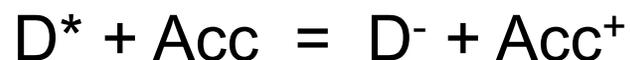


Photoinduced Electron Transfer: Strategies for Organic Synthesis



MacMillan Group Meeting

Alex Warkentin 2.12.08

Contents

- History of photoinduced electron transfer
- Basics of electron transfer versus energy transfer
- Oxidative PET bond cleavage
- Reductive PET bond cleavage
- Enabling of macrocyclic ring closures
- Intramolecular alpha-amino radical additions
- Intermolecular alpha-amino radical additions and applications
- Catalytic asymmetric?
- Mechanistic verification via spectroscopic analysis

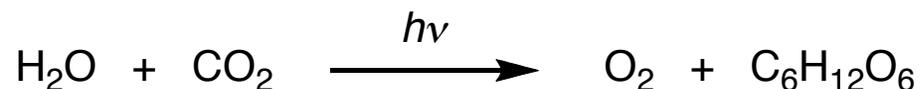
Roth, H. D. *Photoinduced Electron Transfer* / Springer-Verlag, Heidelberg, 1990. 5.

Griesbeck, A. G.; *et. al. Acc. Chem. Res.* **2007**, *40*, 128.

Griesbeck, A. G.; Mattay, J., Eds. *Synthetic Organic Photochemistry* Marcel-Dekker, New York, 2005.

The First Understandings of Photochemistry

- Priestley was the first to discover photosynthesis, albeit fortuitously



Discovered accidentally while Priestley was studying the “influence Of light in the production of ‘dephlogisticated air’ [O₂] in water by Means of a ‘green substance’.”

Priestley, J. *Phil. Trans. Roy. Soc. (London)* **1772**, 62, 147



Joseph Priestley, 1733 - 1804
British chemist

- Ingenhousz developed photosynthesis more rigorously



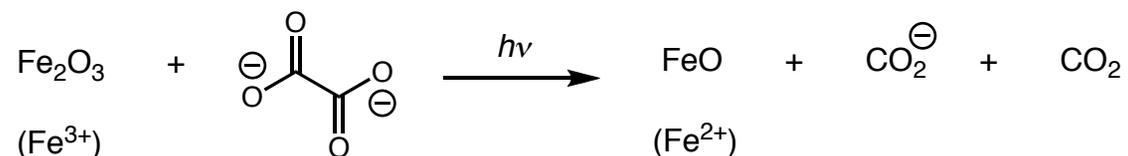
Jan Ingenhousz, 1730 - 1799
Dutch chemist, physicist and physician

Ingenhousz, along with Saussure, established the requirement of light in macroscopic photosynthesis.

But, despite work by Liebig, Baeyer and Willstatter, electron transfer remained unsolved until the 20th century when J. J. Thompson (1897) and Milikan (1913) convinced the community of the presence of the electron.

Electron Transfer and Actinometry

- Dobereiner foreshadowed photo-redox chemistry with actinometry



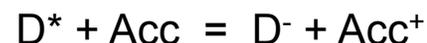
Designed the first actinometer that measures the power of electromagnetic radiation



J. W. Dobereiner, 1780 - 1849
German Chemist

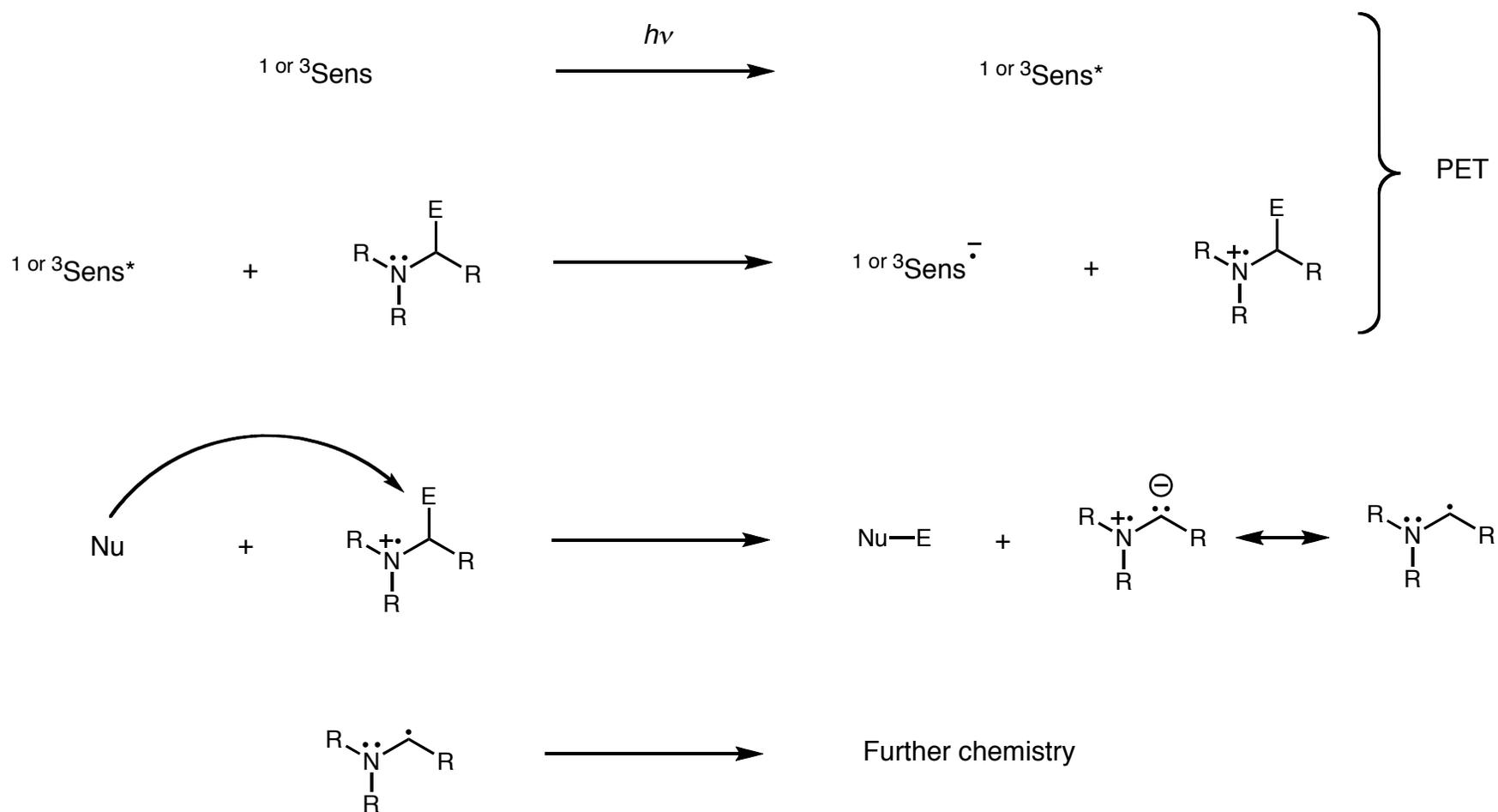
- The place and usefulness of actinometry was fiercely debated and no other photo-redox chemistry was studied in-depth in the 19th century
- Furthermore, prior to the advent of NMR, ESR, and CIDNP the presence of ionic radicals remained highly speculative and their identity often erroneously presumed.
- 20th Century PET contributions were made by Bauer and Weiss. The latter enunciated the basic form of modern PET theory:

“Fluorescence quenching in solution can be considered as a simple electron transfer process.”

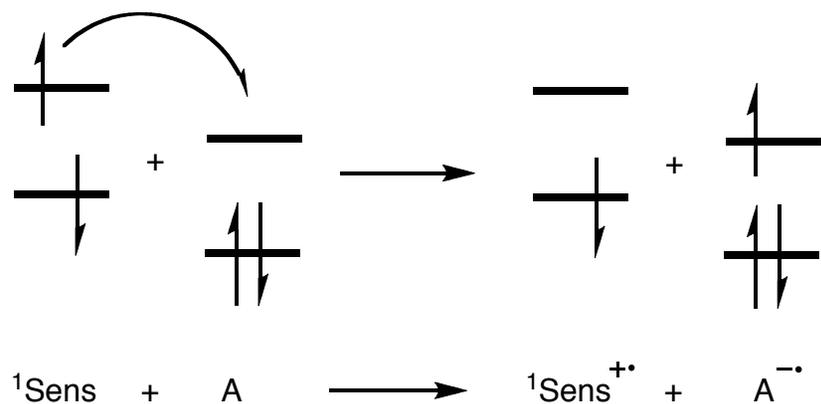


Photoinduced Electron Transfer: A Representative Mechanism

- Understanding α -amino radical formation is important for utilizing its reactivity

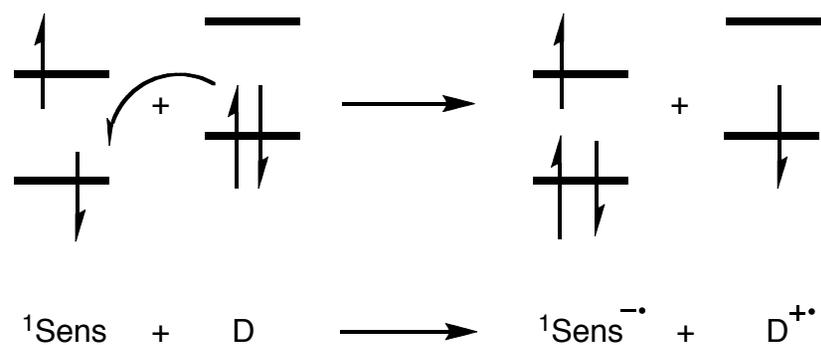


Basics of Photoinduced Electron Transfer



■ More efficient as distance decreases

■ Efficiency dependent on redox potential

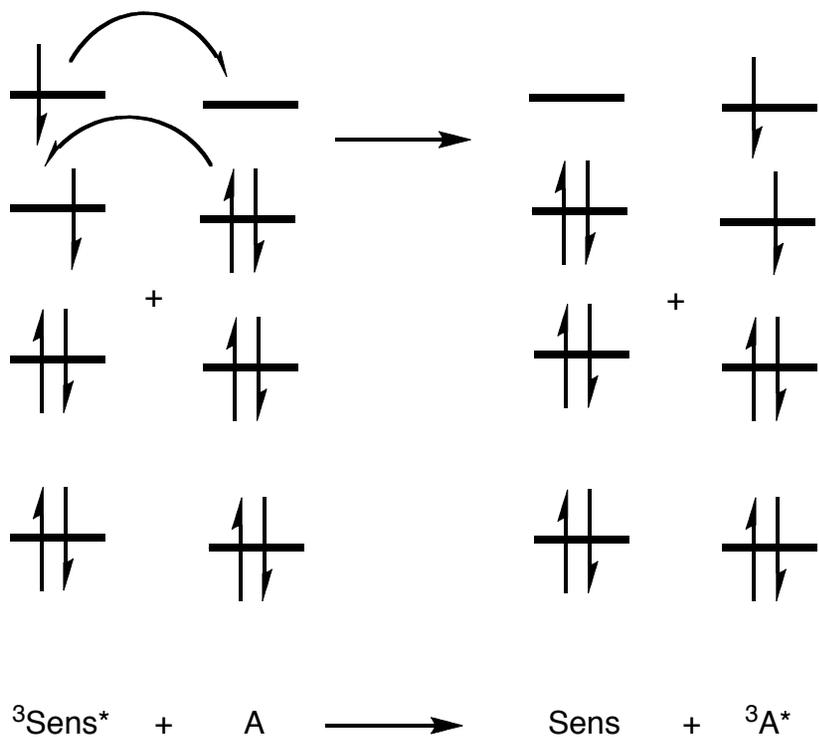


■ Singlet-excited sensitizer is both a better oxidant AND reductant. Both processes quench fluorescence

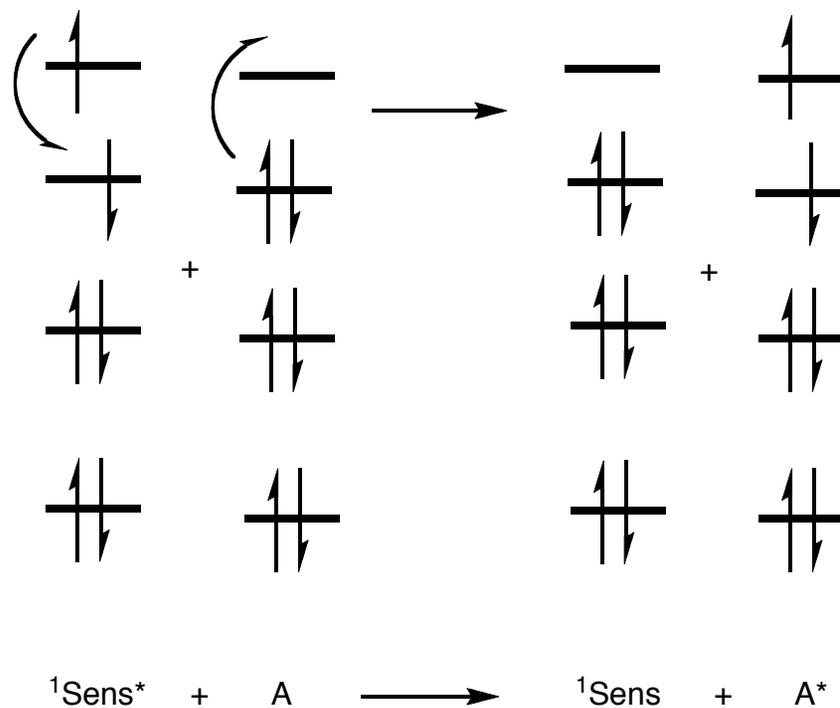
■ Triplet fluorescence quenching is known

Energy Transfer Mechanisms do not Occur Via Polar Intermediates

Energy Transfer I: Dexter Mechanism



Energy Transfer II: Forster Mechanism



Both Energy Transfer Mechanisms Require that $E(\text{excited state D}) > E(\text{excited state A})$

$k_{ee} = KJ_e^{-2} r_{DA}^{-6}$, so $r_{DA} \sim 5 - 10 \text{ \AA}$

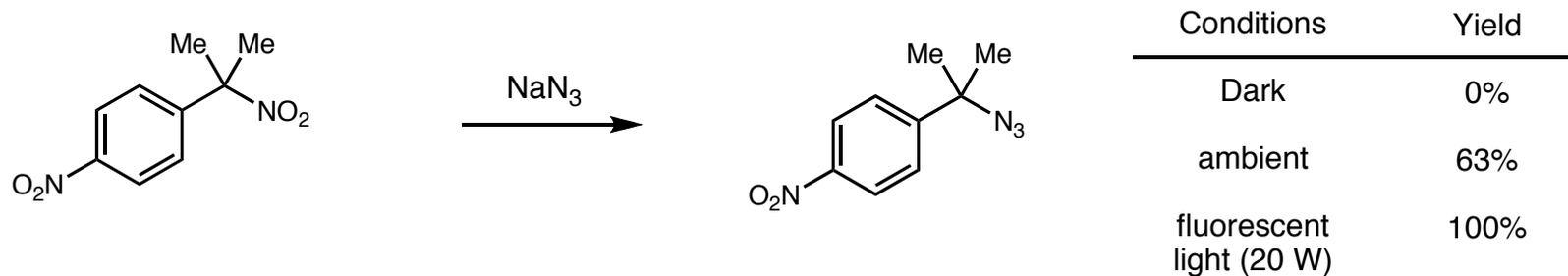
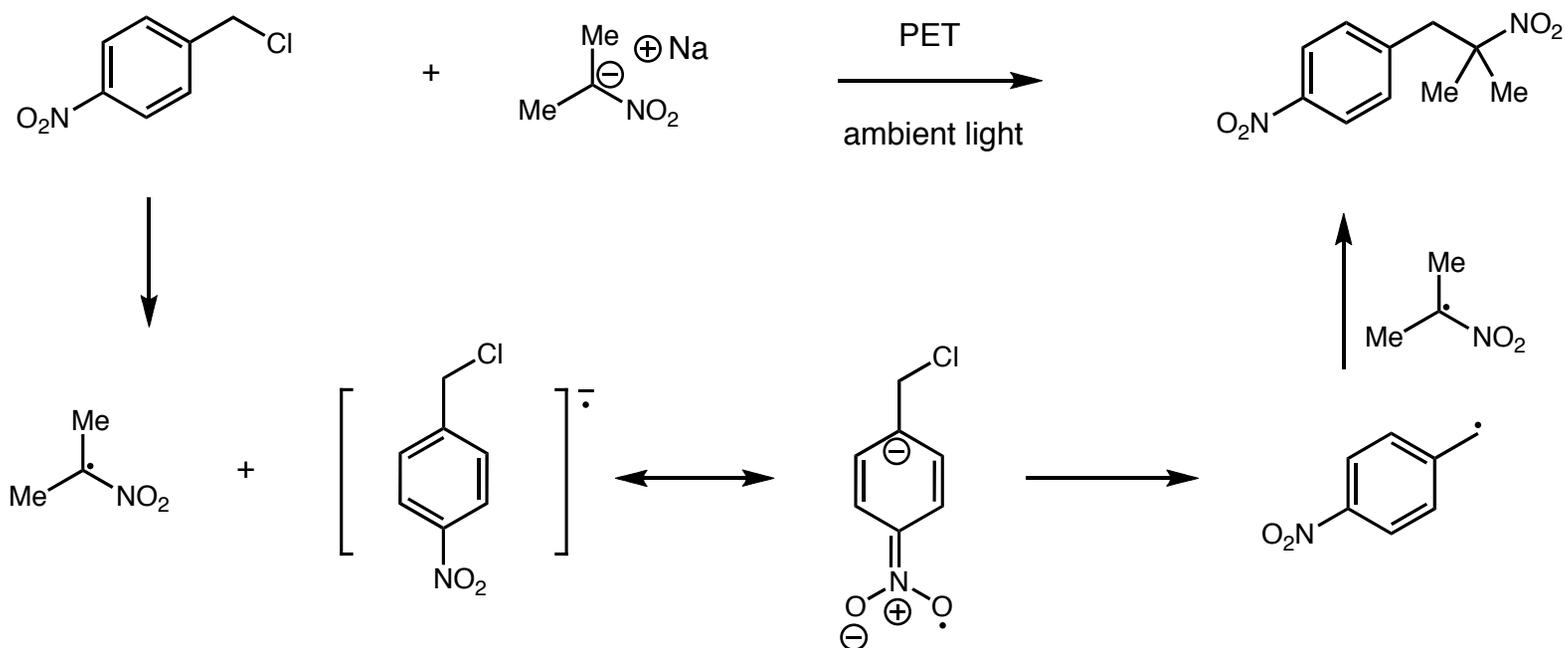
Primarily triplet sensitization

Can operate at over 50 Å via a dipole-dipole (Coulombic) mechanism (transition dipole coupling)

Basis for FRET

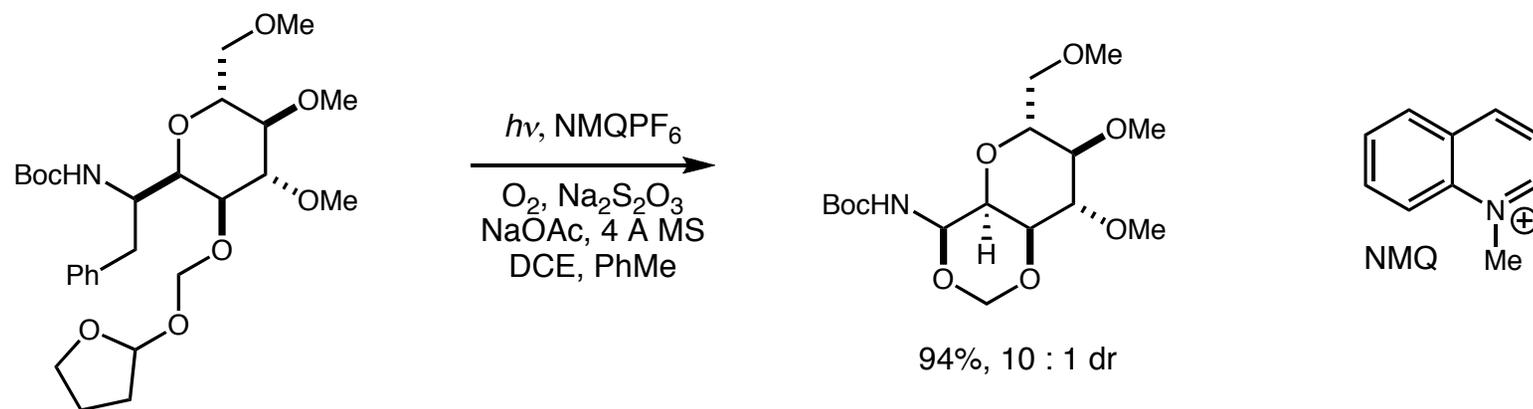
Reductive PET Bond Cleavage

- Reductive cleavage proceeds by electron transfer to benzyl halide or pseudo-halide

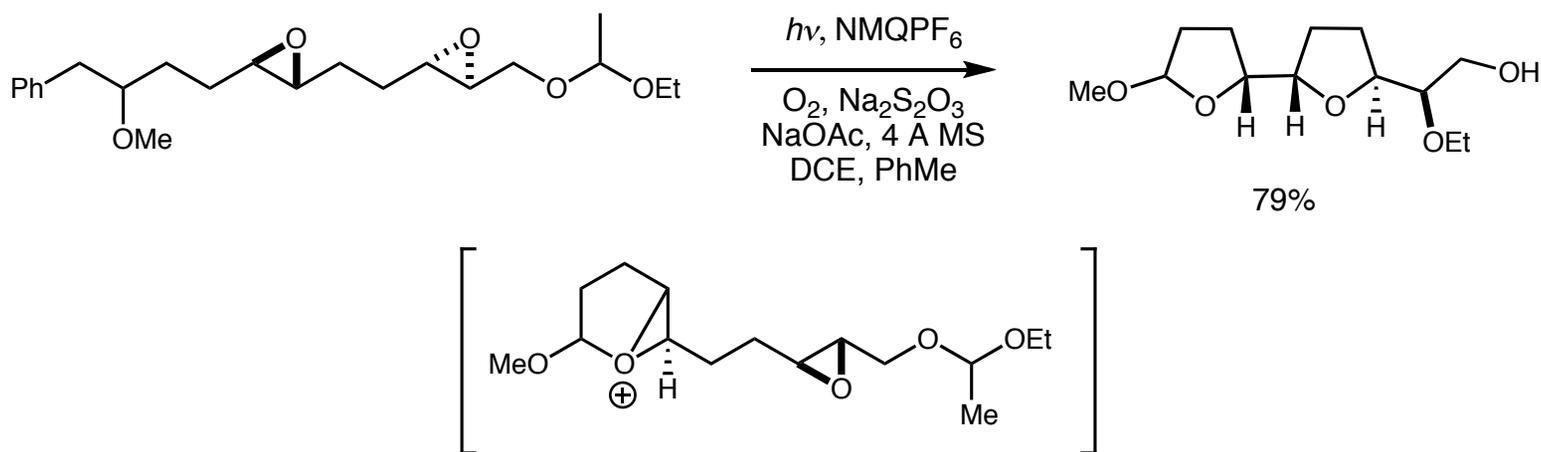


Reductive PET Reactions and Non-Halide Examples

- NBoc substituents stabilize benzylic radical formation

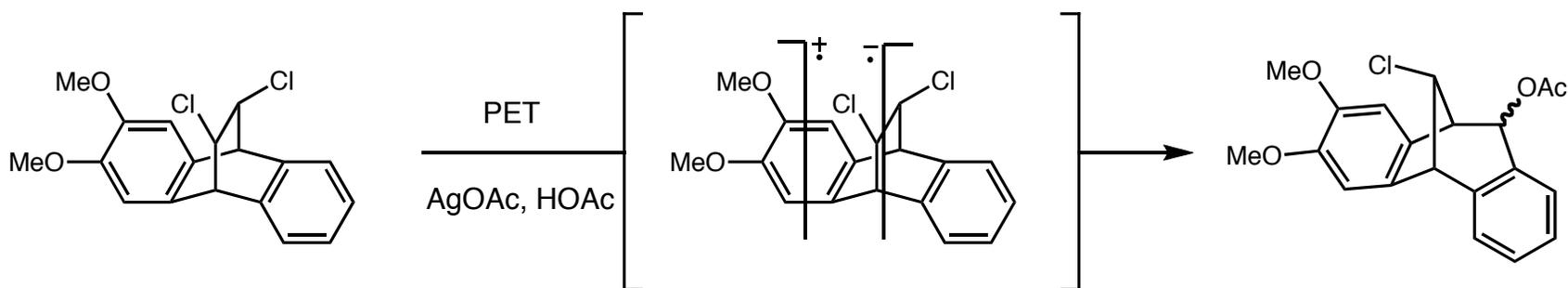


- OMe groups stabilize benzylic nucleofuges toward tandem epoxide ring openings

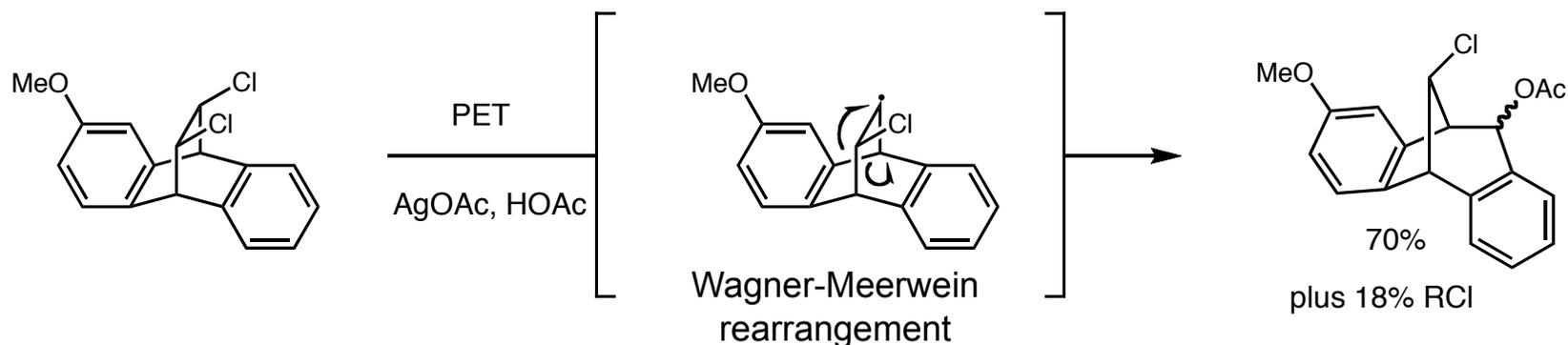


Reductive PET Bond Cleavage

- Homobenzylic chlorides also participate in reductive PET chemistry



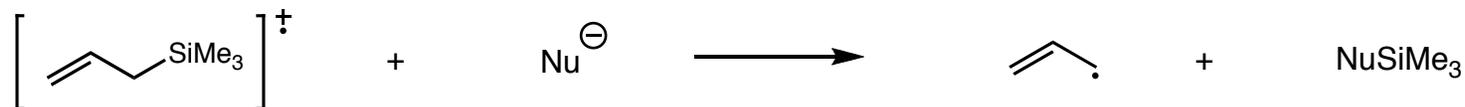
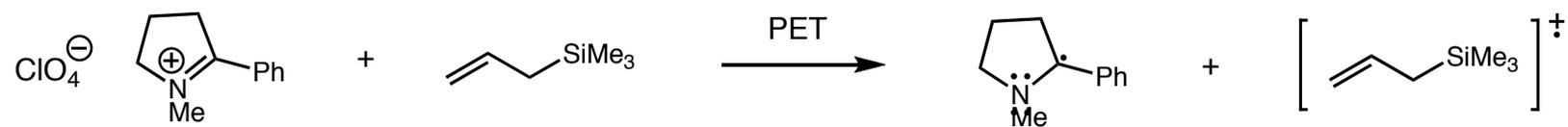
- Besides anti/syn considerations, differences occur between homopara vs. homometa C-X bonds



Cristol, S. J.; *et. al. J. Am. Chem. Soc.* **1987**, *109*, 830
Zimmerman, H.; *et. al. J. Am. Chem. Soc.* **1963**, *85*, 913; *J. org. Chem.* **1986**, *51*, 4681.

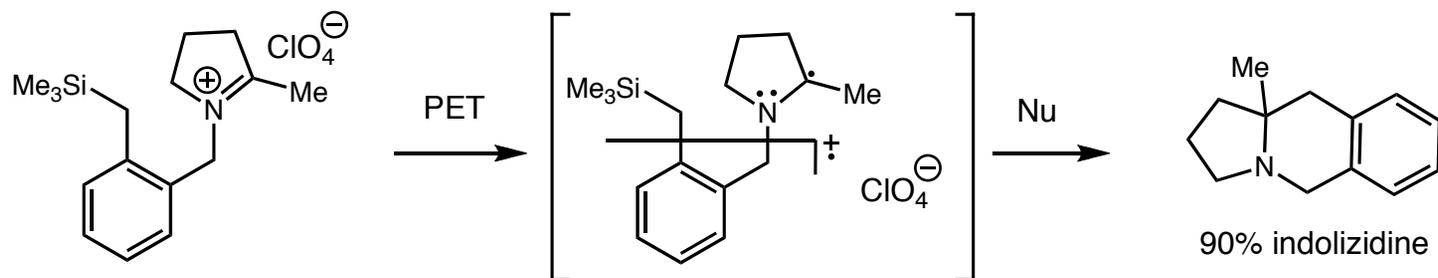
Oxidative PET Bond Cleavage

- A representative and early example of oxidative PET bond cleavage

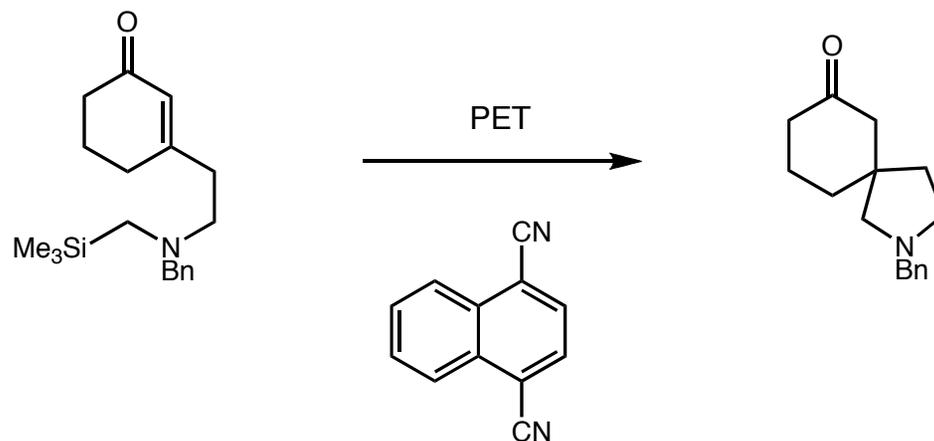


Oxidative Intramolecular PET Bond Cleavage

- Intramolecular C-C bond formation to form indolizidines



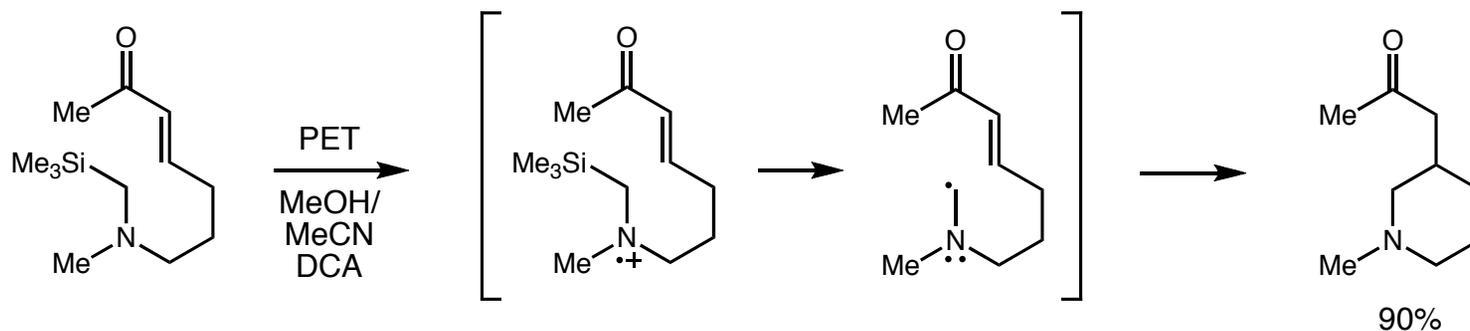
- Intramolecular organocatalytic Hiyama-type coupling



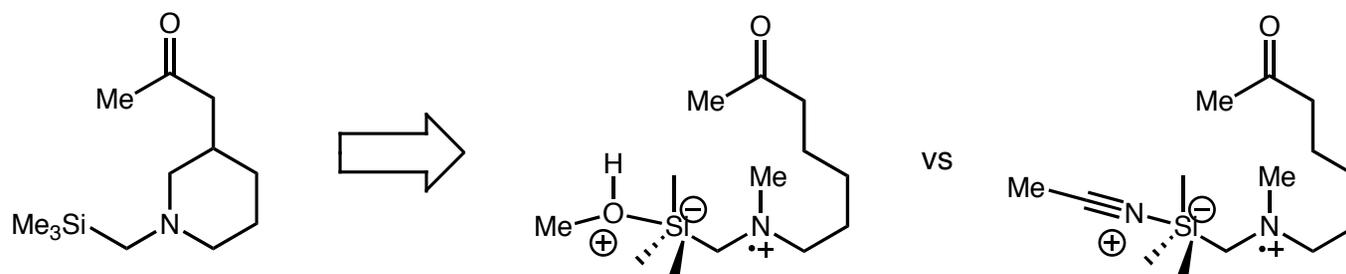
Mariano, P. S.; *et. al. J. Am. Chem. Soc.* **1984**, *106*, 6439.

- Difficult to perform this chemistry as efficiently with a non-PET approach (polar reagents)

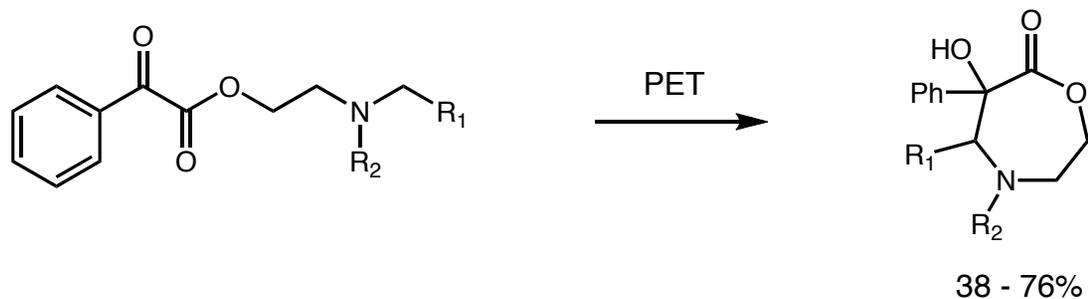
Oxidative PET Bond Cleavage



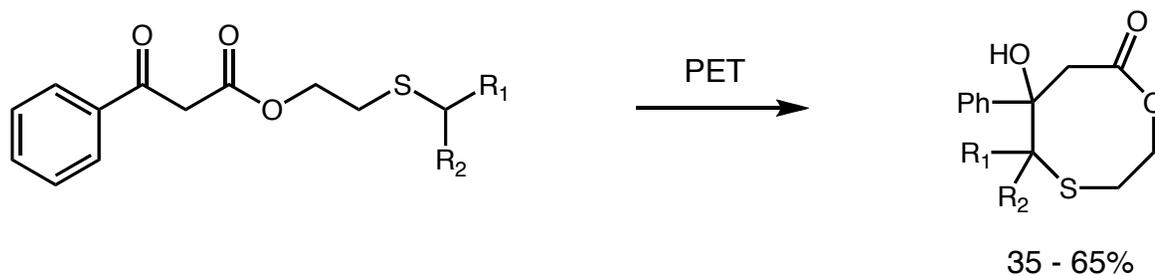
- Less polar and aprotic solvents (MeCN alone) afford product retaining silyl group



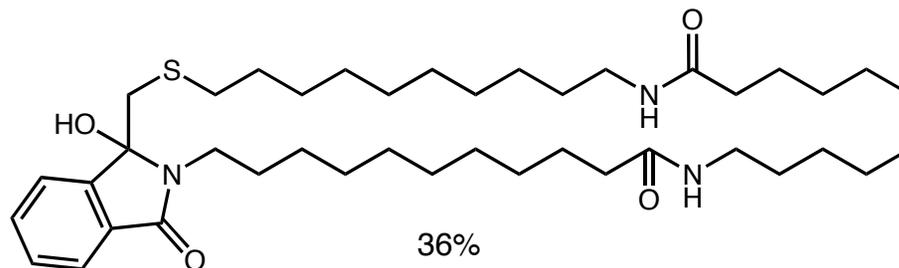
Application to Macrocyclic Ring Closures



Hasegawa, T. *Tetrahedron*, **1998**, *54*, 12223

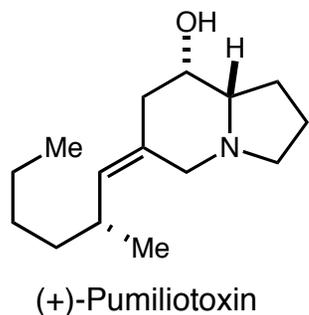


Hu, S.; Neckers, D. C. *Tetrahedron* **1997**, *53*, 2751



Application to Poison Frog Therapeutics

■ Carbohydrate-mimetic hydroxylated indolizidines

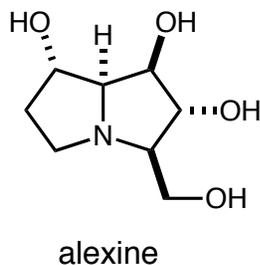


- Antidiabetics, antiviral, anticancer, immunosuppressant, transplantation medicine

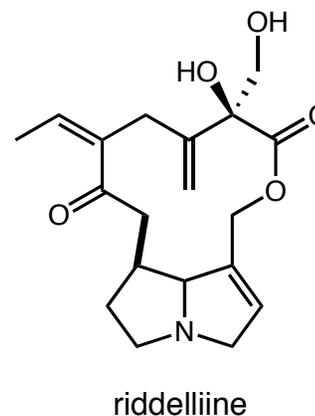


Dendrobates spp.

■ Pyrrolizidines also offer opportunities for synthetic application



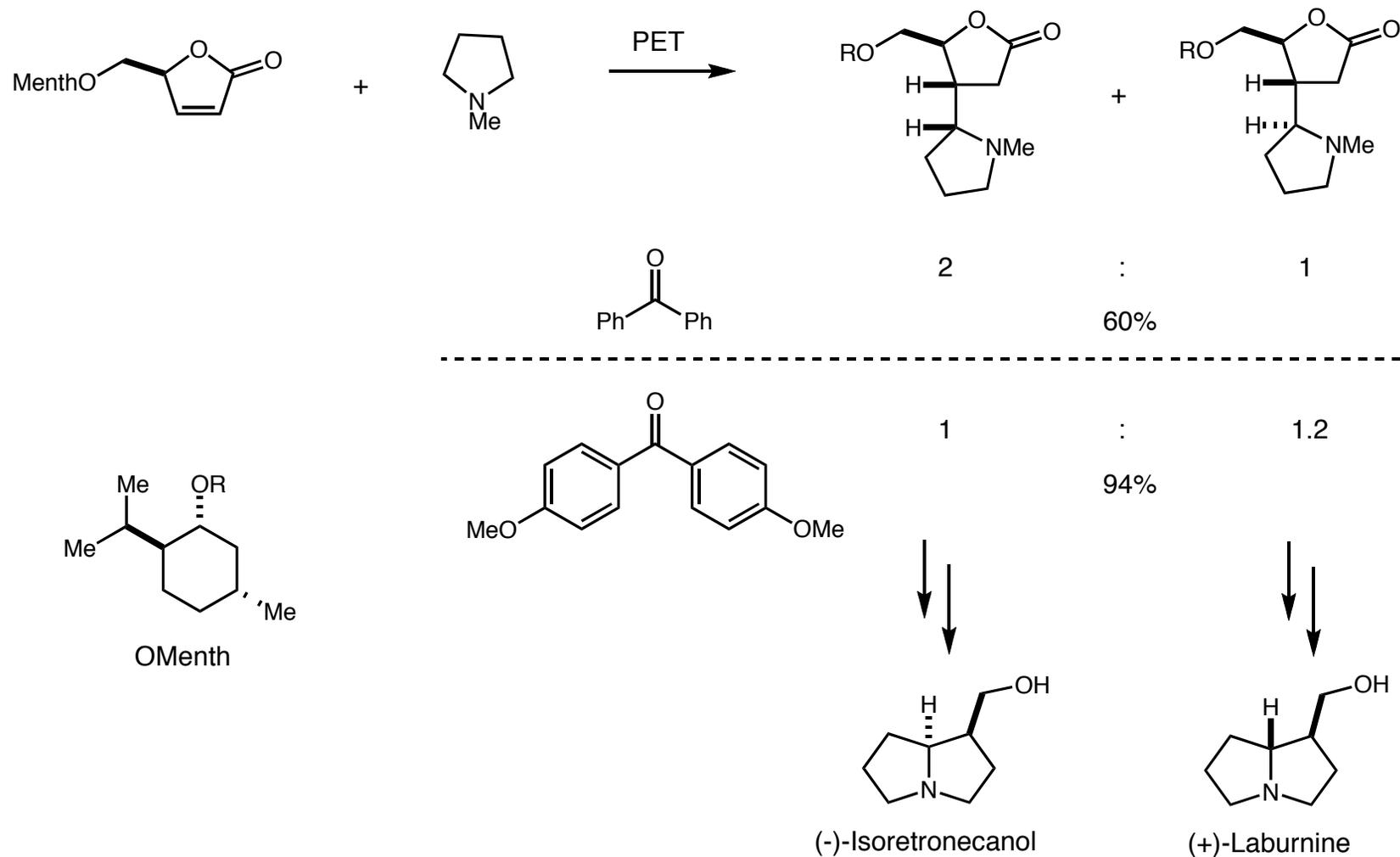
- Potent glycosidase inhibitor, antiviral, anti HIV, anticancer



- Insect defense agent

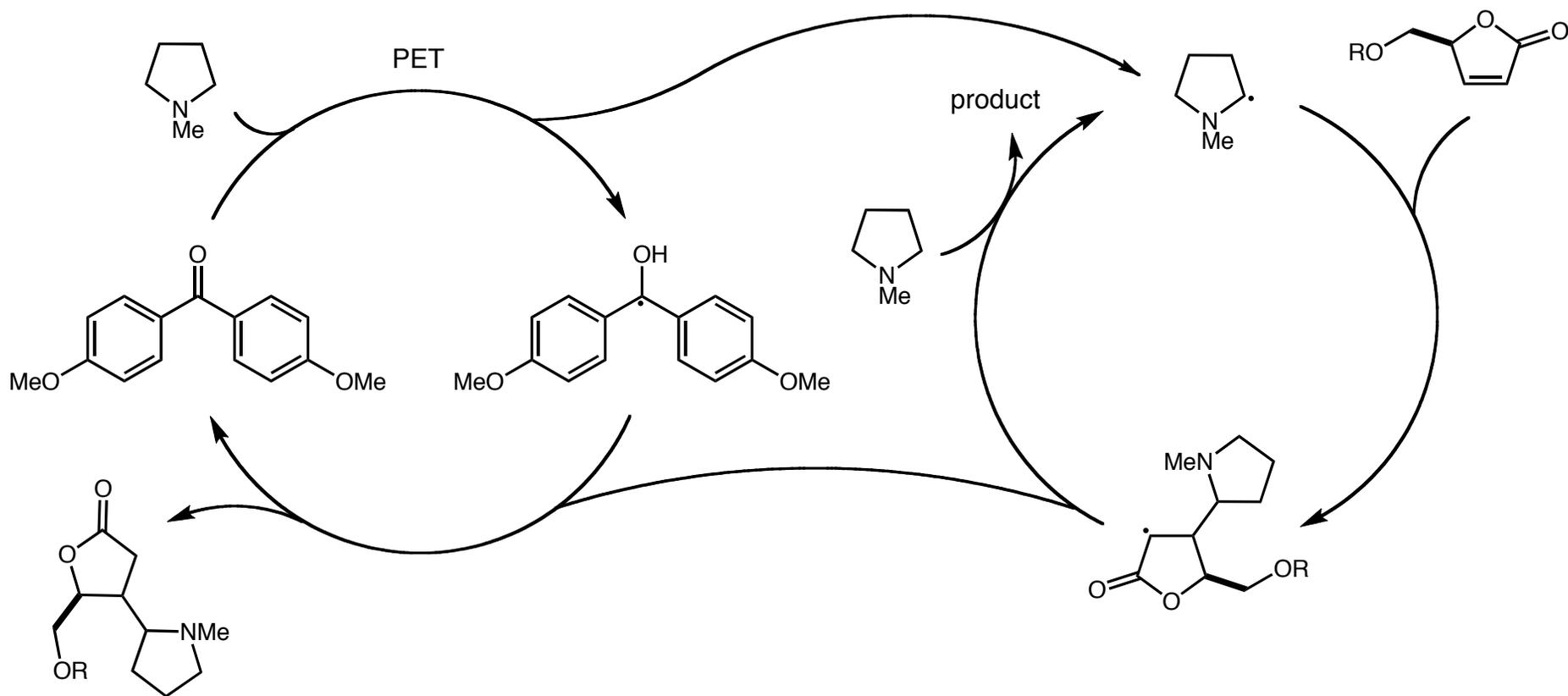
Intermolecular Non-Silylated, Simple Amino-Alkyl Additions

- Triplet sensitizers have very specific transition energies and can markedly improve reaction efficiency



Proposed Mechanism for Pyrrolidine Addition

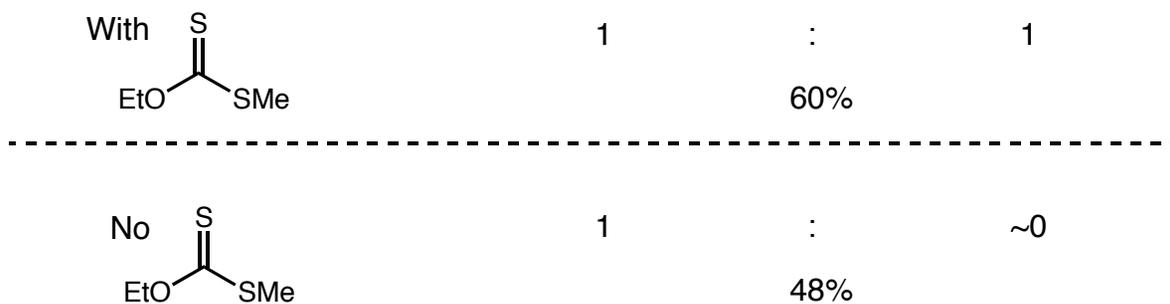
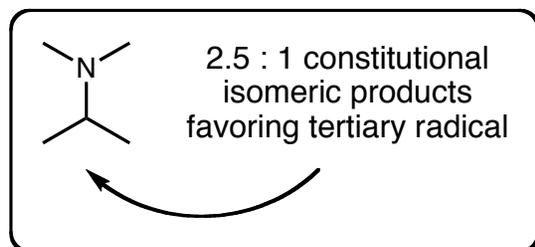
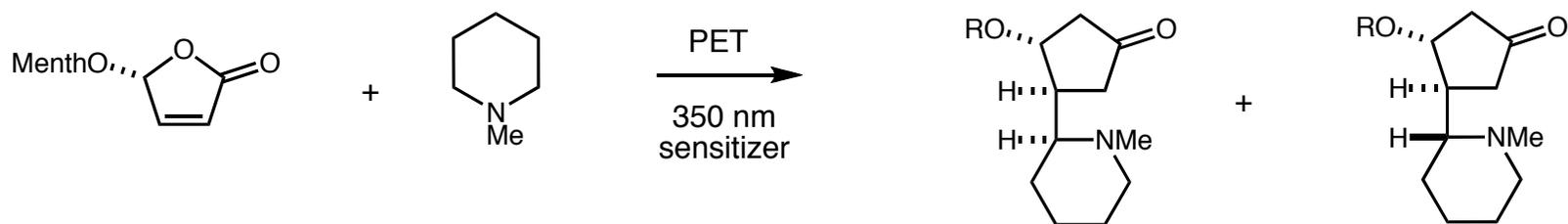
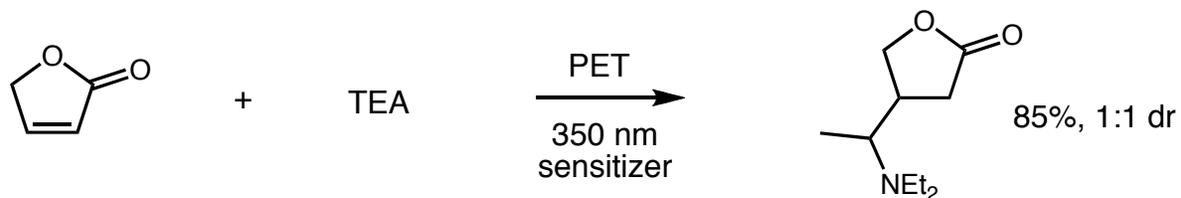
- The catalytic cycle may provide more than one opportunity for a product forming step



77 - 94%
5 examples

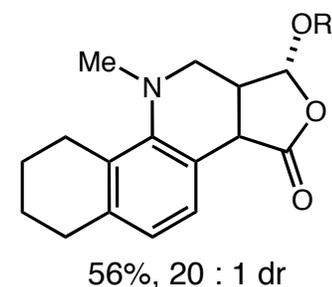
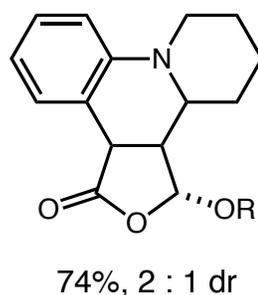
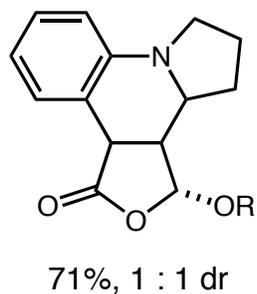
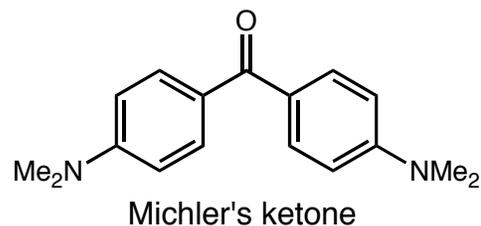
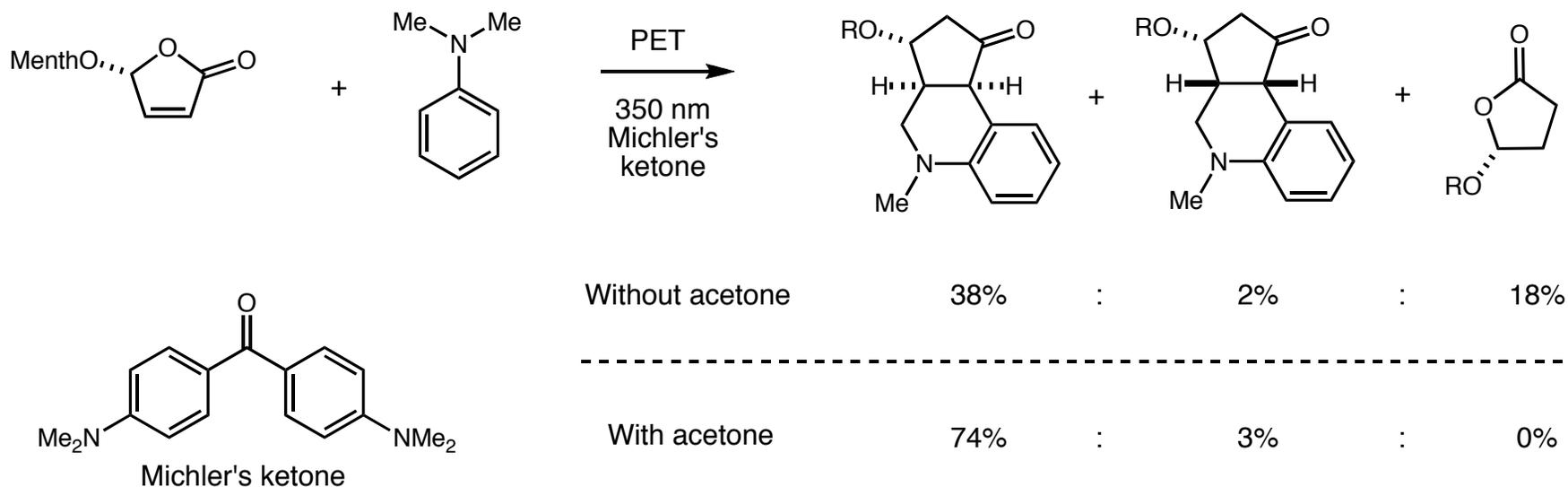
Further Development of Amine Coupling Partners

- Triethyl amine, piperidone and other amines are a viable coupling partner in PET C-C bond construction



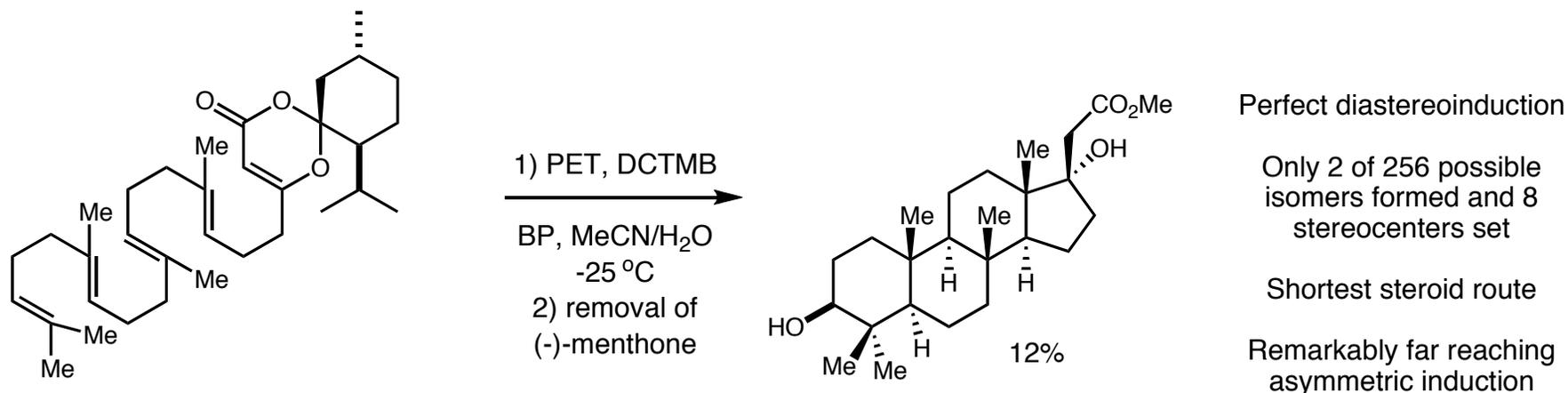
Intramolecular Trapping of Presumed Oxy-allyl Radical

- When trapping oxy-allyl radical acetone was necessary to act as benign oxidant

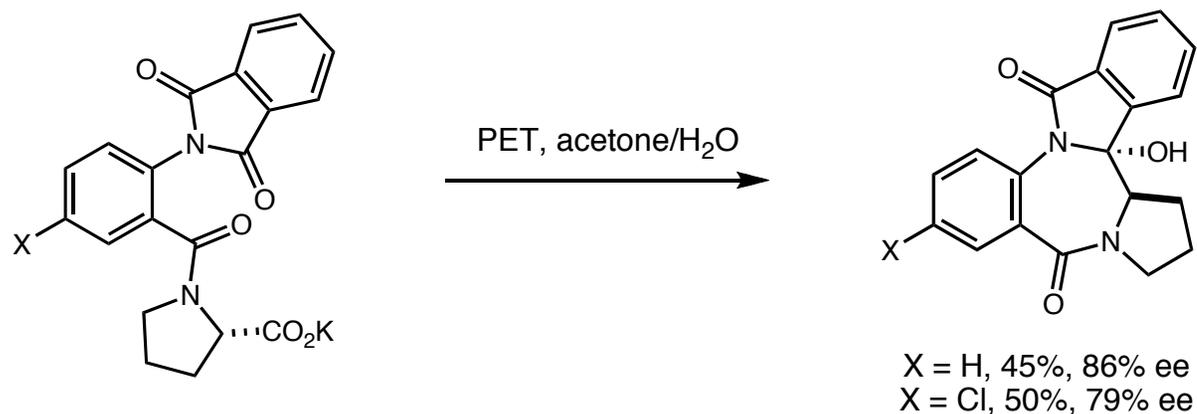


Non-Direct Methods for Enantioinduction in PET Reactions

■ Cascade cyclization of terpene polyolefins via photoinduced electron transfer



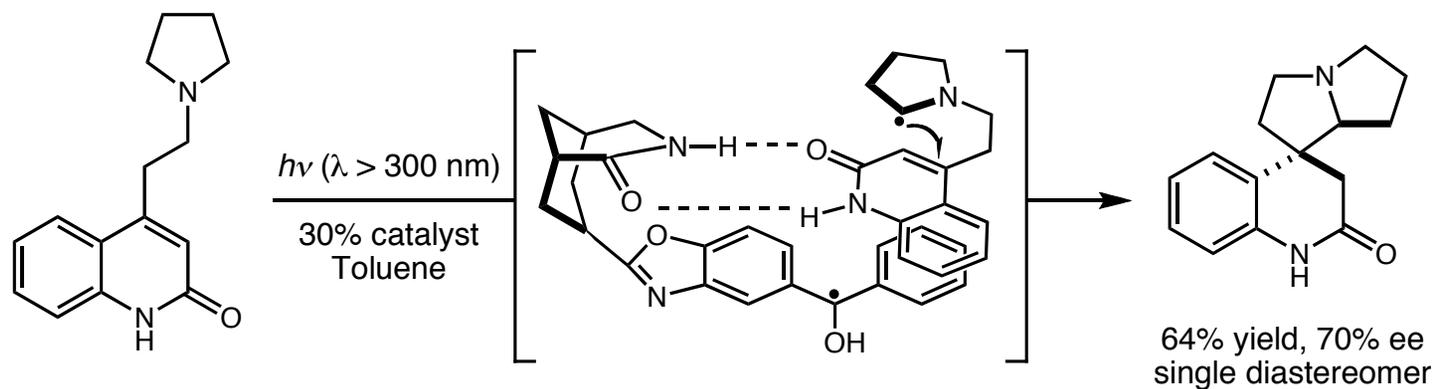
■ Memory of chirality PET study explained by rigidity of amide and aniline bonds toward rotation



With ethylene di-ortho linker: 0% ee

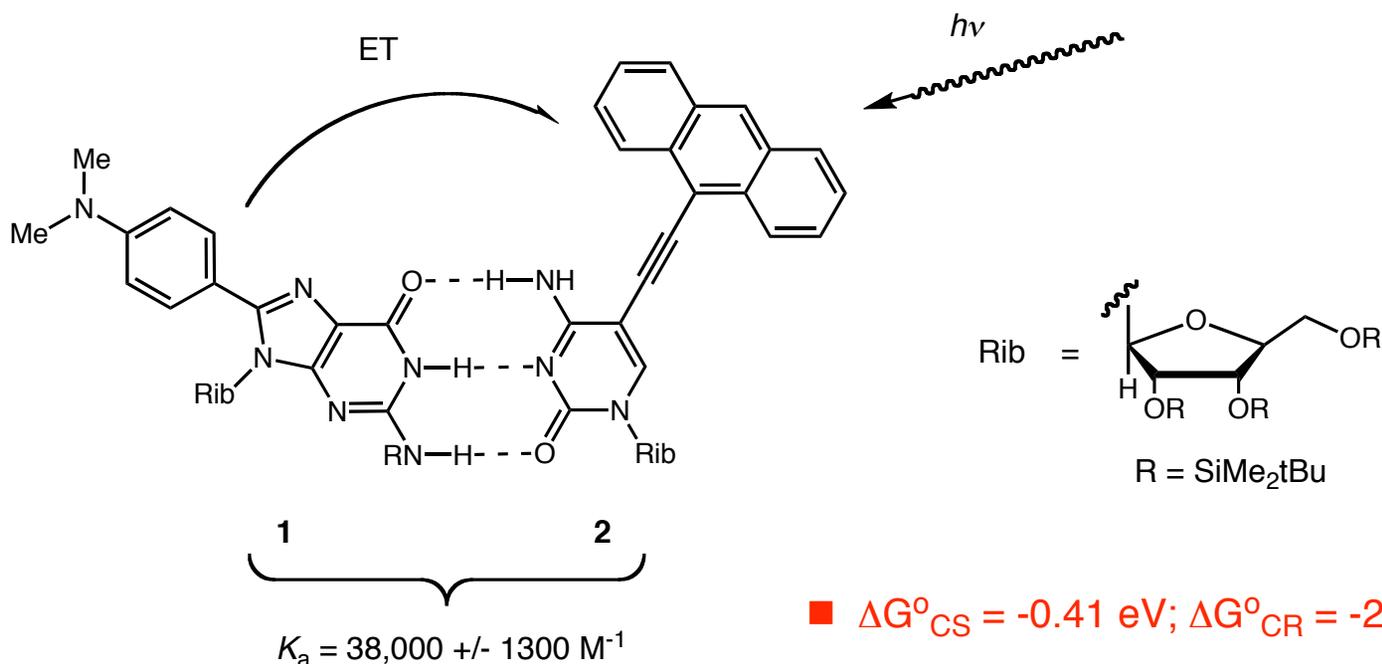
Recent Precedent for Catalytic Asymmetric PET Carbon-Carbon Bond Formation

- The Bach example is the only method thus far for a direct, catalytic, asymmetric reaction with chemical yields above 1%



Evidence Supporting the Occurrence of Charge Separation

- Why should we trust that charge separation is occurring?

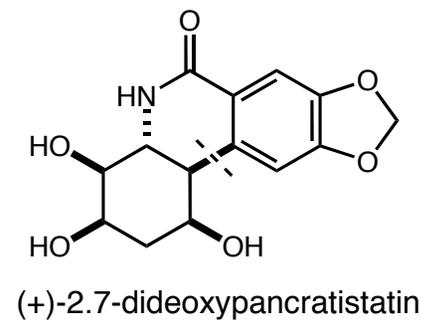
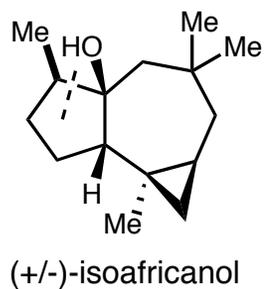
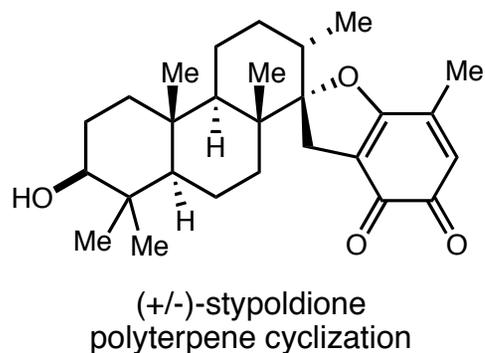
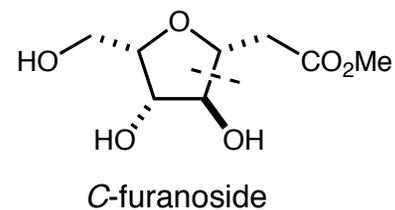
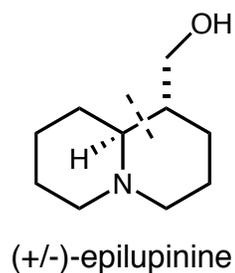
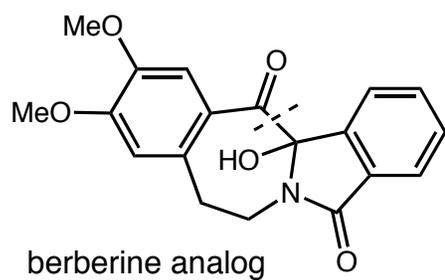
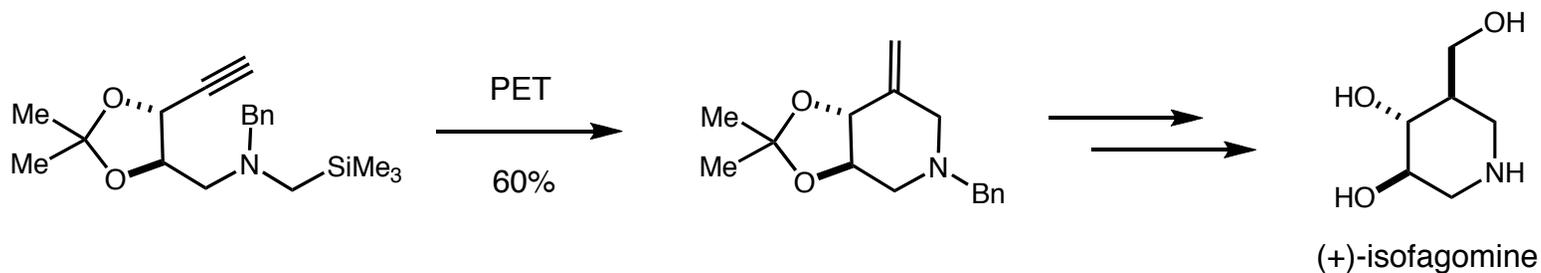


■ $\Delta G^{\circ}_{CS} = -0.41 \text{ eV}$; $\Delta G^{\circ}_{CR} = -2.5 \text{ eV}$

- 2 Fluoresces upon irradiation and is quenched upon increasing concentration of 1 in solution. This levels off at 1 molar equivalent of 1.
- Quenching of simple anthracene* fluorescence by addition of aniline only occurs at 2%.
- If masked donor (R = COCHMe₂) is used, little quenching occurs.
- Thus, diffusion controlled collisional quenching cannot be responsible for electron transfer.

PET Projects in Total Synthesis

Selected natural products formed by PET bond-constructive key steps



Conclusions

- Photoinduced electron transfer (PET) utilizing alpha-amino radicals was shown to be applicable to problem solving in organic synthesis.
- Alpha oxo- and alpha thio-radicals are also useful.
- Advantages - unique and/or expedited carbon-carbon bond construction; vastly underexploited asymmetric potential for interesting reactivity.
- Disadvantages - Limited substrate scope and/or specific wavelength for some methods.