = Me	R^2 = H	*79%*	90% *ee*
R = Me	R^1 = H	R^2 = Me	*65%*	92% *ee*
R = Et	R^1 = H	R^2 = Me	*76%*	90% *ee*

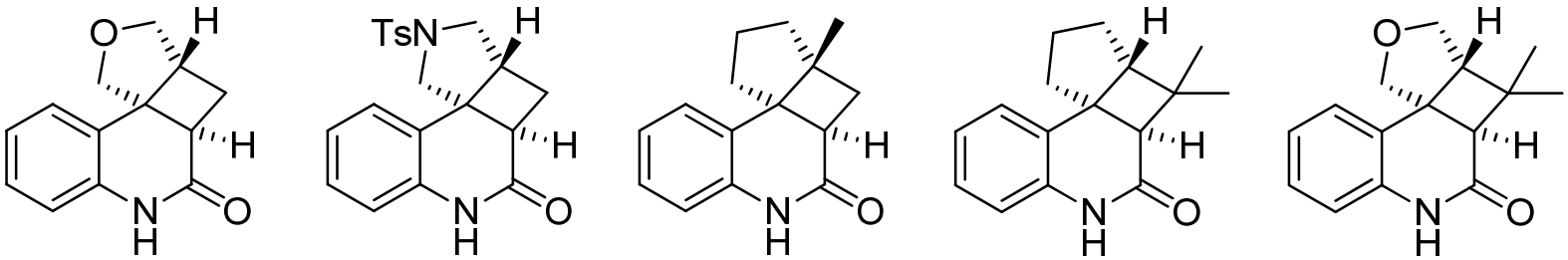


M. M. Maturi, T. Bach, *Angew. Chem. Int. Ed.* **2014**, *53,* 7661-7664

K. Somekawa, Y. Okumura, K. Uchida, T. Shimo, *J. Heterocycl. Chem.* **1988**, *25*, 731-734

Visible Light Catalysis

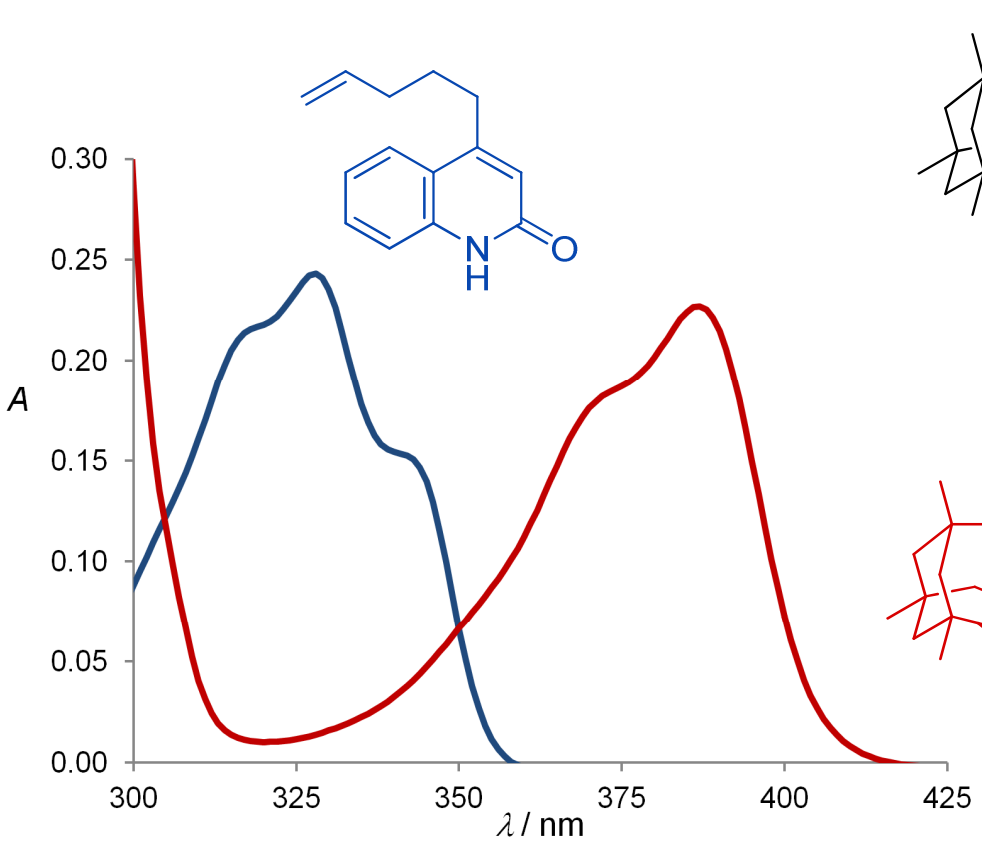


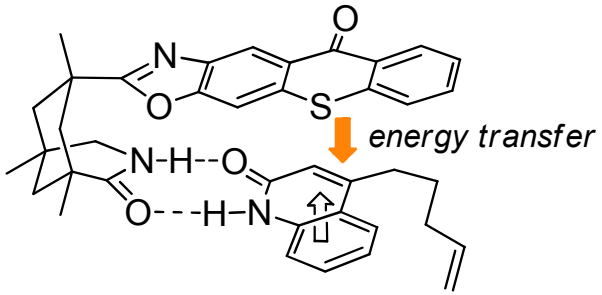


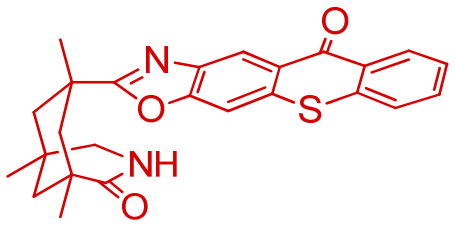
95%, 87% *ee* | 79%, 88% *ee* | 95%, 94% *ee* | 97%, 94% *ee* | 89%, 89% *ee*

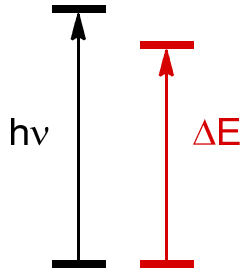
R. Alonso, T. Bach, *Angew. Chem. Int. Ed.* **2014**, *53,* 4368-4371

UV/Vis Spectrum and Mode of Action



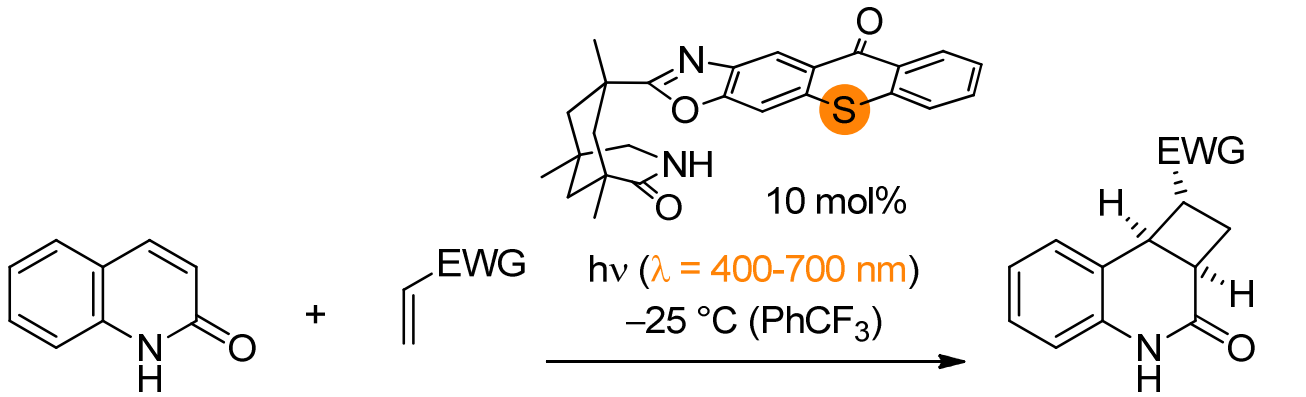






R. Alonso, T. Bach, *Angew. Chem. Int. Ed.* **2014**, *53,* 4368-4371

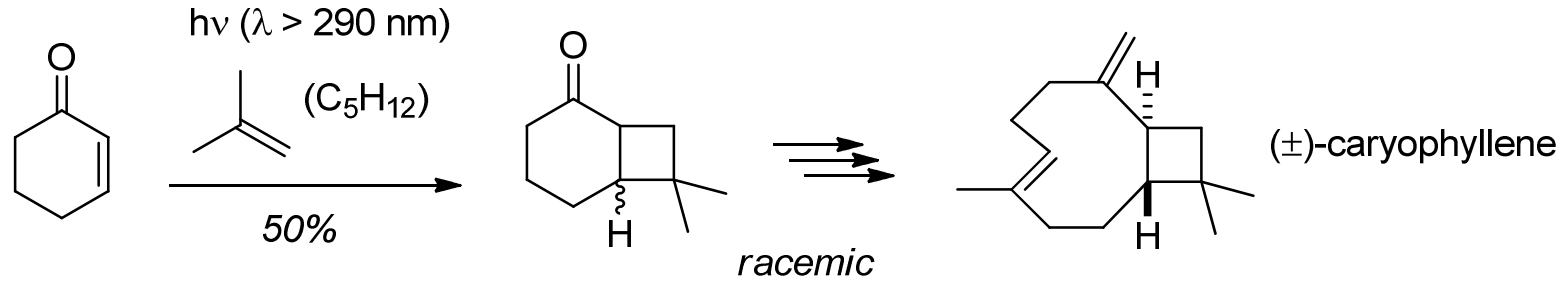
Intermolecular [2+2] Photocycloaddition



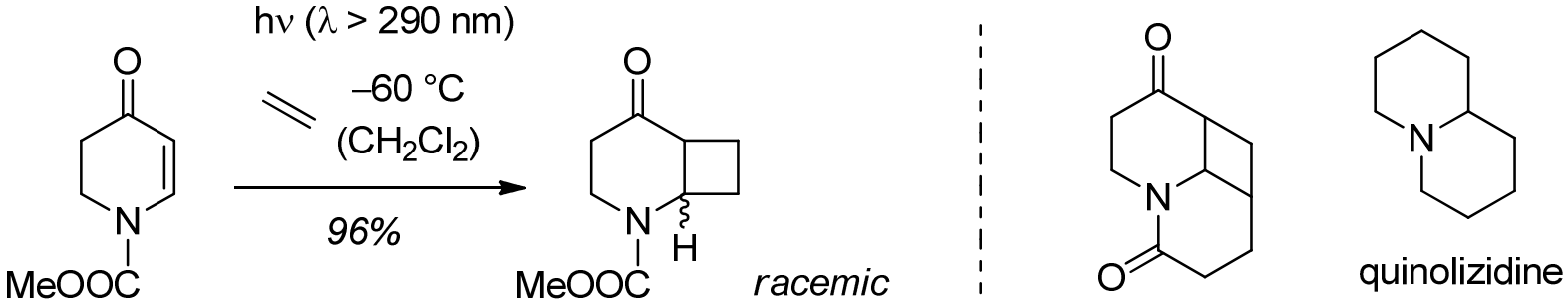
80%, 91% *ee* *89%*, 91% *ee* *66%*, 90% *ee* *44%*, 91% *ee*

R. Alonso, A. Tröster, T. Bach, *J. Am. Chem. Soc.* **2016**, *138*, 7808-7811

Enantioselectivity in Enone Photochemistry

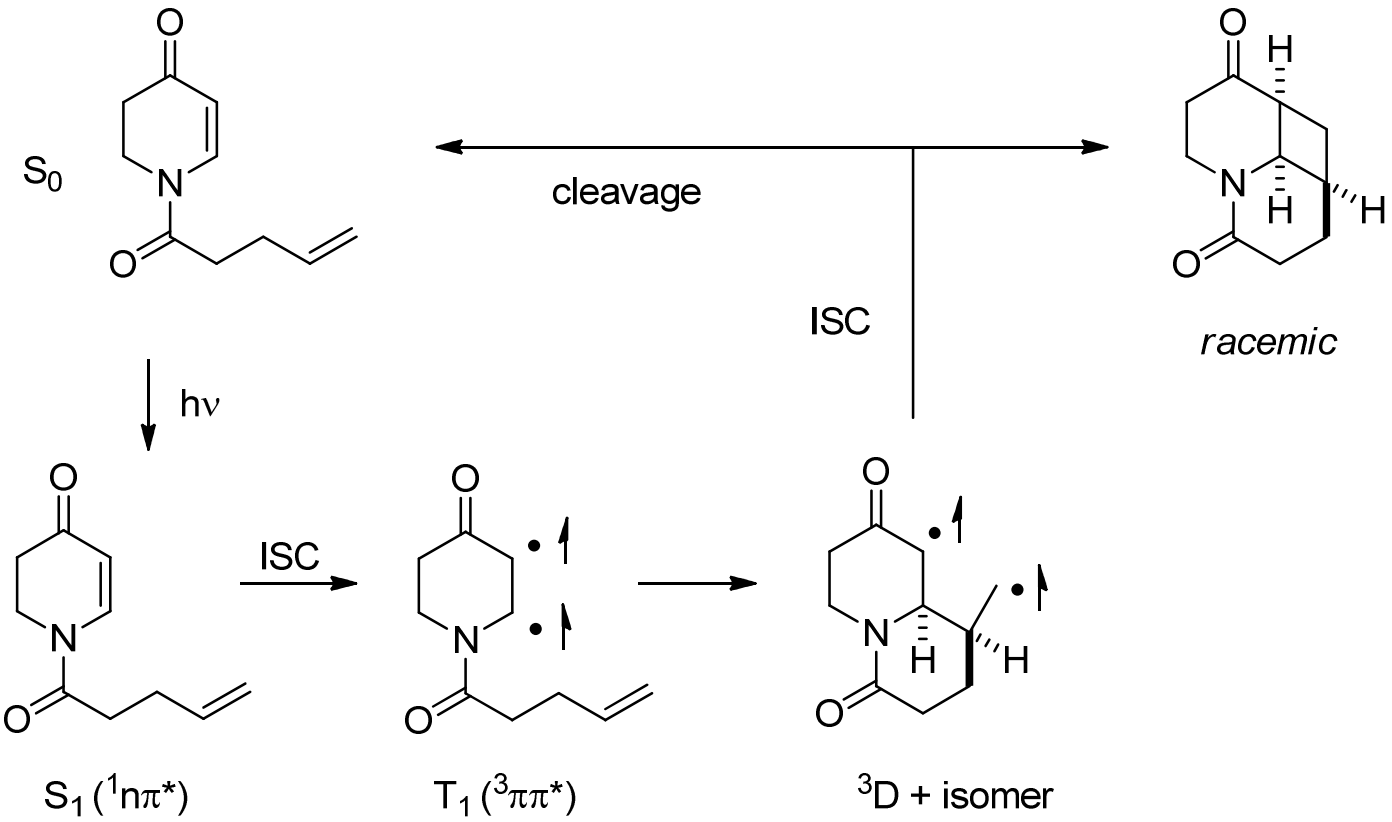


E. J. Corey, R. B. Mitra, H. Uda, *J. Am. Chem. Soc.* **1963**, *85*, 362-363



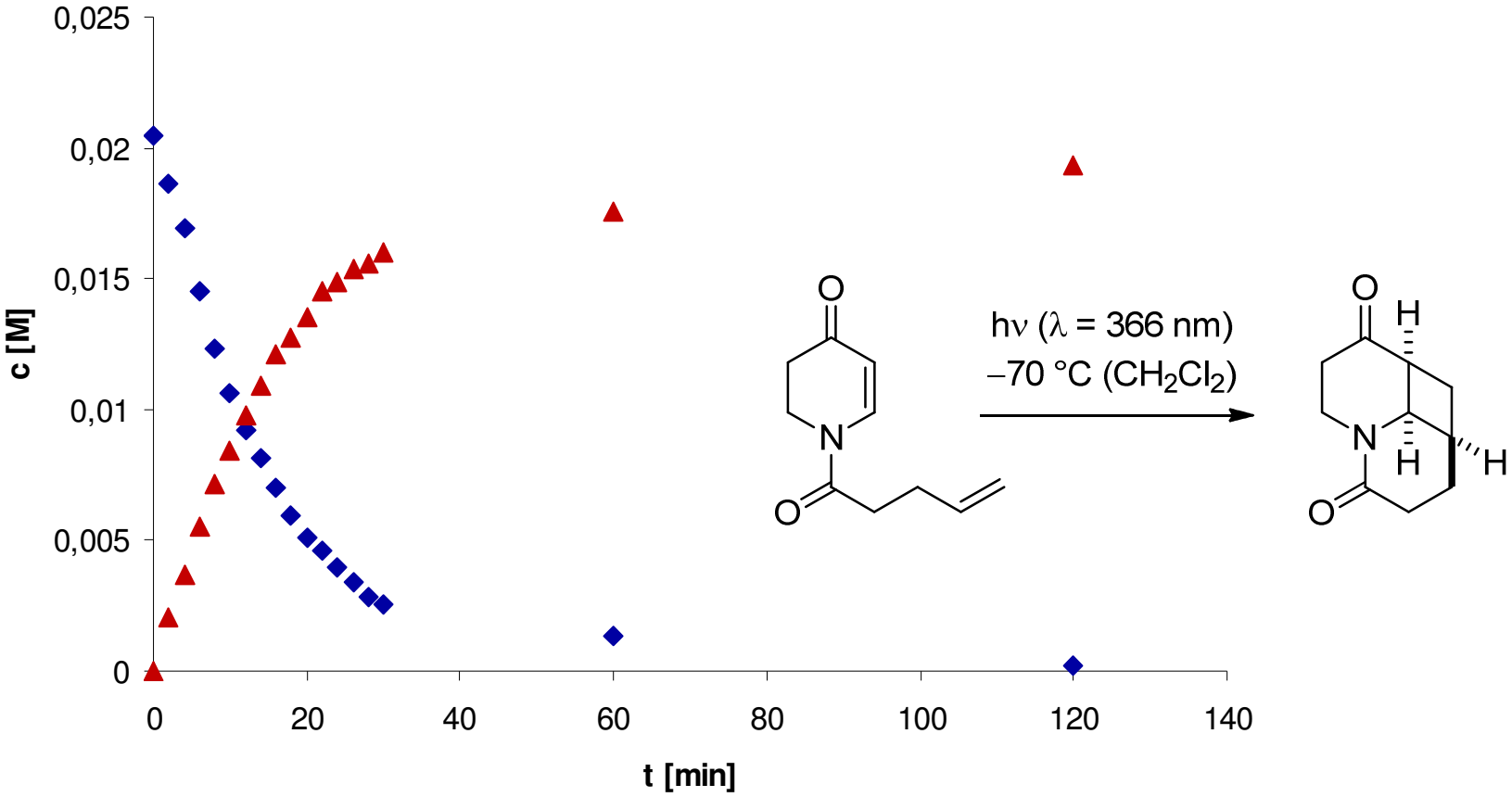
P. Guerry, P. Blanco, H. Brodbeck, O. Pasteris, R. Neier, *Helv. Chim. Acta* **1991**, *74*, 163-178

[2+2] Photocycloaddition: Intramolecular Example



cf. P. Guerry, P. Blanco, H. Brodbeck, O. Pasteris, R. Neier, *Helv. Chim. Acta* **1991**, *74*, 163-178

Fast Reaction on the Triplet Hypersurface



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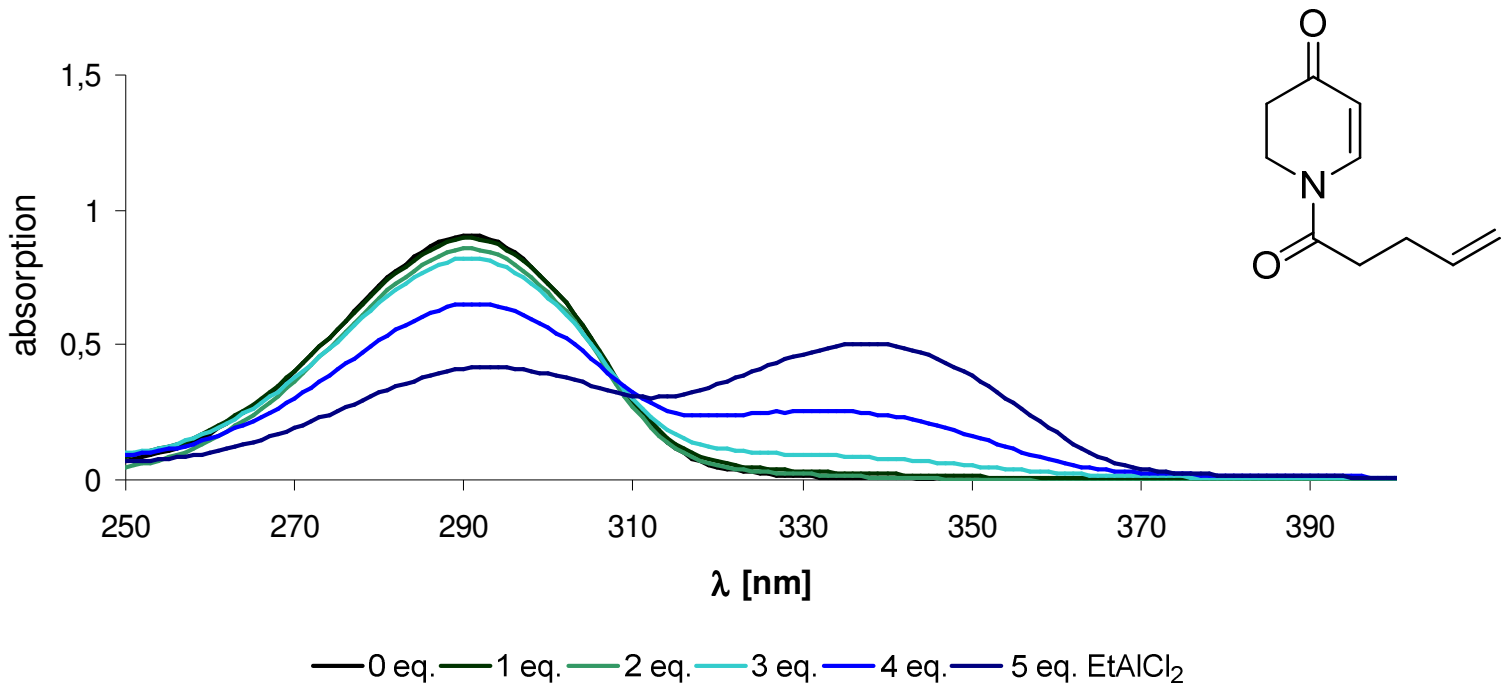
N-Acyl-2,3-dihydro-4-pyridones: UV/Vis Absorption



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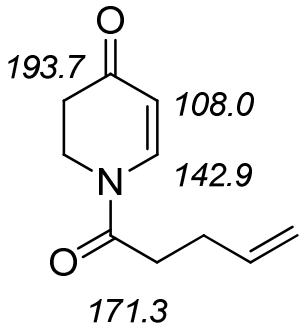
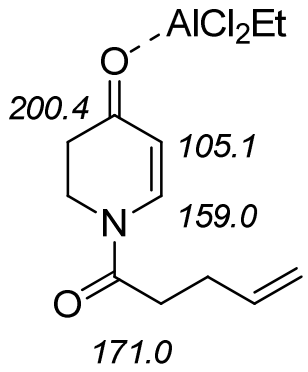
Complexation and Absorption Change

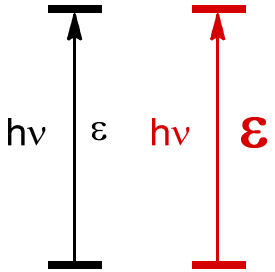
^{13}C-NMR



ε (360 nm) ≅ 70 M^{-1} cm^{-1}



ε (360 nm) ≅ 14000 M^{-1} cm^{-1}



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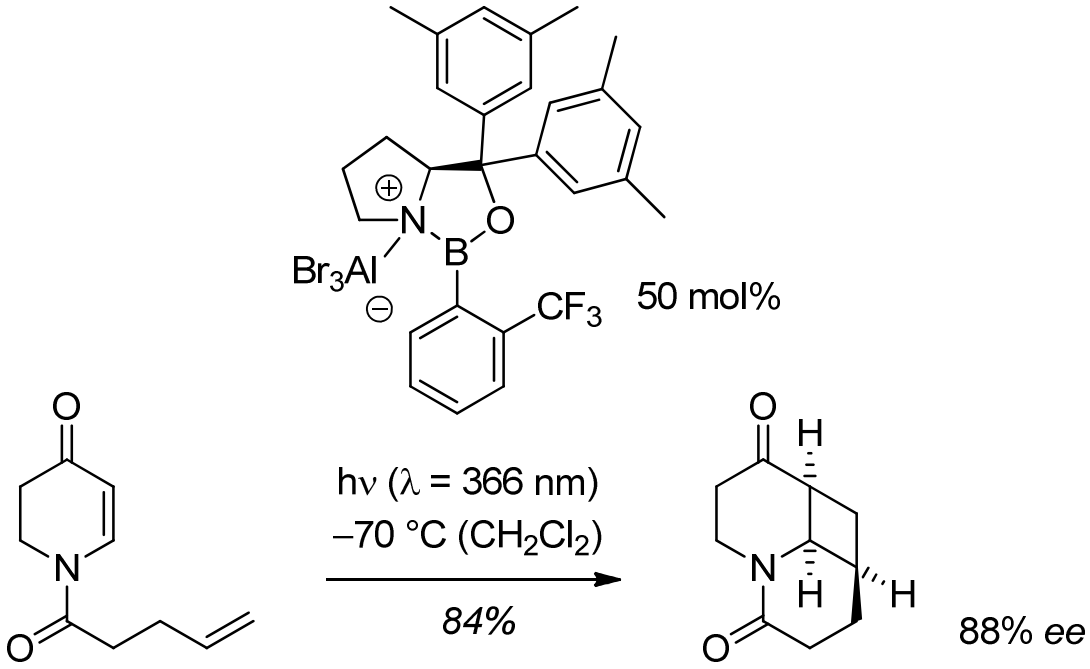
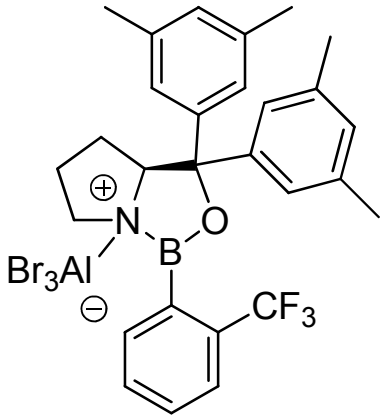
Enantioselective Lewis Acid Catalysis



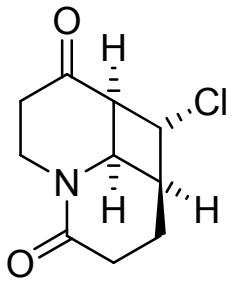
R. Brimioulle, T. Bach, *Science* **2013**, *342*, 840-843

Lewis acid: **H. Guo**, E. Herdtweck, T. Bach, *Angew. Chem. Int. Ed.* **2010**, *49,* 7782-7785

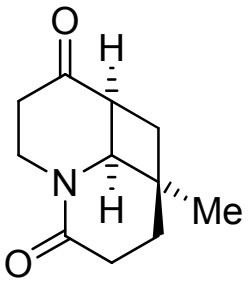
Preliminary Substrate Scope



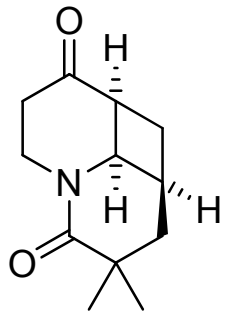
50 mol%
hν (λ = 366 nm)
–70 °C (CH_2Cl_2)



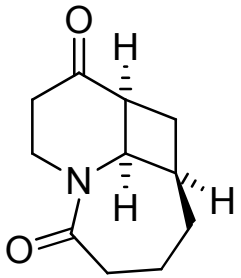
83% (82% *ee*)



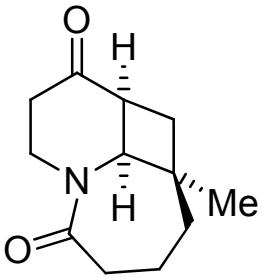
81% (88% *ee*)



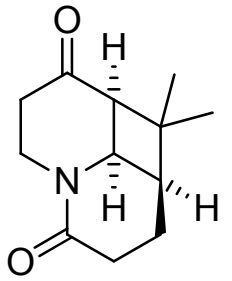
87% (80% *ee*)



75% (90% *ee*)



83% (80% *ee*)



48% (82% *ee*)

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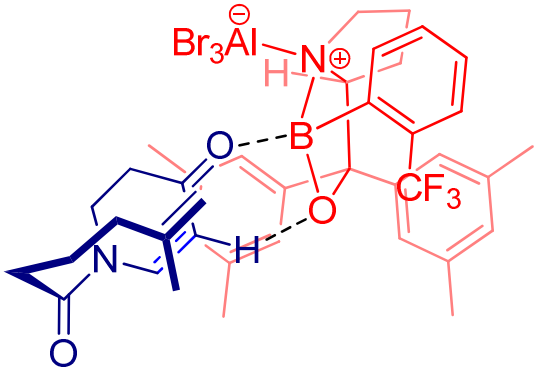
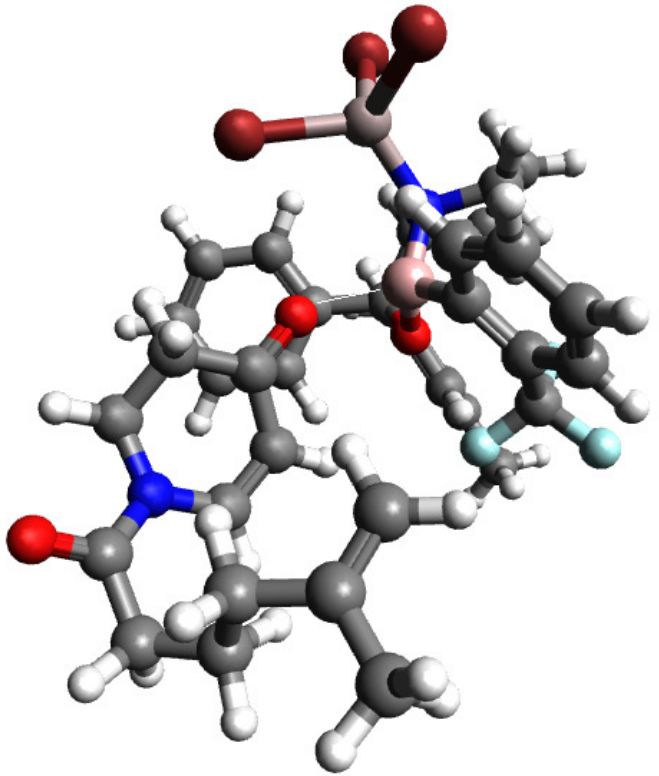
Direction of Attack – Absolute Configuration





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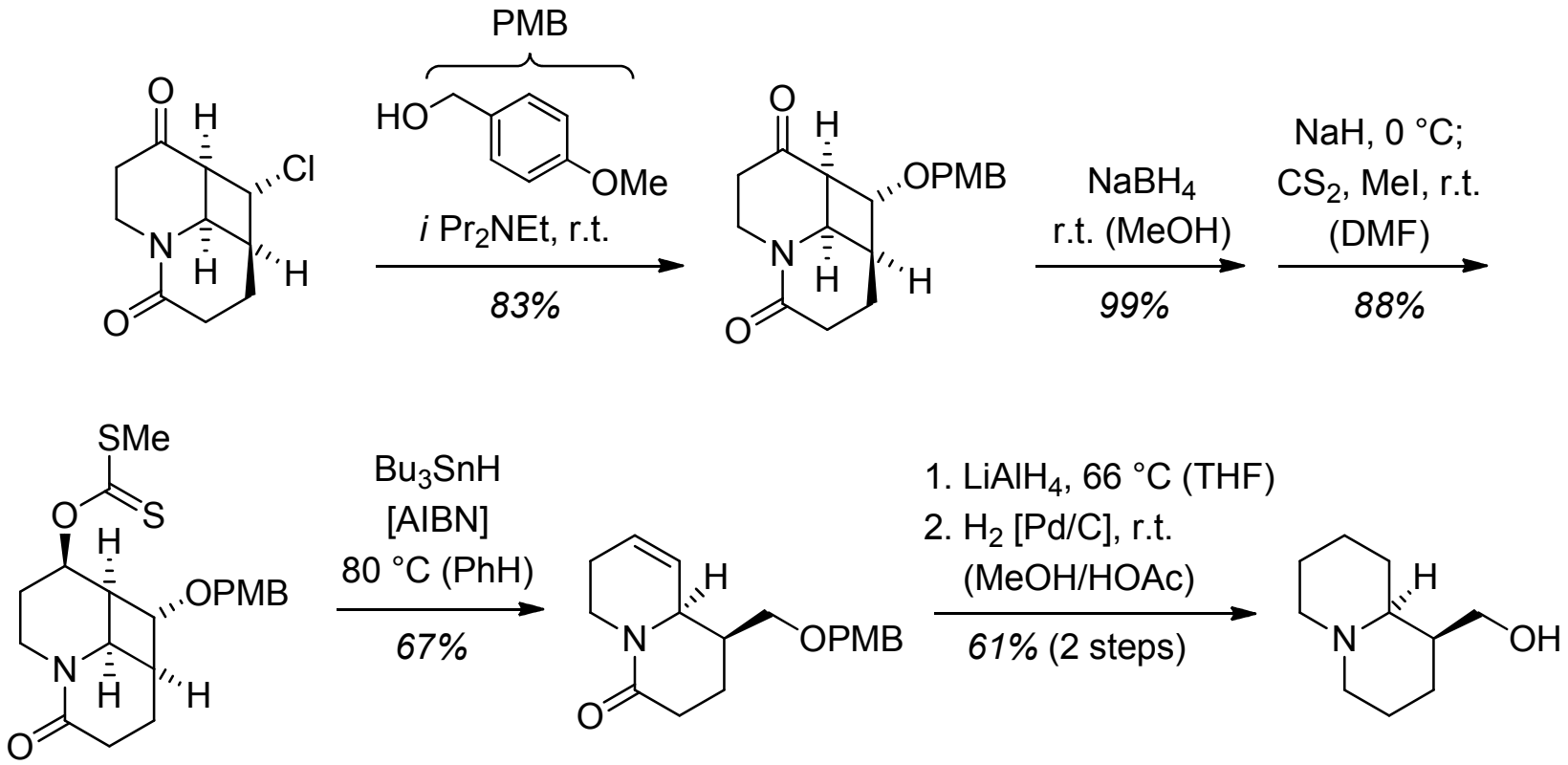
Total Synthesis of (+)-Lupinine



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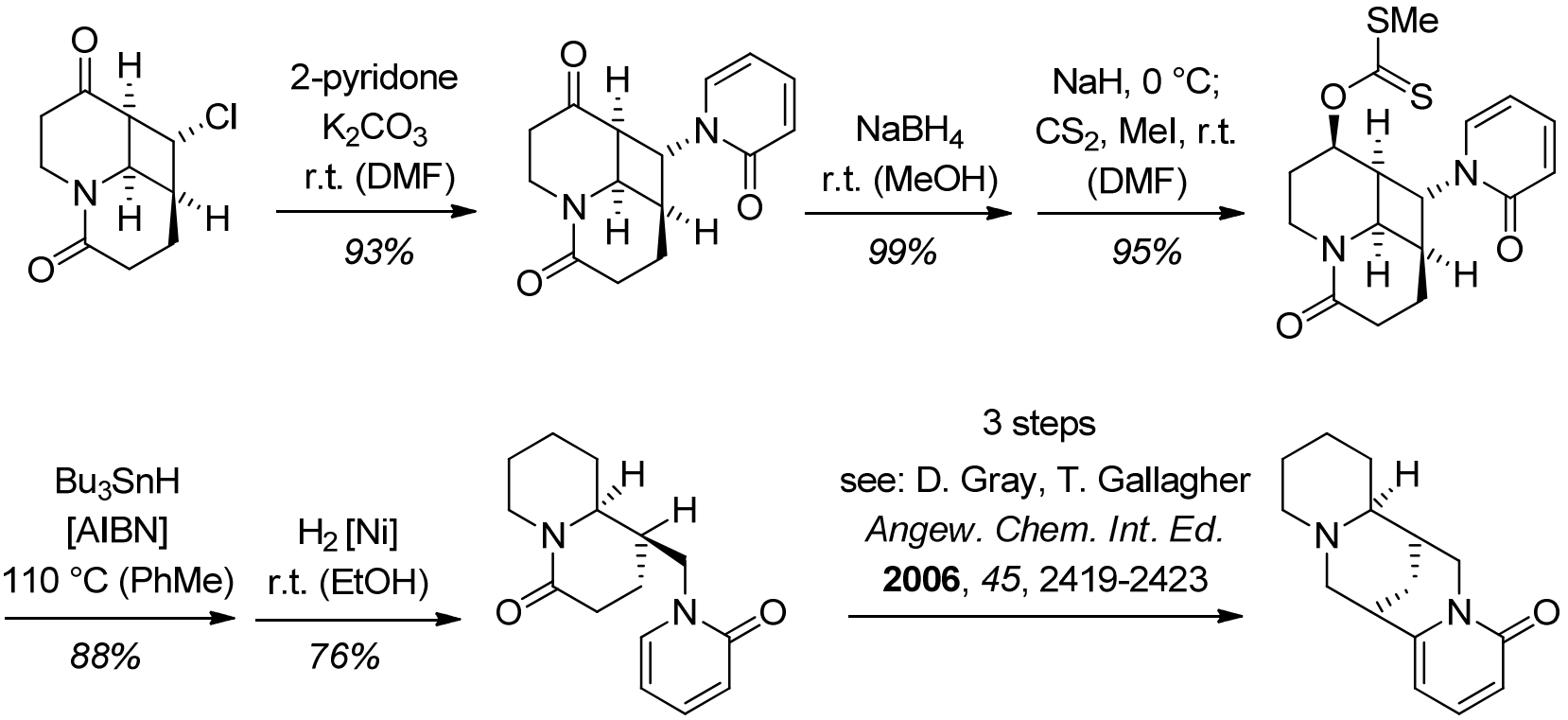
Formal Total Synthesis of (+)-Thermopsine



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