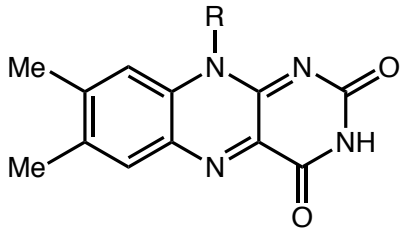
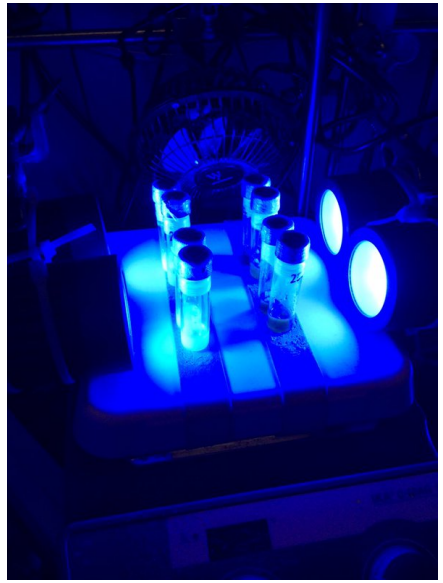
Flavins: A Bio-Inspired Approach to Photocatalysis





Group Meeting: 3/02/2017

Steven Bloom

MacMillan Group

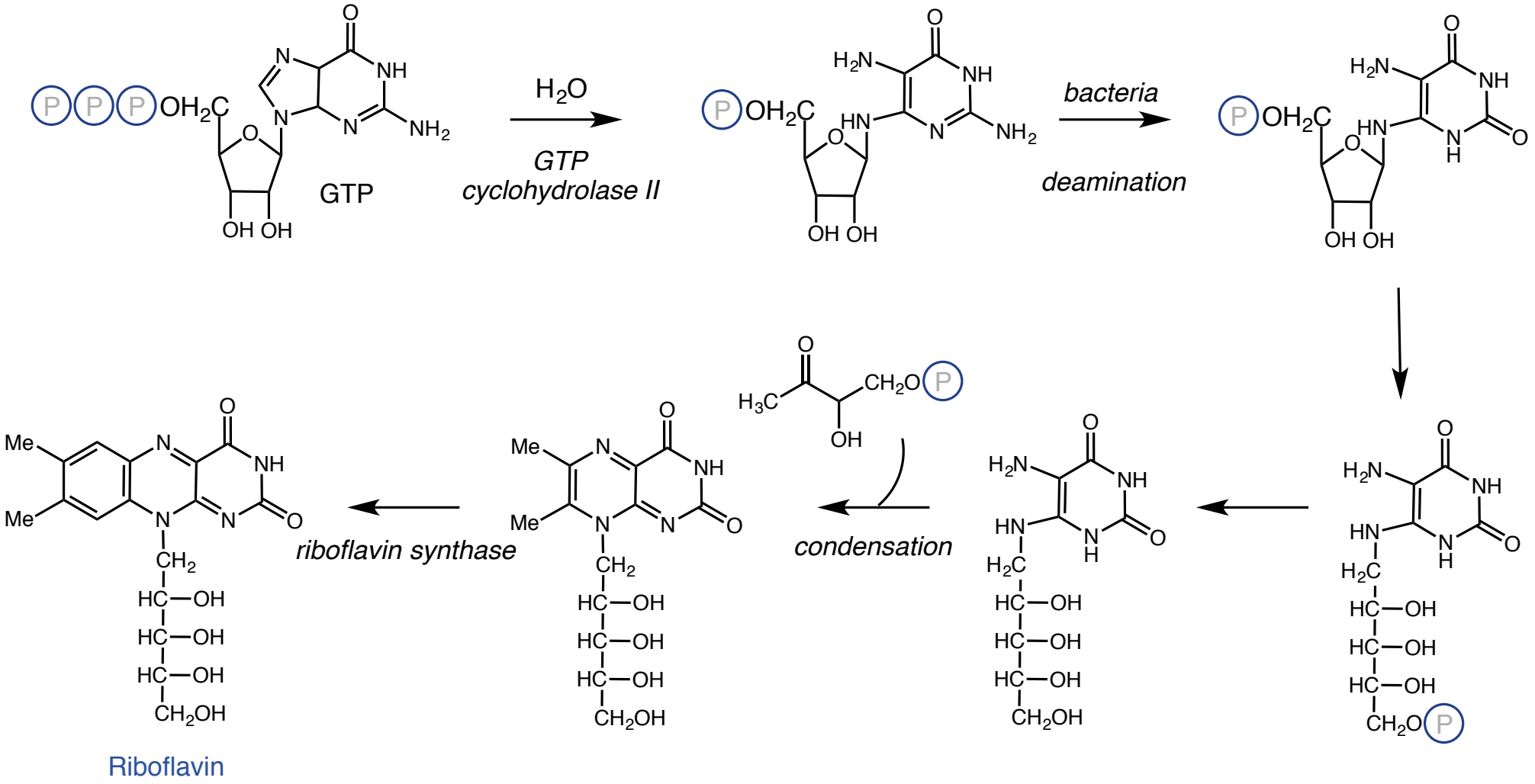
Flavins: A Bio-Inspired Approach to Photocatalysis

Outline

- Introduction to Flavins: A Brief History
- Role of Flavins in Biolgy and Basic Mechanisms
- Photophysical properties of Flavins
- Flavins in organic synthesis: Photoredox
- Oxidation
- Halogenation
- Energy transfer
- Substitution reactions

Flavins: A Bio-Inspired Approach to Photocatalysis

Riboflavin Biosynthesis



Bachner, A.; Eberhardt, S.; Fischer, M.; Kis, K.; Richter, G. *Annu. Rev. Nutr.* **2000**, *20*, 153-167.

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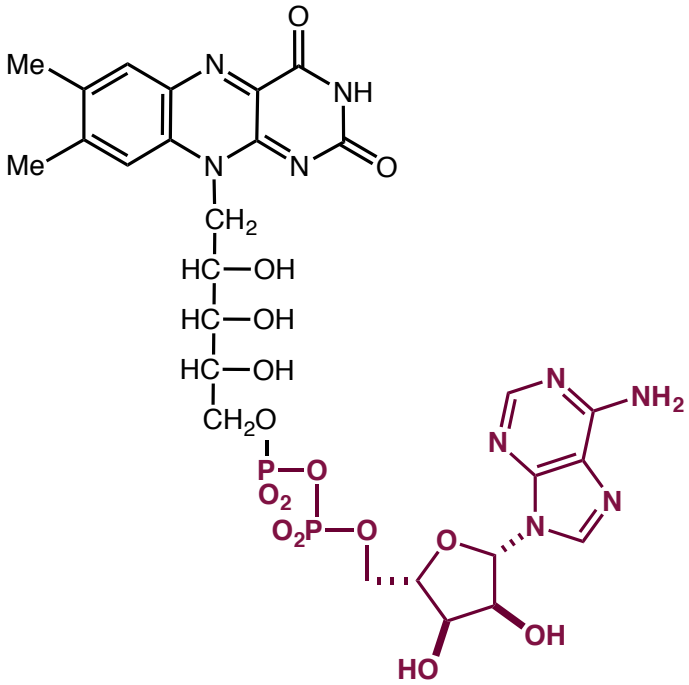
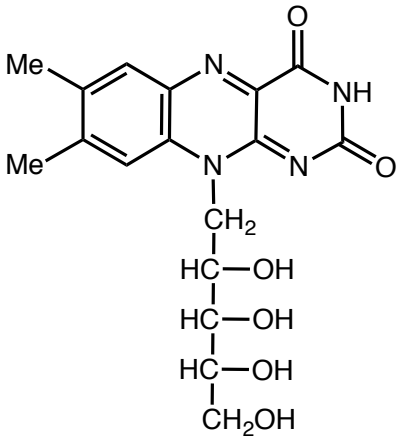
Riboflavin Biosynthesis

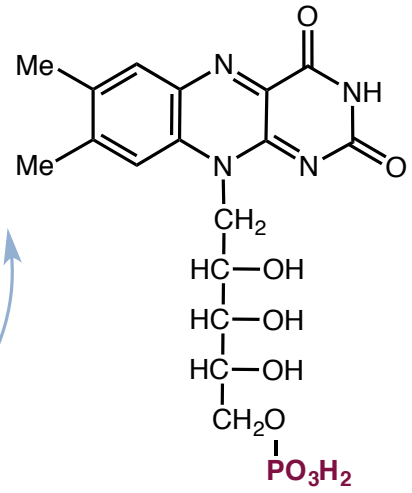
post-modification



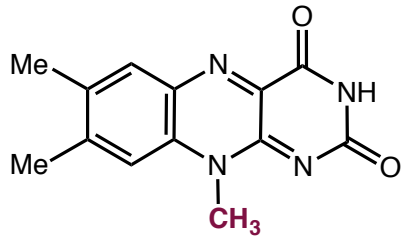
flavin adenine dinucleotide
(FAD)



Riboflavin
(vitamin B_2)



flavin mononucleotide
(FMN)



Lumiflavin
(LF)

Bachner, A.; Eberhardt, S.; Fischer, M.; Kis, K.; Richter, G. *Annu. Rev. Nutr.* **2000**, *20*, 153-167.

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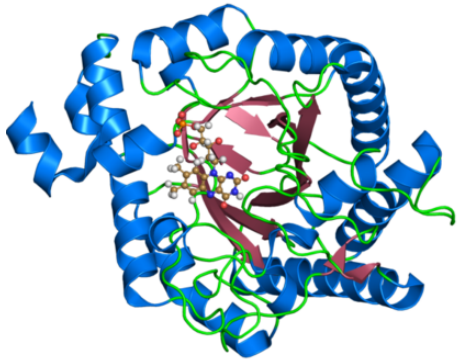
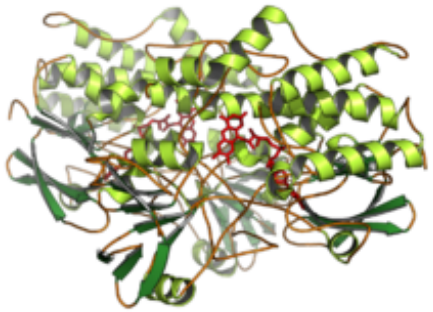
Flavoproteins

flavodoxin



old yellow enzyme



yeast FMO

EpiD

- FAD first isolated in 1879 from bovine milk
- FAD structure determined in 1934
- 90 Flavoproteins found in the human genome
- 84% contain FAD and 16% FMN
- located in the mitochondria
- 90% perform redox reactions, 10% are transferases, lyases, isomerases, and ligases

Ghisla, S.; Massey, V. *J. Biochem.* **1986**, *239*, 1-12.
Fraaije, M. W.; Mattevi, A. *Trends Biochem. Sci.* **2000**, *25*, 126-132.

Flavins: A Bio-Inspired Approach to Photocatalysis

Conference
19th International Symposium on Flavins and Flavoproteins
Organised by RUG
Date Sun 2 July 2017 until Thu 6 July 2017
Venue Groningen

Newly discovered flavoproteins

Flavin-based chemistry

Flavoenzyme mechanisms & structures

Flavoenzyme engineering

Flavoproteins & light

Flavoenzymes & health

Flavoenzymes & industrial applications

Flavins: A Bio-Inspired Approach to Photocatalysis

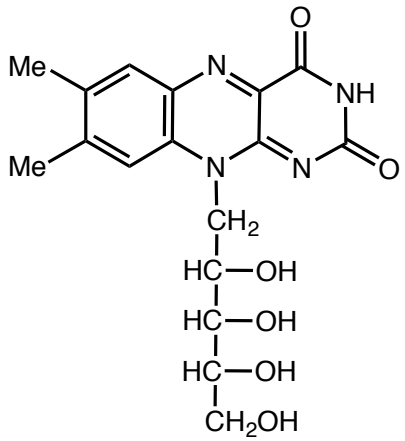
Riboflavin Biochemistry

- break down fats and carbohydrates
-provides electrons for electron transport chain

metabolism

-activates Cyt P_{450} for drug metabolism

drug processing



Riboflavin

(vitamin B_2)

antioxidant

-neutralizes reactive oxygen species directly
-activates glutathione reductase

photochemical processes

-circadian rhythms
-phototropism
-phototaxis

Hemmerich, P.; Nagelschneider, G. *F.E.B.S. Lett.* **1970**, *8*, 69-83.

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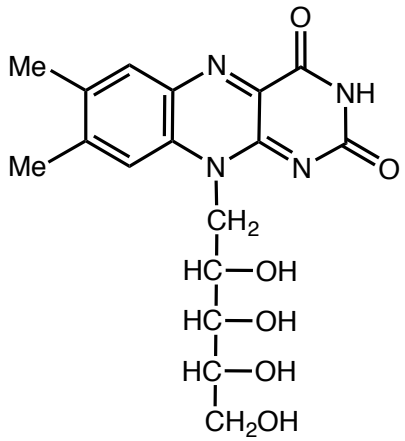

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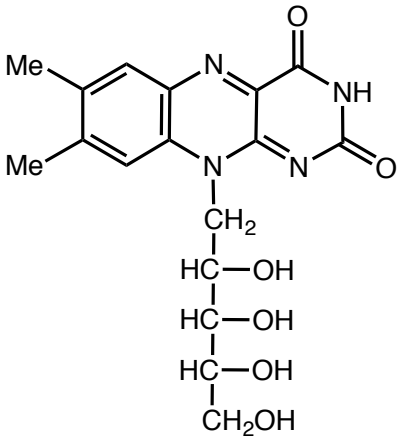

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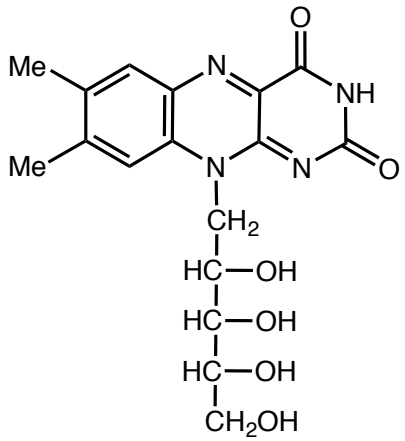

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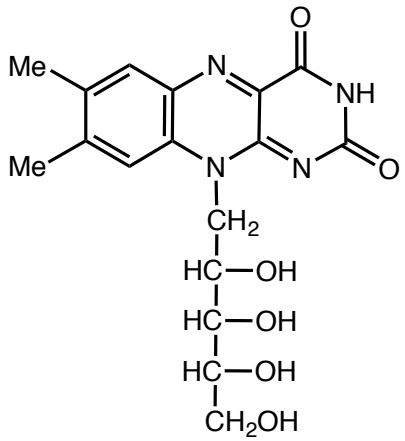

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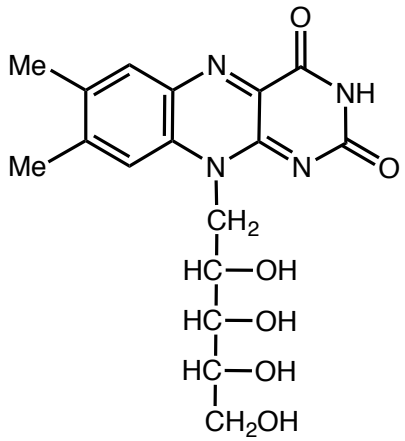
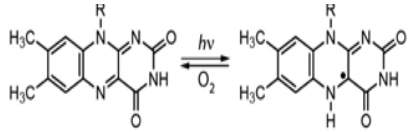
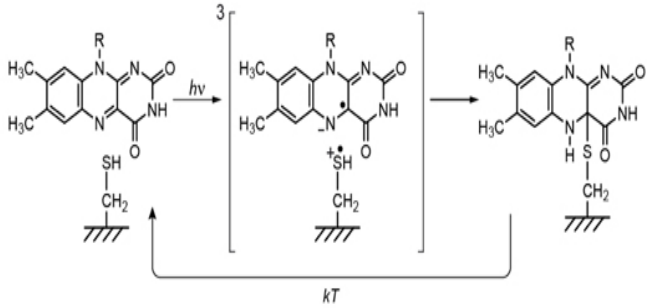


Riboflavin
(vitamin B_2)

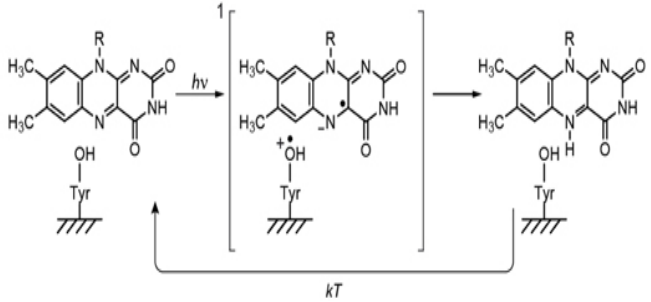
cryptochromes



LOV domains



BLUF domains



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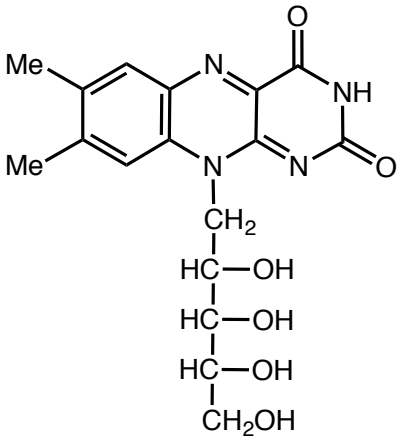
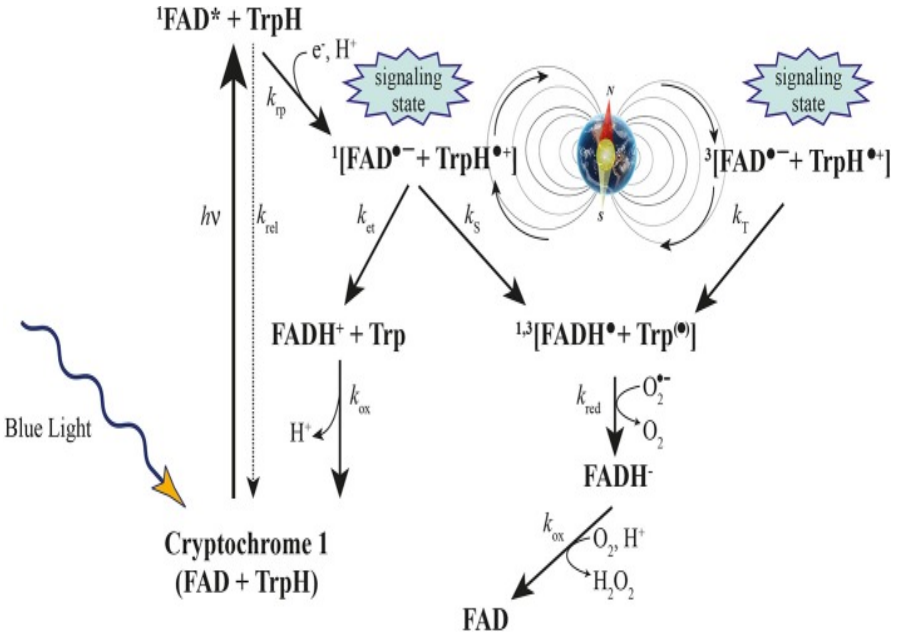


Riboflavin
(vitamin B_2)



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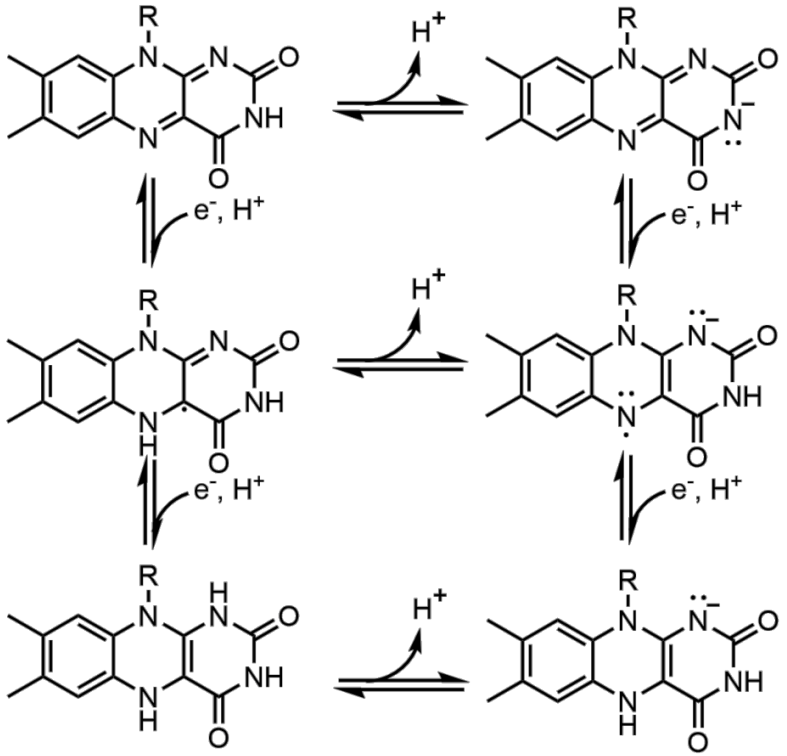

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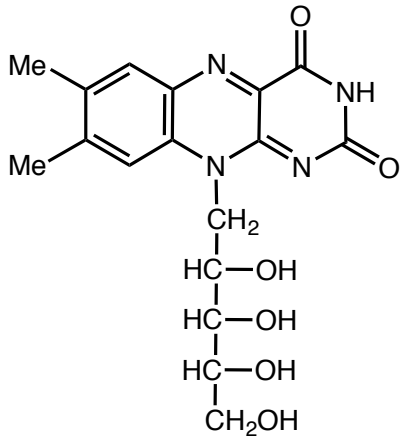
Riboflavin Photochemistry



Riboflavin

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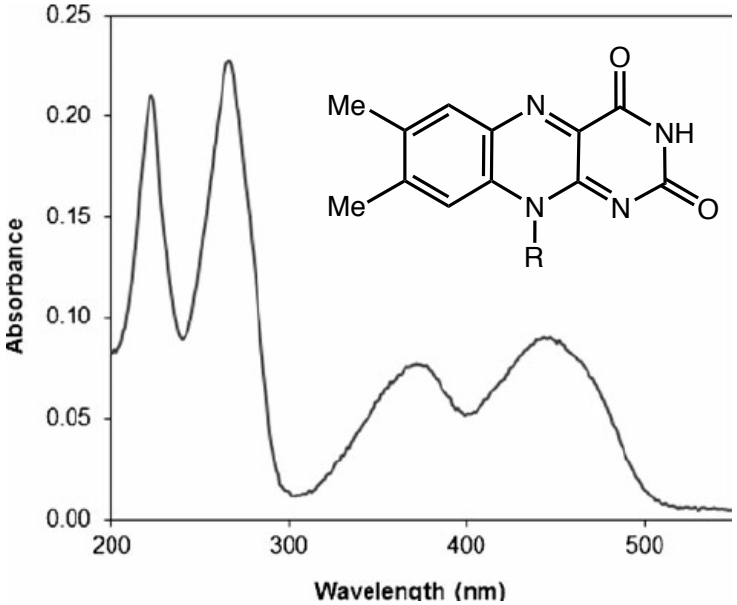

Halwer, M. *J. Am. Chem. Soc.* **1951**, *73*, 4870-4874.

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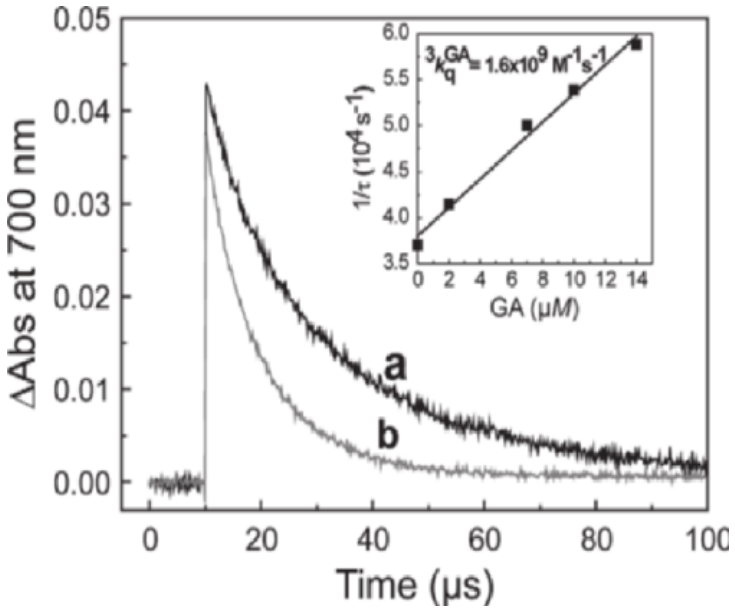
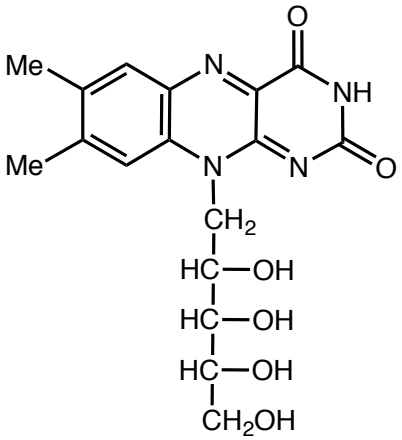


^{1}Riboflavin* $\xrightarrow[0.67]{\Phi_{ISC}}$ ^{3}Riboflavin*

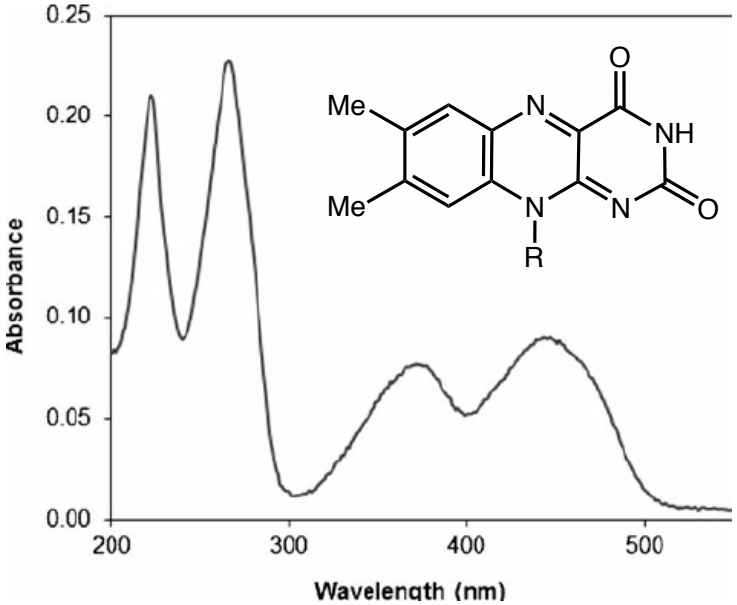
^{3}RF*= 15 μs

Riboflavin Photochemistry



Riboflavin

(vitamin B_2)



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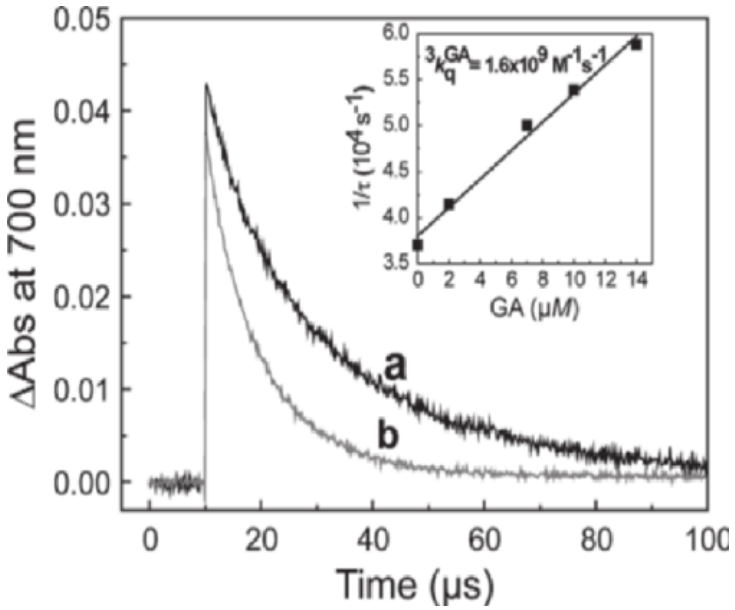
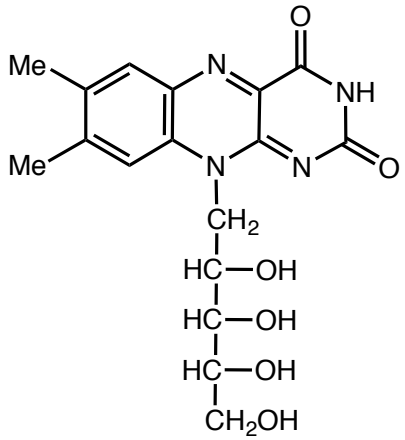


Riboflavin Photochemistry



Riboflavin
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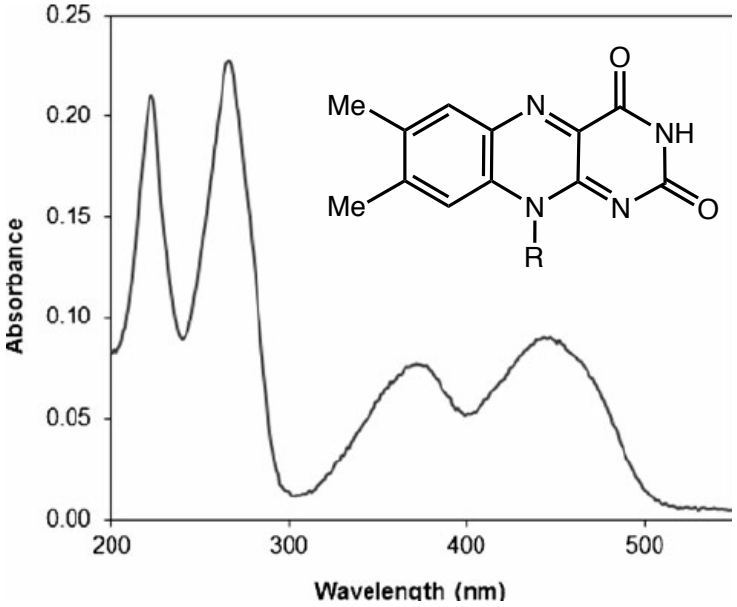
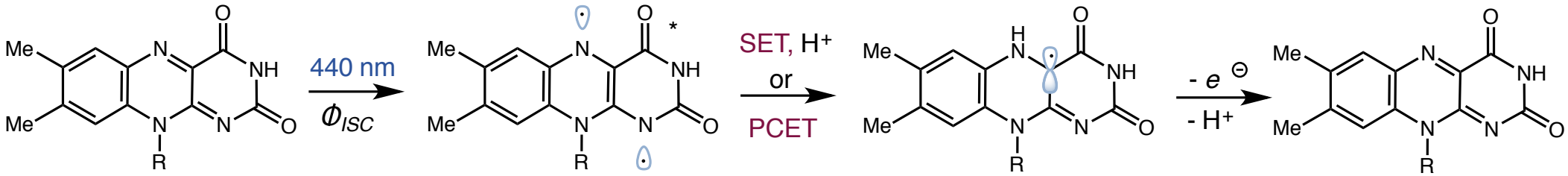


^{1}Riboflavin* $\xrightarrow[0.67]{\Phi_{ISC}}$ ^{3}Riboflavin*

^{3}RF*= 15 μs

pk_a of $RF^{\cdot\ominus}$ = 8.3



$^3RF^*/RFH^{\cdot}$ = 1.5 V

$RFH^{\cdot}/RF$ = -0.5 V

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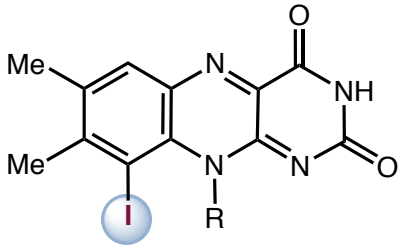


SET to S_1 (unproductive, ~ 50 ps)

SET to T_1 (productive, ~ 15 μs)

heavy element substitutuion inreases S_1 to T_1 $_{ISC}$ by spin-orbit coupling

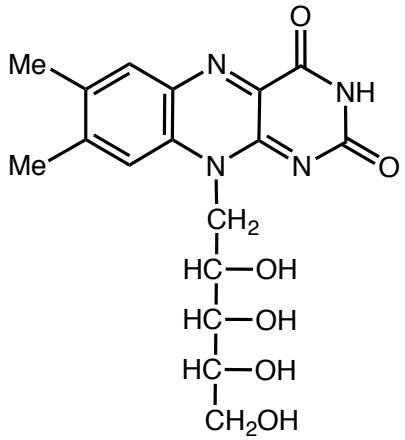
(100 x faster)

increases oxidation potential

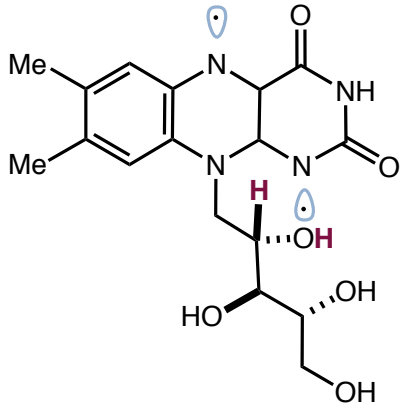
RF = 1.5 V ($_{ISC}$ = ns), ^{3}RF* = 15.0 μs

IRF = 1.65 V ($_{ISC}$ = ps), ^{3}RF* = 5.8 μs

Riboflavin Photochemistry

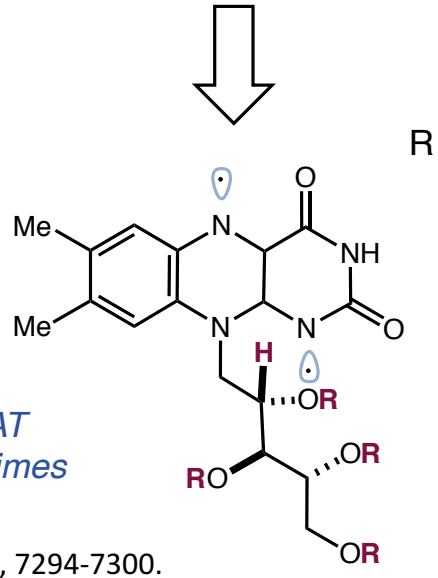


Riboflavin
(vitamin B_2)



intramolecular HAT from T_1 competes with SET

HAT from OH is 2x faster than α-C-H



R = OAc
= OBu

acylation prevents HAT and increases T_1 lifetimes

Korvinson, K. A.; Hargenrader, G. N.; Stevanovic, J.; Xie, Y.; Joseph, J. Maslak, V.; Hadad, C. M.; Glusca, K. *J. Phys. Chem.* **2016**, *120*, 7294-7300.

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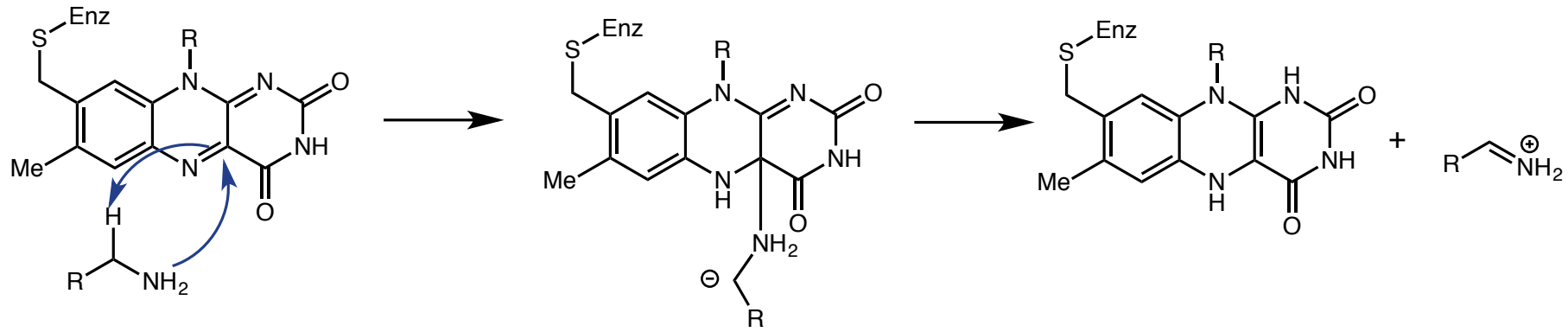
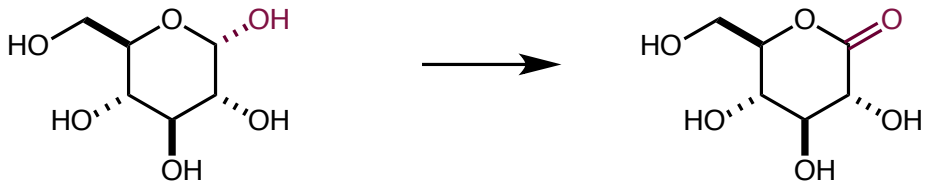
Riboflavin Mechanisms

Monoamine oxidase (MAO)



Glucose oxidase



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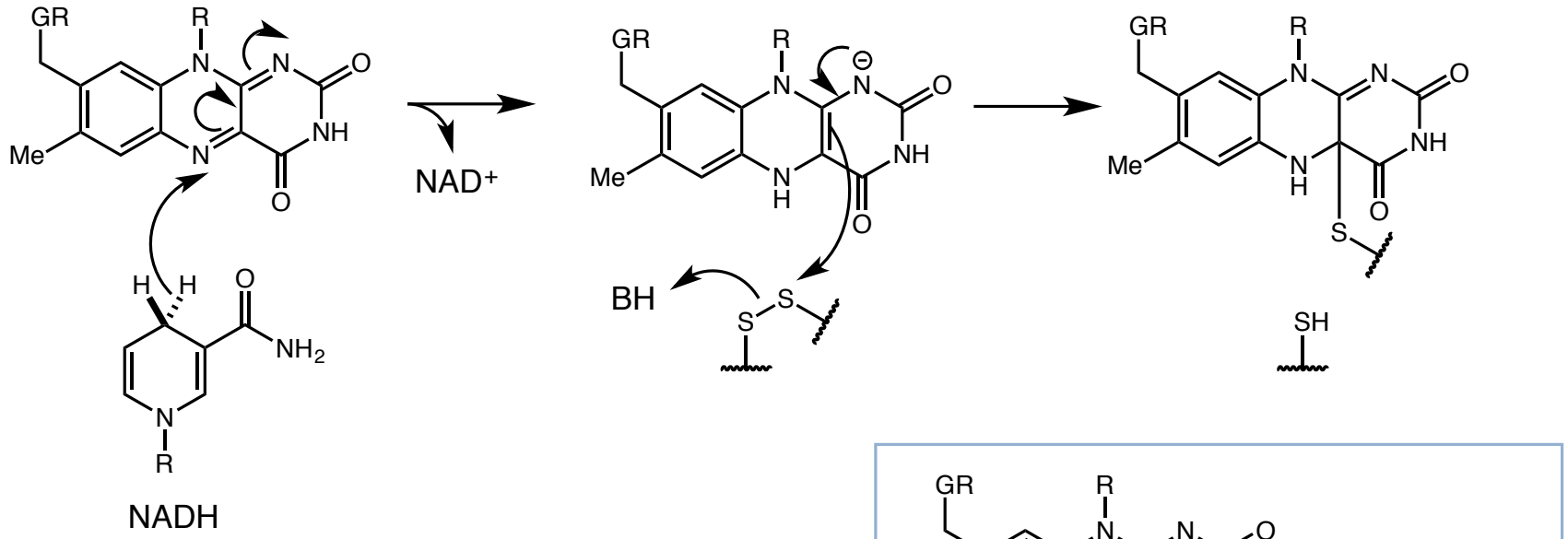
Riboflavin Mechanisms

Glutathione reductase



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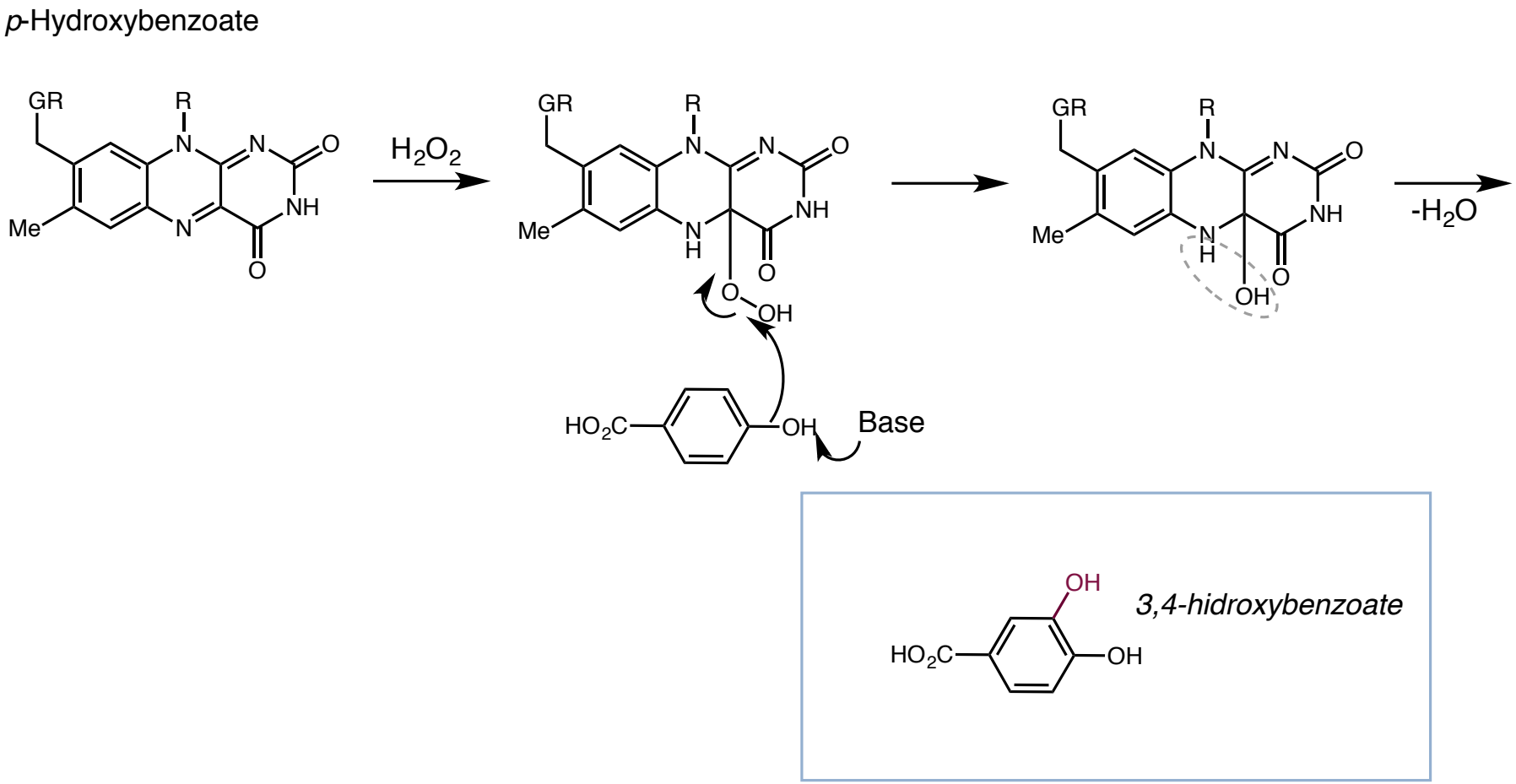

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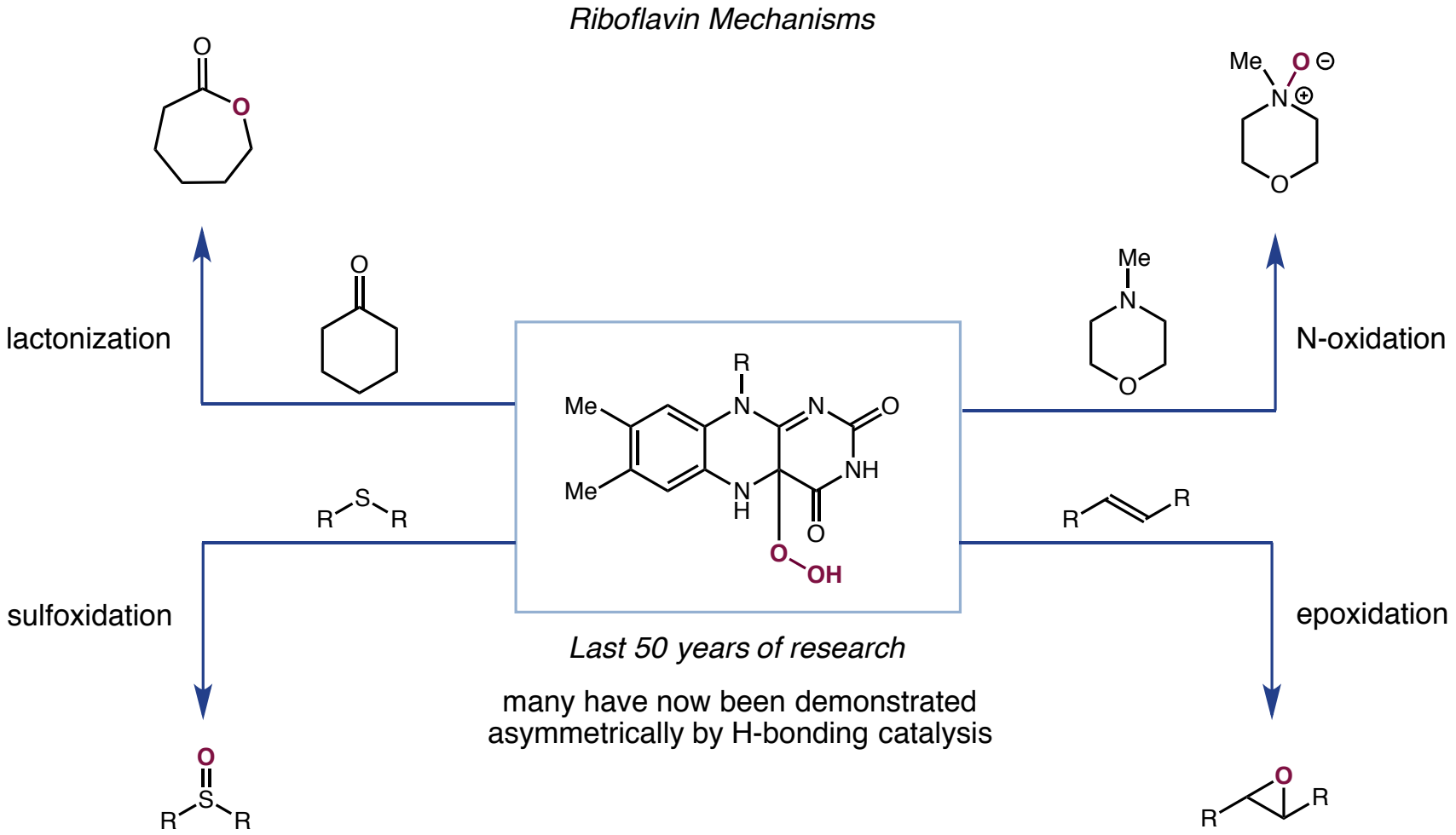

Massey, V. *J. Biol. Chem.* **1994**, *269*, 22462-22462.

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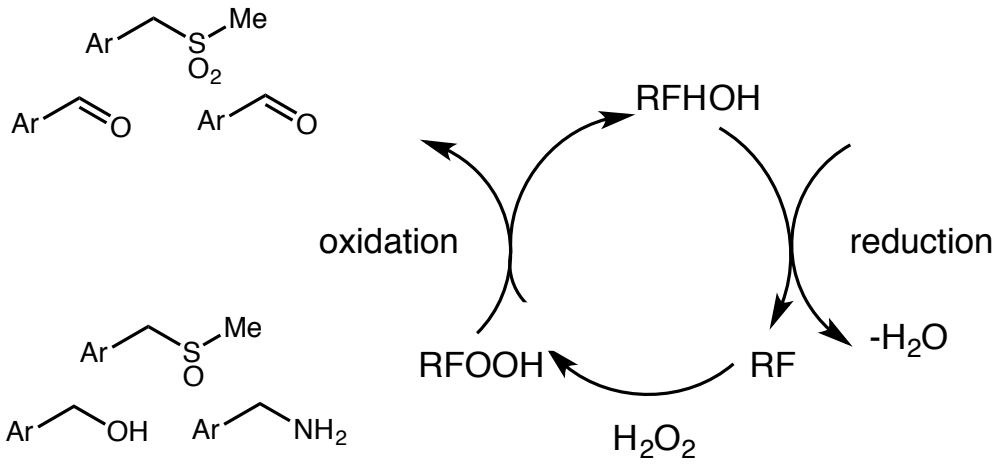
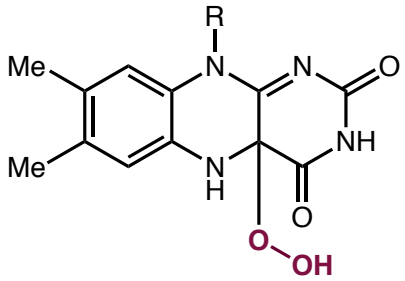
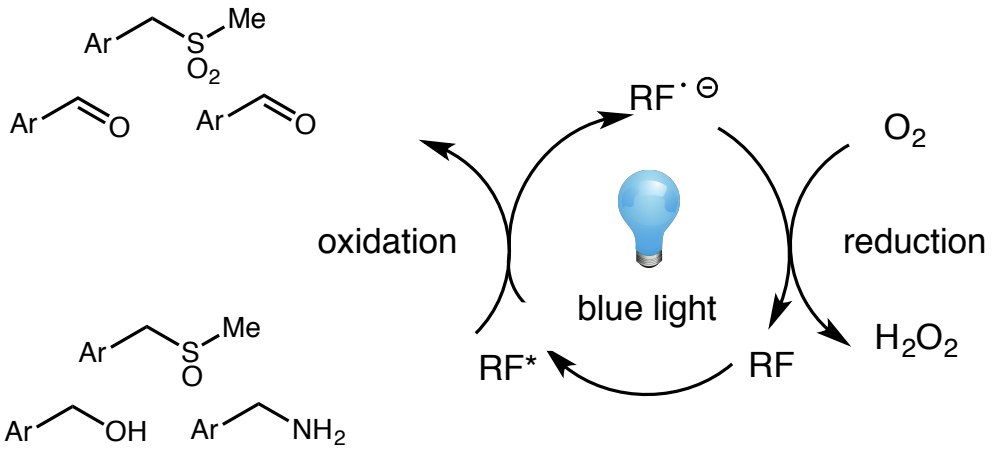


SLOW REACTION

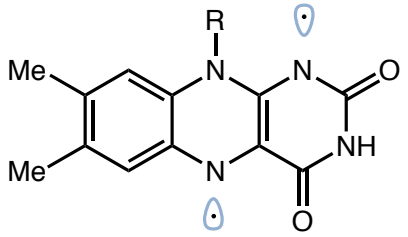


RF

flow of $2e^-$ and $2H^+$



FAST REACTION



RF

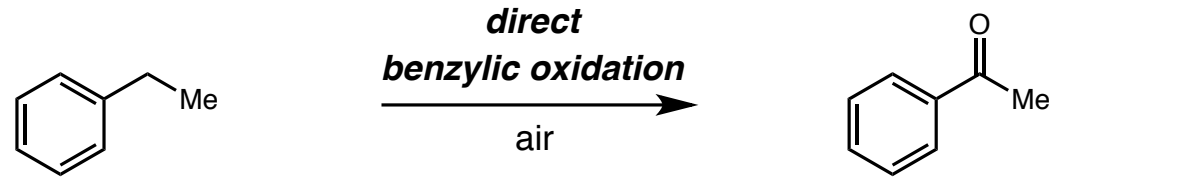
flow of $1e^-$ and $1H^+$

λ_{max} = 440 nm

Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355-360.

Flavins: A Bio-Inspired Approach to Photocatalysis

Direct Benzylic oxidation

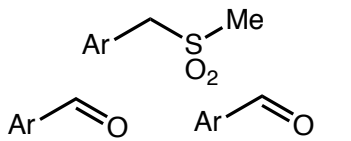


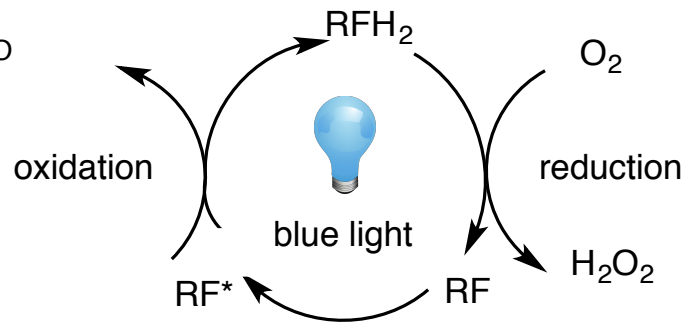
simple benzylic

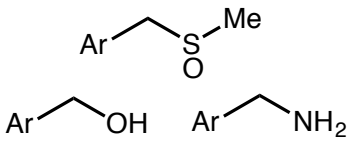
- first oxidation is difficult (> 1.8 V)
- catalyst deactivation by O_2
- competing O_2 sensitization

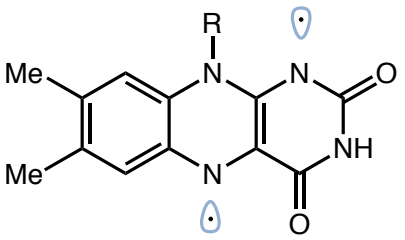
oxidized product

FAST REACTION









RF

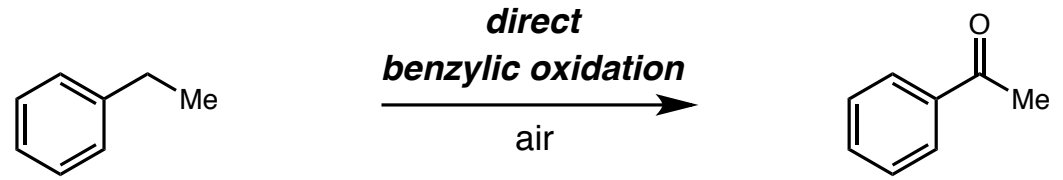
flow of $1e^-$ and $1H^+$

λ_{max} = 440 nm

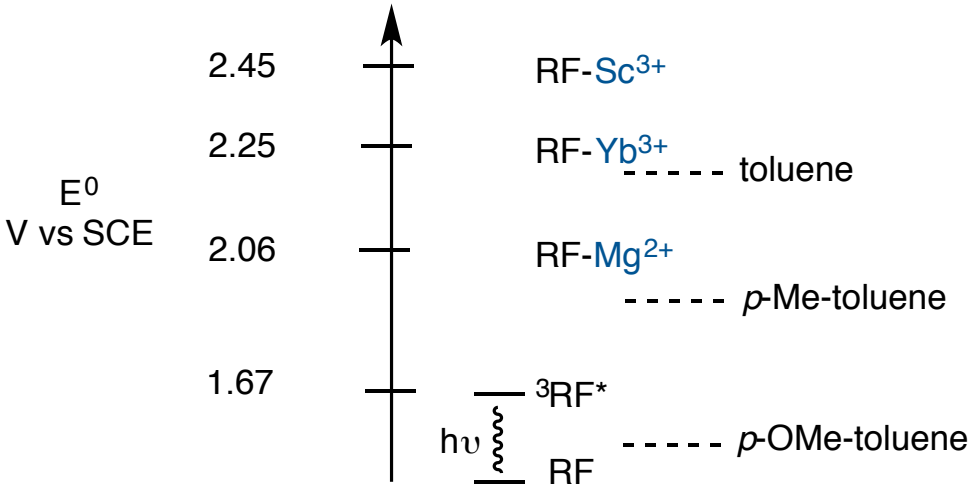
Nicewicz, D. A.; Nguyen, T. M. *ACS Catal.* **2014**, *4*, 355-360.

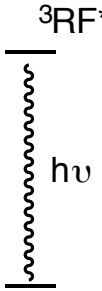
Flavins: A Bio-Inspired Approach to Photocatalysis

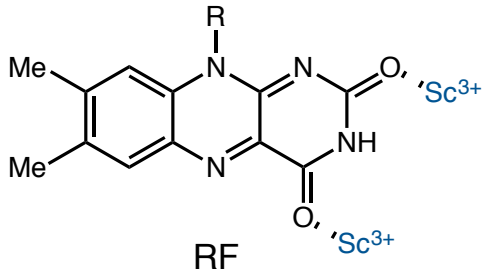
Direct Benzylic oxidation



simple benzylic *oxidized product*







RF

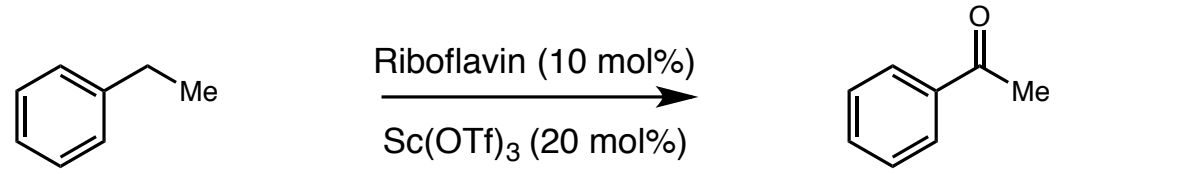
λ_{max} = 440 nm

Lewis acid coordination increases reduction potential

Wolf, R.; Muhldorf, B. *Chem. Commun.* **2015**, *51*, 8425-8428.

Flavins: A Bio-Inspired Approach to Photocatalysis

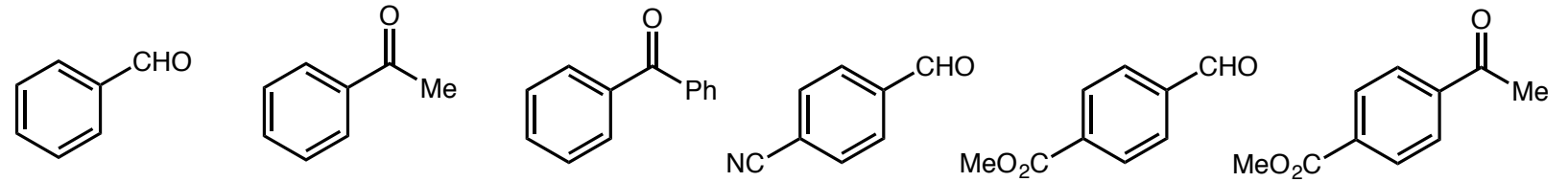
Direct Benzylic oxidation



simple benzylic → *oxidized product*

---

no Sc*, *with Sc



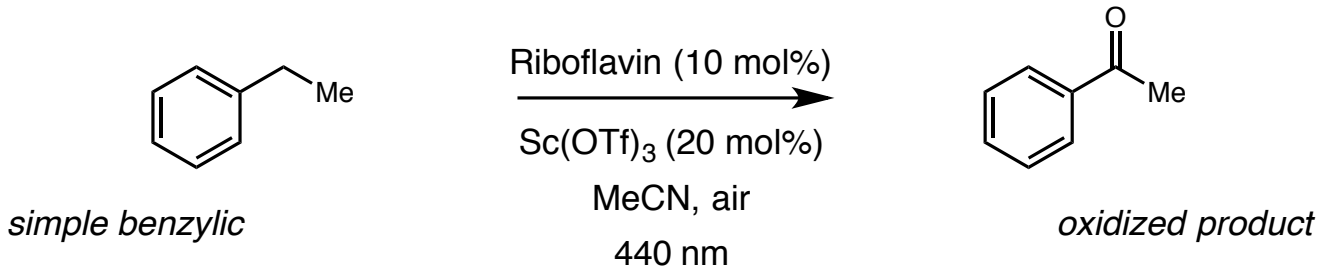
0%, ***71%*** | *3%*, ***60%*** | *4%*, ***93%*** | *0%*, ***29%*** | *0%*, ***15%*** | *0%*, ***49%***

deactivated arenes

Wolf, R.; Muhldorf, B. *Chem. Commun.* **2015**, *51*, 8425-8428.

Flavins: A Bio-Inspired Approach to Photocatalysis

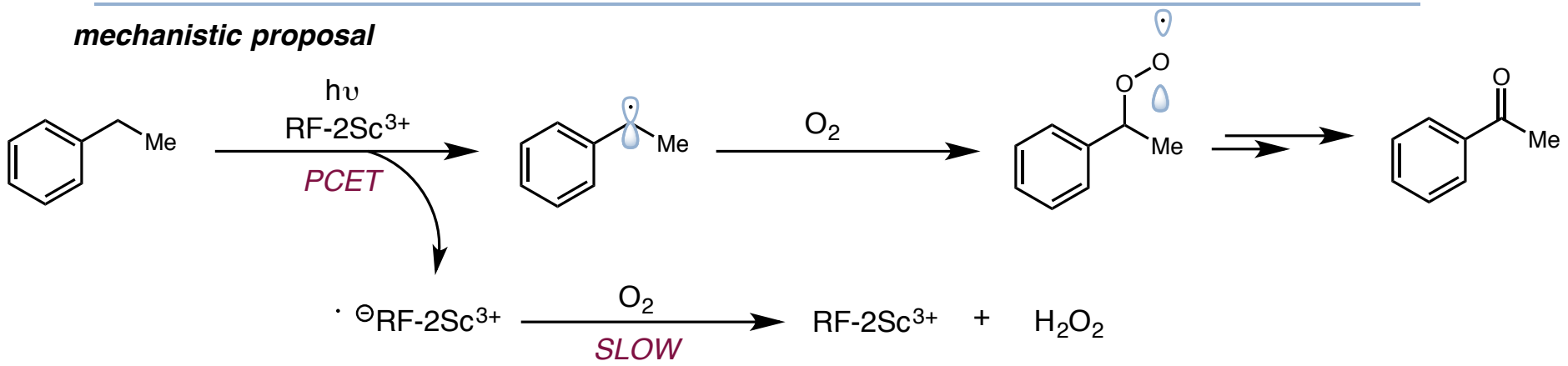
Direct Benzylic oxidation



simple benzylic

oxidized product

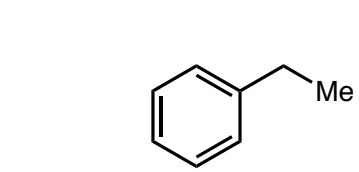
mechanistic proposal



Wolf, R.; Muhldorf, B. *Chem. Commun.* **2015**, *51*, 8425-8428.

Flavins: A Bio-Inspired Approach to Photocatalysis

Direct Benzylic oxidation



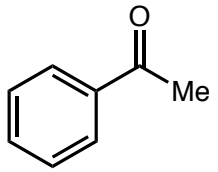
simple benzylic

Riboflavin (10 mol%)

$Sc(OTf)_3$ (20 mol%)

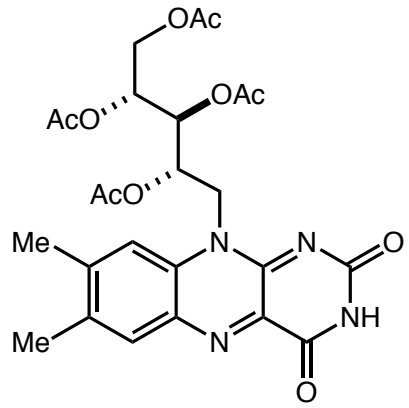
MeCN, air

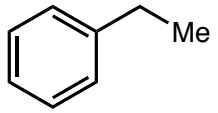
440 nm



oxidized product

Flavin catalyst





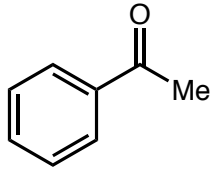
simple benzylic

Riboflavin (10 mol%)

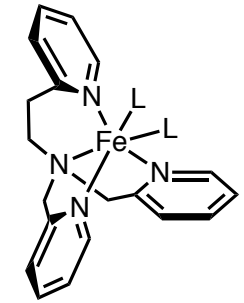
$[Fe(TPA)(MeCN)_2](ClO_4)_2$

MeCN, H_2O air

440 nm



oxidized product



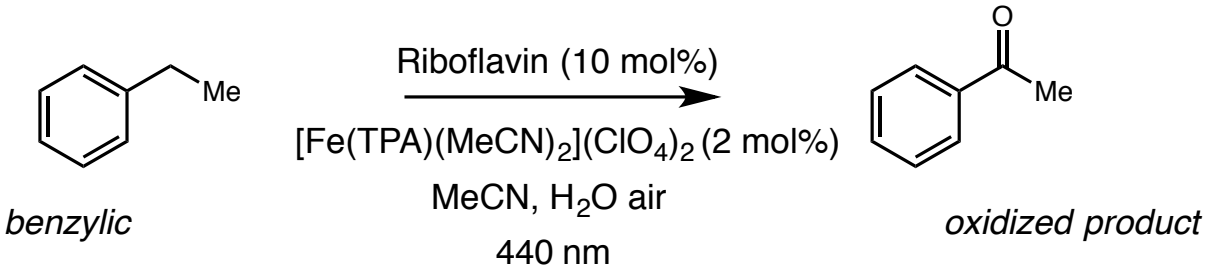
$Fe(TPA)L_2$

*disproportions H_2O_2 byproduct

Wolf, R.; Muhldorf, B. *Agnew. Chem. Int. Ed.* **2016**, *55*, 427-430.

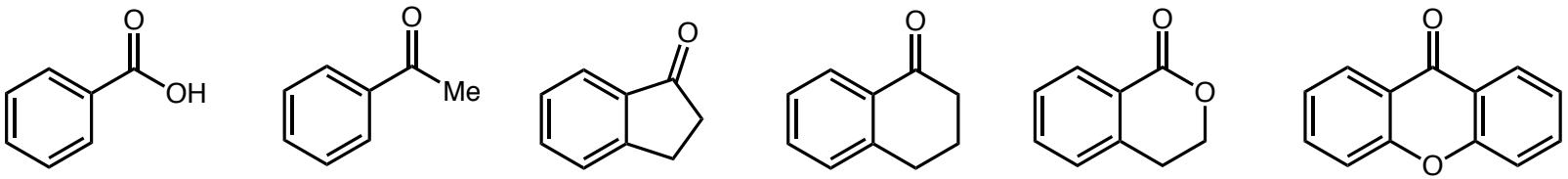
Flavins: A Bio-Inspired Approach to Photocatalysis

Direct Benzylic oxidation



simple benzylic

oxidized product



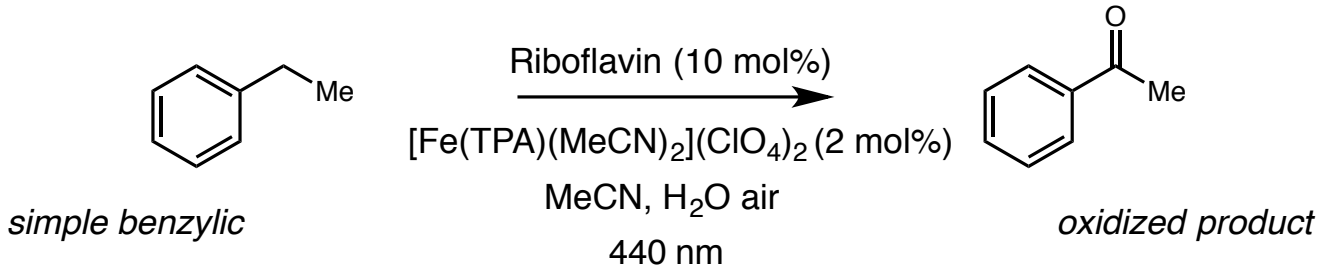
60% ***74%*** ***70%*** ***70%*** ***66%*** ***96%***

overoxidation

Wolf, R.; Muhldorf, B. *Agnew. Chem. Int. Ed.* **2016**, *55*, 427-430.

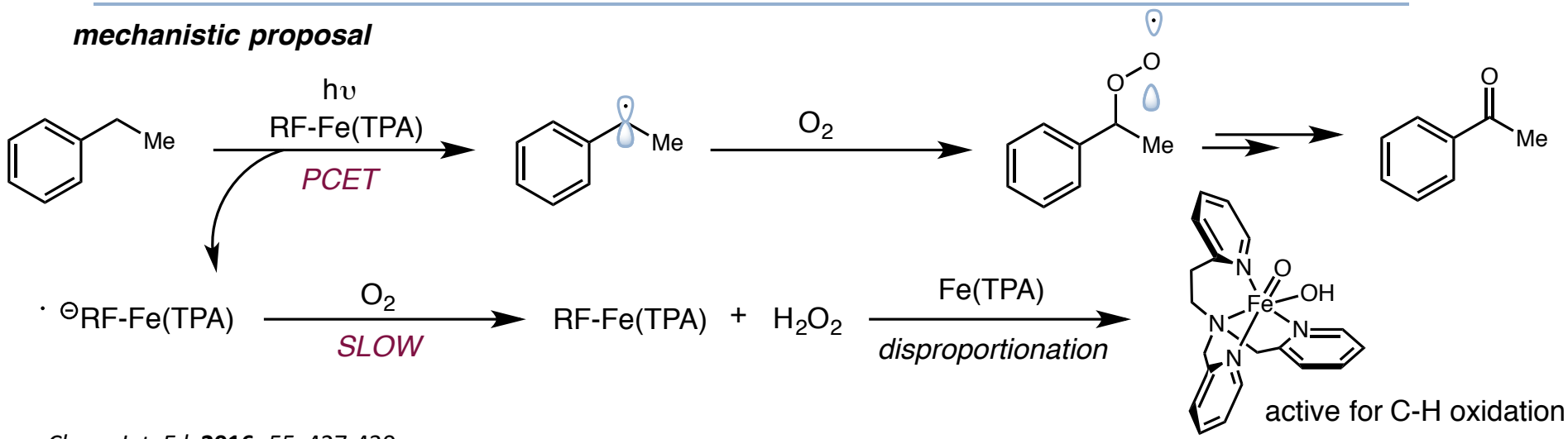
Flavins: A Bio-Inspired Approach to Photocatalysis

Direct Benzylic oxidation



simple benzylic → *oxidized product*

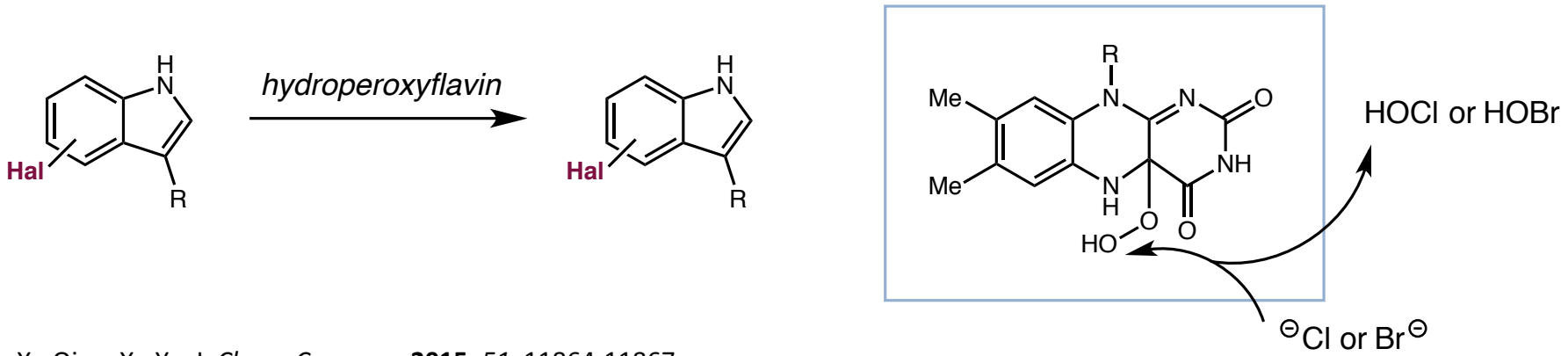
mechanistic proposal



active for C-H oxidation

Wolf, R.; Muhldorf, B. *Agnew. Chem. Int. Ed.* **2016**, *55*, 427-430.

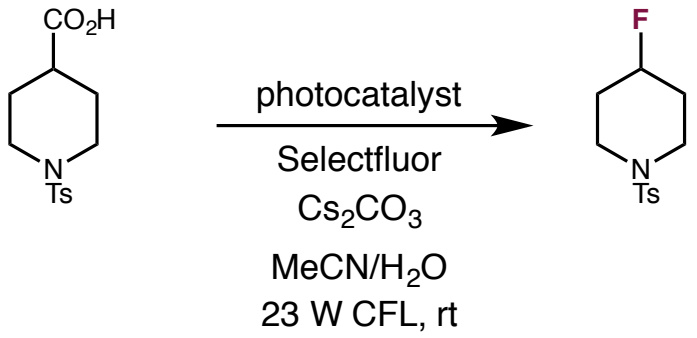
Flavins: A Bio-Inspired Approach to Photocatalysis



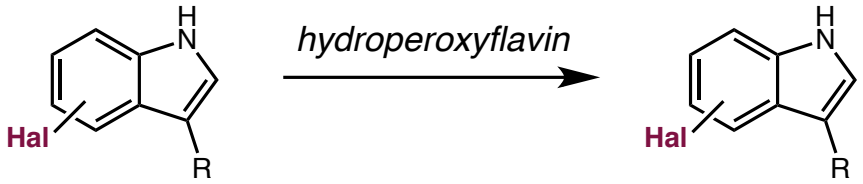
Wu, X.; Meng, C.; Yuan, X.; Jia, X.; Qian, X.; Ye, J. *Chem. Commun.* **2015**, *51*, 11864-11867.

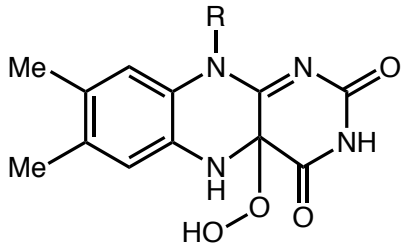
Flavins: A Bio-Inspired Approach to Photocatalysis

Decarboxylative Fluorination



photocatalyst	yield
Mes-Acr ClO_4	58%
Riboflavin	55%
Eosin Y	trace
Rhodamine B	trace

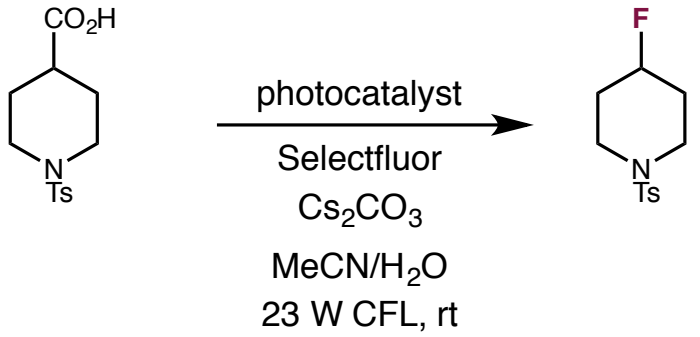




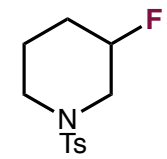
Wu, X.; Meng, C.; Yuan, X.; Jia, X.; Qian, X.; Ye, J. *Chem. Commun.* **2015**, *51*, 11864-11867.

Flavins: A Bio-Inspired Approach to Photocatalysis

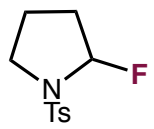
Decarboxylative Fluorination



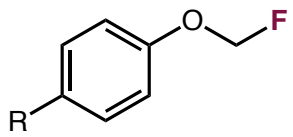
photocatalyst	yield
Mes-Acr ClO_4	58%
Riboflavin	55%
Eosin Y	trace
Rhodamine B	trace



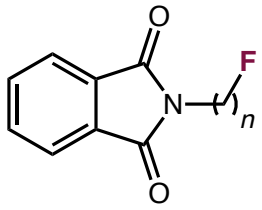
71%



36%



R = Ph, ***73%***
R = ^{t}Bu, ***76%***
R = Br, ***45%***

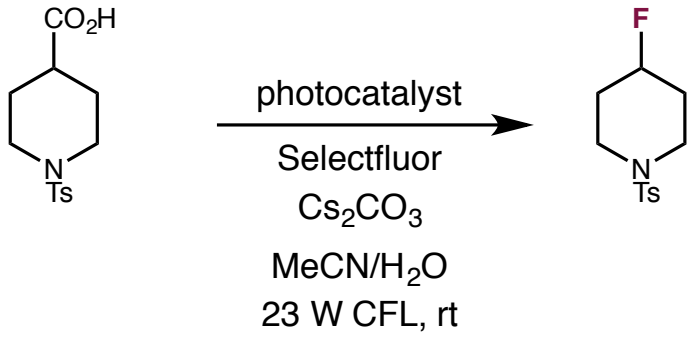


n = 2, ***35%***
n = 3, ***40%***
n = 4, ***39%***
n = 5, ***42%***

Wu, X.; Meng, C.; Yuan, X.; Jia, X.; Qian, X.; Ye, J. *Chem. Commun.* **2015**, *51*, 11864-11867.

Flavins: A Bio-Inspired Approach to Photocatalysis

Decarboxylative Fluorination



photocatalyst	yield
Mes-Acr ClO_4	58%
Riboflavin	55%
Eosin Y	trace
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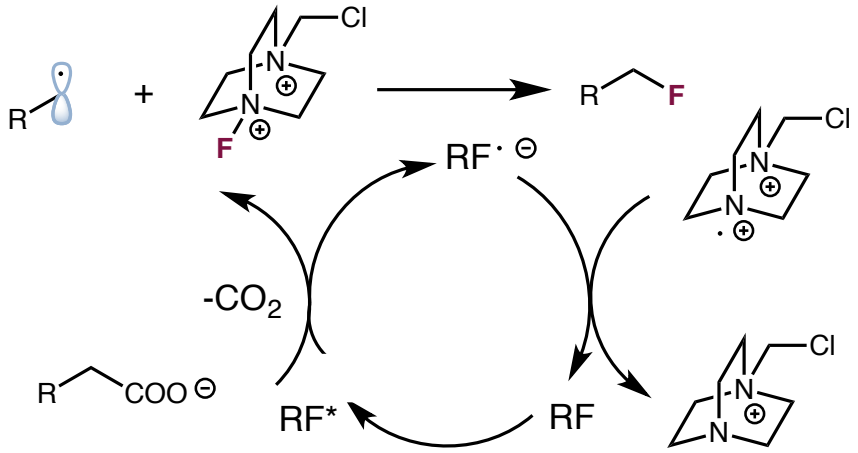
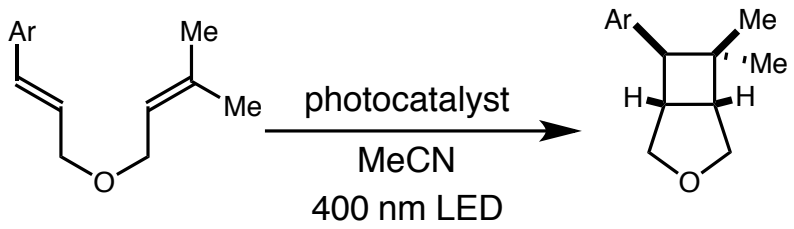
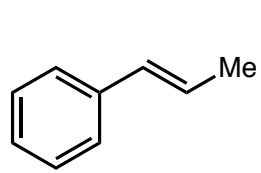


Wu, X.; Meng, C.; Yuan, X.; Jia, X.; Qian, X.; Ye, J. *Chem. Commun.* **2015**, *51*, 11864-11867.

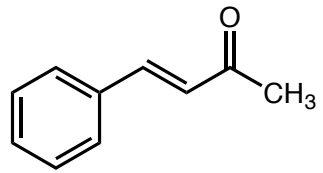
Flavins: A Bio-Inspired Approach to Photocatalysis

Energy Transfer [2+2] cycloaddition





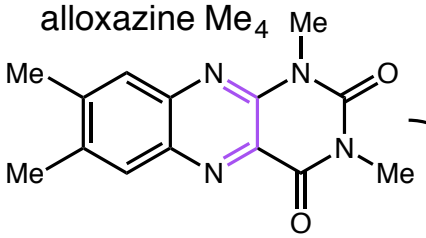
E_T = 59 kcal/mol^{-1}



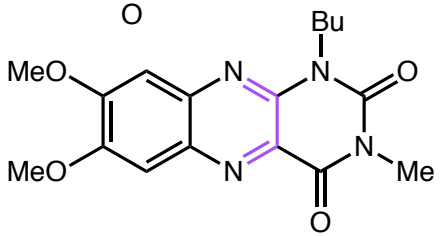
E_T = 63 kcal/mol^{-1}

photocatalyst	λ_{max}	E_T	yield
Riboflavin $(OH)_4$	450 nm	50 kcal/mol^{-1}	0%
Riboflavin $(OAc)_4$	450 nm	57 kcal/mol^{-1}	0%
Alloxazine Me_4	350 nm	59 kcal/mol^{-1}	*trace*
Alloxazine OMe_2	400 nm	69 kcal/mol^{-1}	87% (10 min)

alloxazine Me_4



E^{0-0} = 59 kcal/mol^{-1}

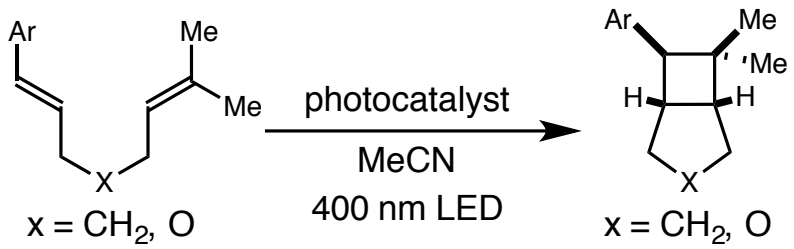


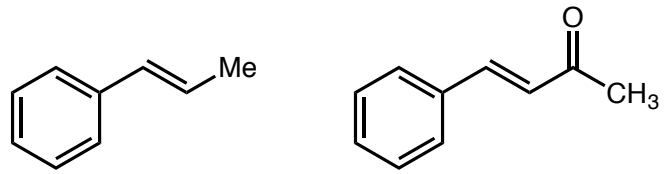
E^{0-0} = 69 kcal/mol^{-1}

Mojr, V.; Svobodova, Strakova, K.; Nevesely, T.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Chem. Commun.* **2015**, *51*, 12036-12039.

Flavins: A Bio-Inspired Approach to Photocatalysis

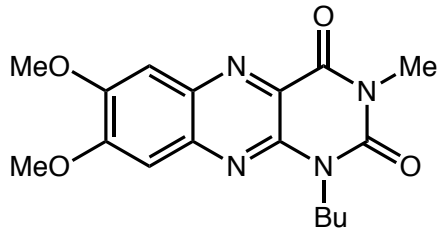
Energy Transfer [2+2] cycloaddition





E_T = 59 kcal/mol^{-1} E_T = 62 kcal/mol^{-1}

photocatalyst	E_T (kcal)
Alloxazine OMe_2	69.0
$Ir[dFCF_3ppy)]_2dttbpy$	61.0
$Ir(ppy)_3$	53.6
Riboflavin $(OH)_4$	50.0
$Ir(ppy)_2$ 4,4'-$(MeO)_2$bpy	47.7
$Ir(ppy)_2$ 4,4'-Me_2bpy	47.6
$Ir(ppy)_2$ bpy	46.3
$Ru(bpy)_3$	45.4
$Ir(ppy)_2$ 4,4'-$(CO_2Me)_2$bpy	39.7

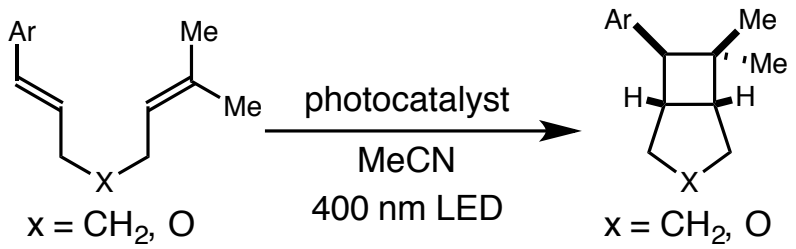


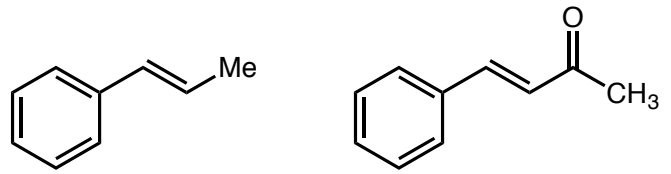
Alloxazine OMe_2

Mojr, V.; Svobodova, Strakova, K.; Nevesely, T.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Chem. Commun.* **2015**, *51*, 12036-12039.

Flavins: A Bio-Inspired Approach to Photocatalysis

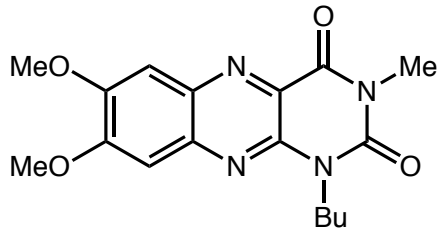
Energy Transfer [2+2] cycloaddition





E_T = 59 kcal/mol^{-1} E_T = 62 kcal/mol^{-1}

photocatalyst	E_T (kcal)
Acetophenone	74.0
Alloxazine OMe_2	69.0
Benzoquinone	69.0
Naphthalene	61.0
Mesityl Acridinium	55.0
Fluorenone	53.0
Riboflavin $(OH)_4$	50.0
Fluorescein	47.0
Eosin Y	45.0
Anthracene	43.0
Rose bengal	41.0

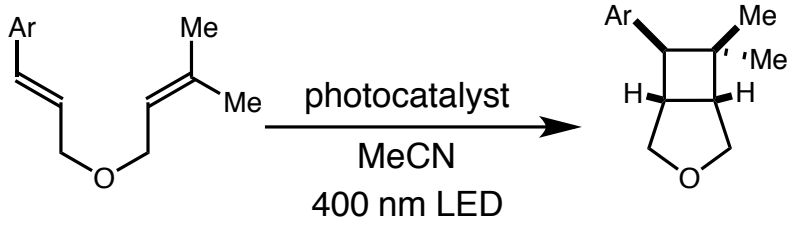


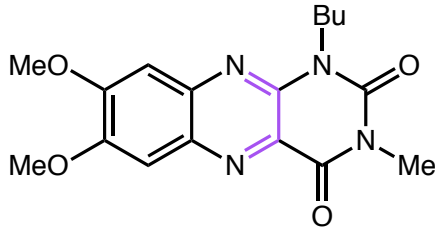
Alloxazine OMe_2

Mojr, V.; Svobodova, Strakova, K.; Nevesely, T.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Chem. Commun.* **2015**, *51*, 12036-12039.

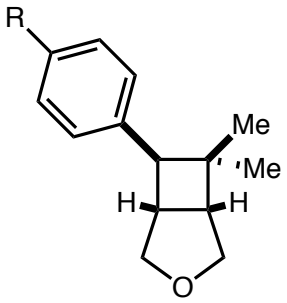
Flavins: A Bio-Inspired Approach to Photocatalysis

Energy Transfer [2+2] cycloaddition

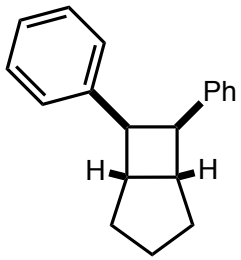




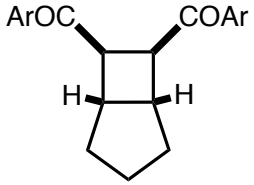
$E^{0\text{-}0}$ = 69 kcal/mol^{-1}



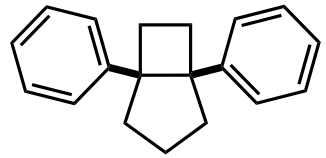
R = OMe, ***82%*** (>10:1)
R = H, ***87%*** (>10:1)
R = Br, ***76%*** (>10:1)
R = CF_3, ***81%*** (>10:1)



42% (7:1)



Ar = Ph, ***70%*** (5:1)
Ar = 4-OMePh, ***67%*** (4:1)
Ar = 4-CF_3Ph, ***58%*** (1:1)

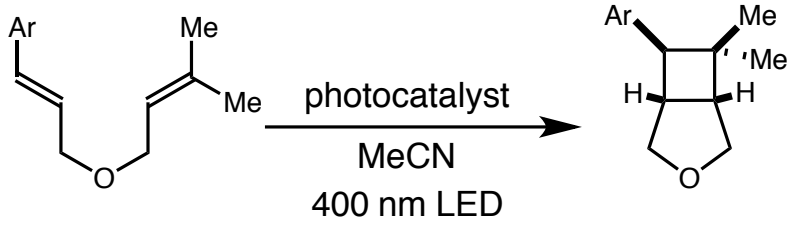


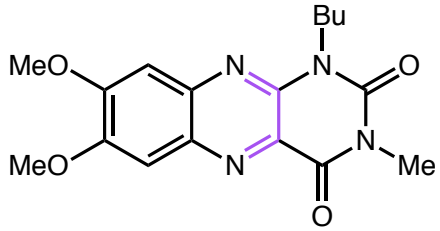
80%

Mojr, V.; Svobodova, Strakova, K.; Nevesely, T.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Chem. Commun.* **2015**, *51*, 12036-12039.

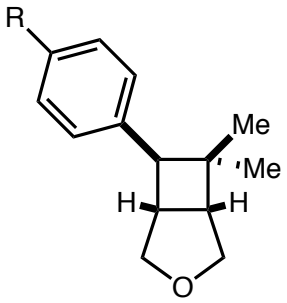
Flavins: A Bio-Inspired Approach to Photocatalysis

Energy Transfer [2+2] cycloaddition





$E^{0\text{-}0}$ = 69 kcal/mol^{-1}



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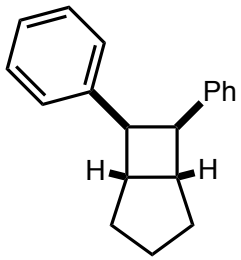
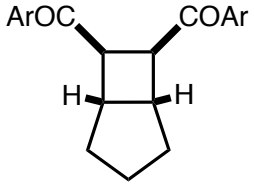
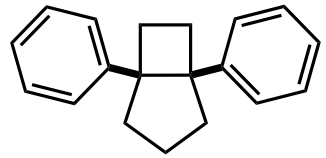
R = H, ***87%*** (>10:1)
R = Br, ***76%*** (>10:1)
R = CF_3, ***81%*** (>10:1)



42% (7:1)



Ar = Ph, ***70%*** (5:1)
Ar = 4-OMePh, ***67%*** (4:1)
Ar = 4-CF_3Ph, ***58%*** (1:1)

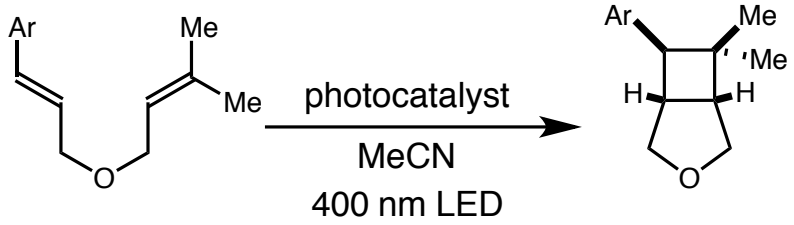


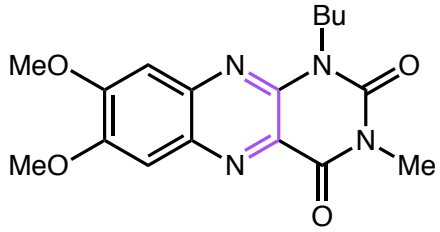
80%

Mojr, V.; Svobodova, Strakova, K.; Nevesely, T.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Chem. Commun.* **2015**, *51*, 12036-12039.

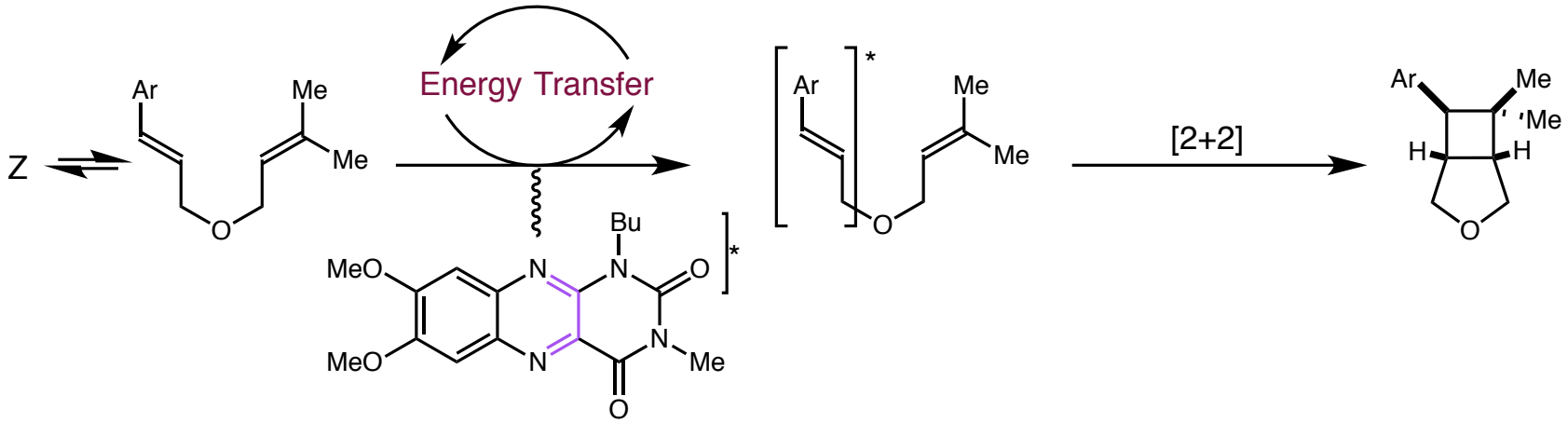
Flavins: A Bio-Inspired Approach to Photocatalysis

Energy Transfer [2+2] cycloaddition





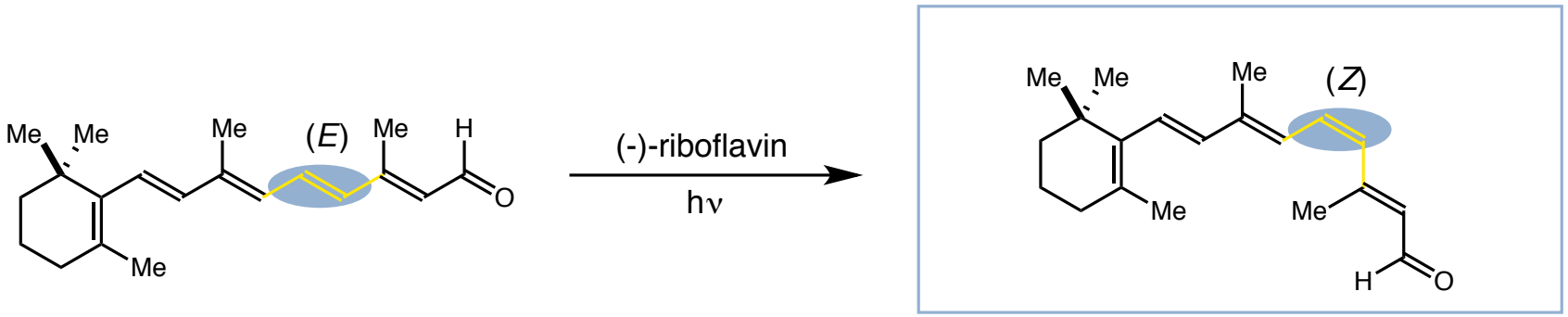
$E^{0\text{-}0}$ = 69 kcal/mol^{-1}



Mojr, V.; Svobodova, Strakova, K.; Nevesely, T.; Chudoba, J.; Dvorakova, H.; Cibulka, R. *Chem. Commun.* **2015**, *51*, 12036-12039.

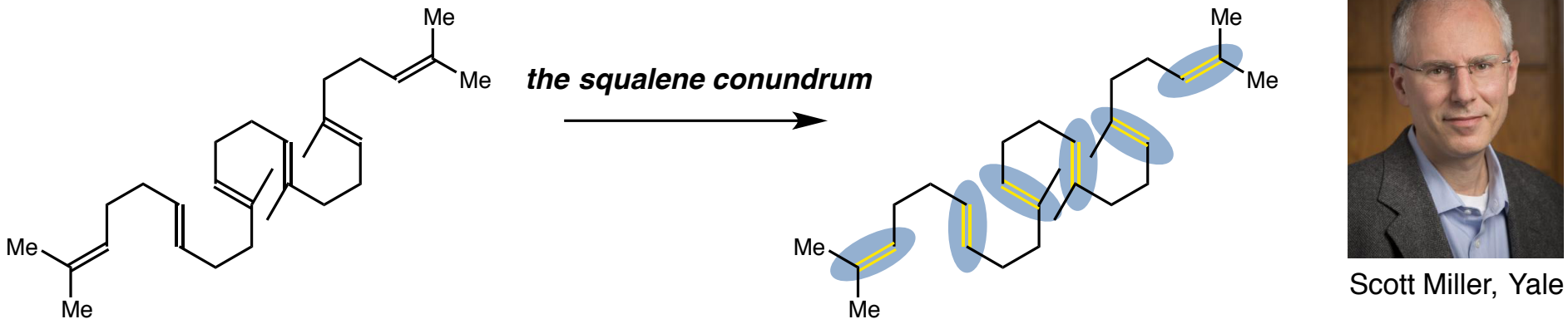
Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization



retinal

Nature **1967**, *215*, 1483.



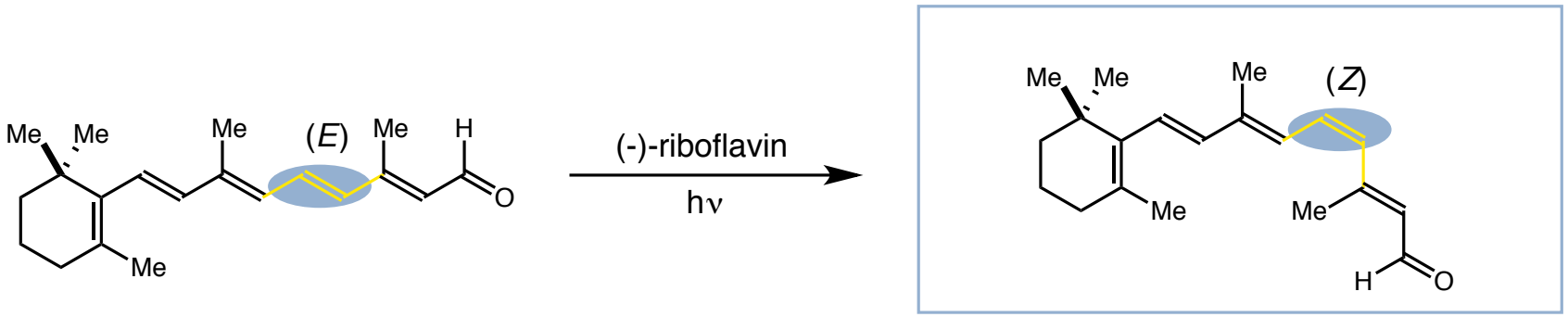
Scott Miller, Yale

selective functionalization of polyenes

Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

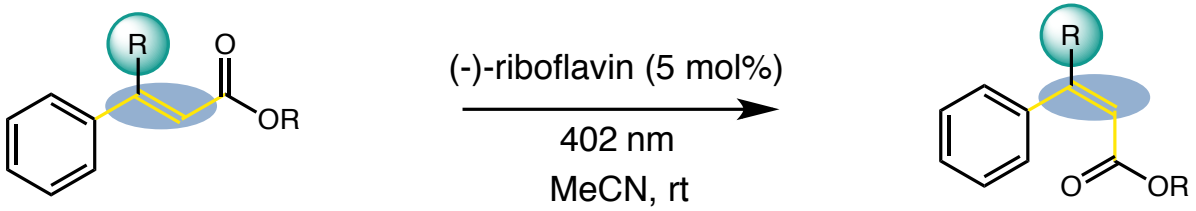
Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization



retinal

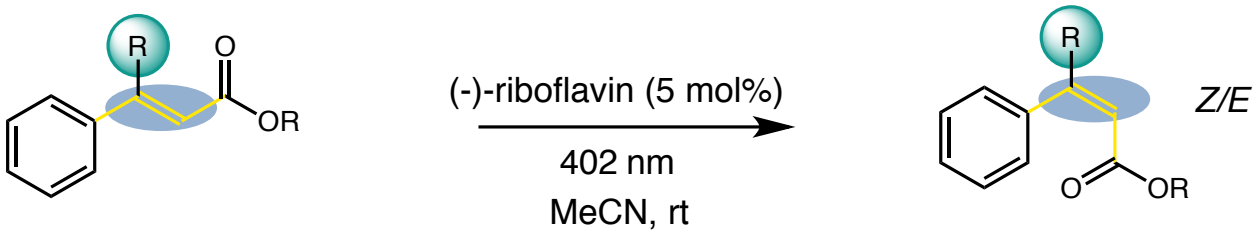
Nature **1967**, 215, 1483

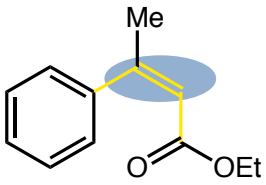


Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

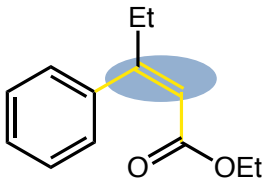
Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization

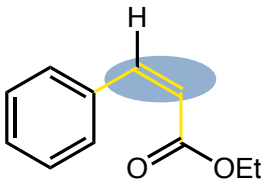




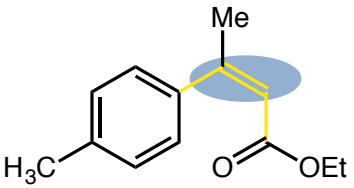
quant., 99:1



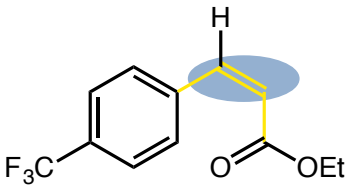
quant., 95:5



99%, 59:41



quant., 95:5



quant., 97:3

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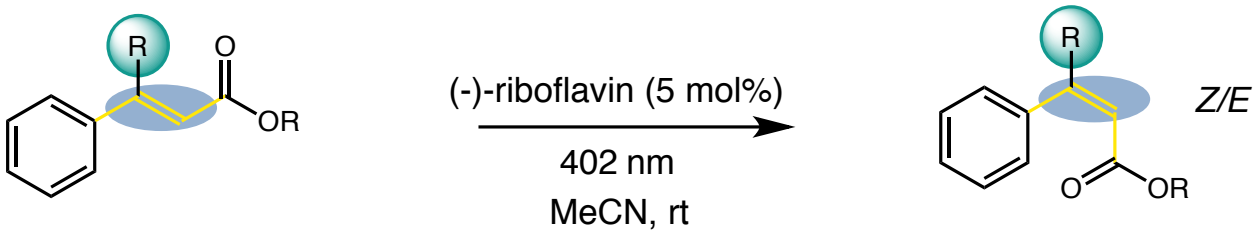
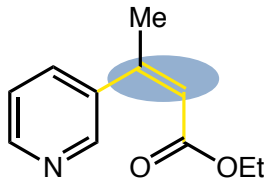
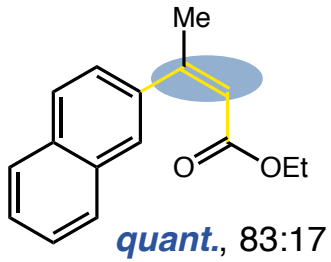
Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization

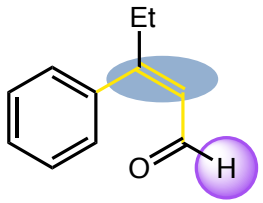




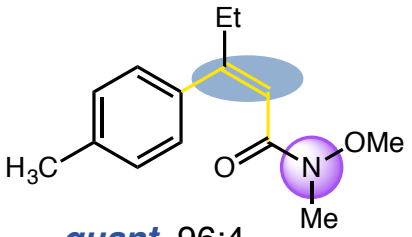
88%, 95:5



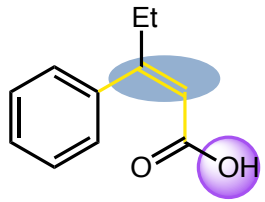
quant., 83:17



quant., 87:13



quant, 96:4

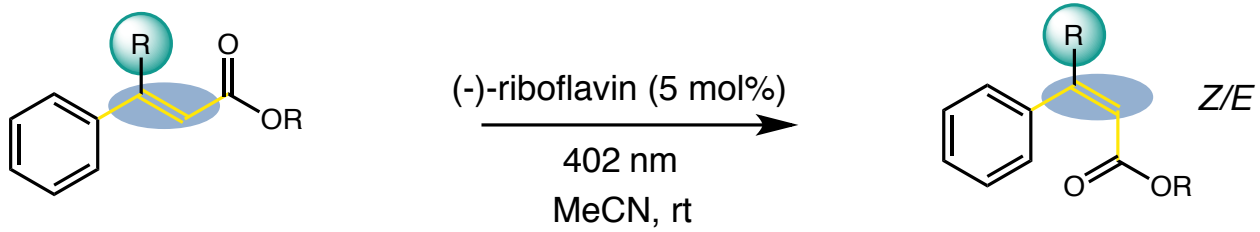


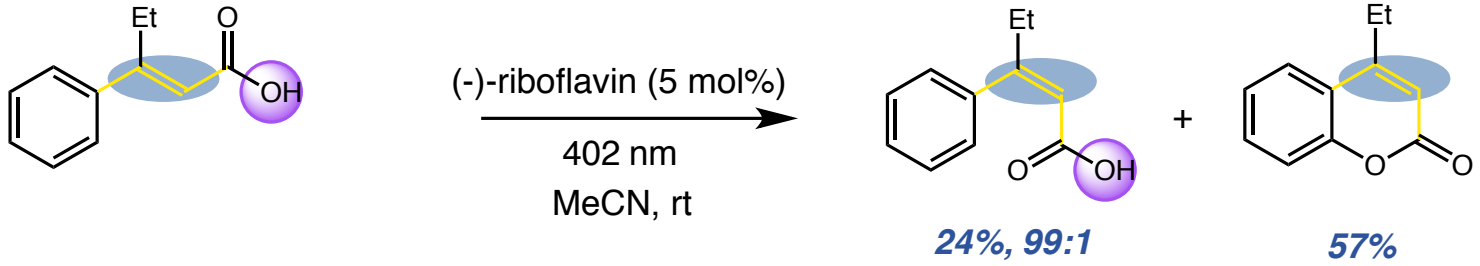
24%, 99:1

Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization





Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

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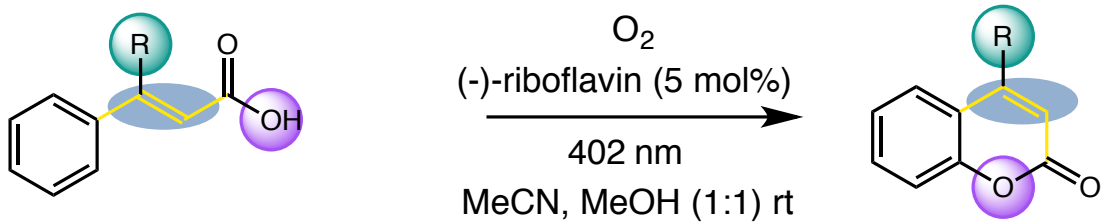
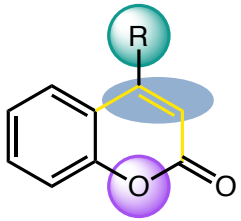
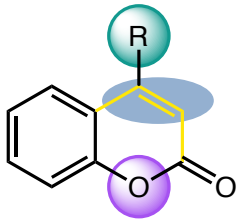
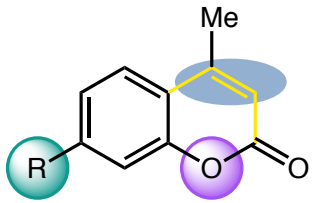




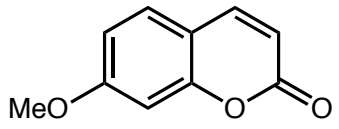
R = H, 79%



R = Alkyl, 60-90%



R = OMe, 65%
R = CF_3, 48%
R = Me, 60%



herniarin

hepatoprotectent

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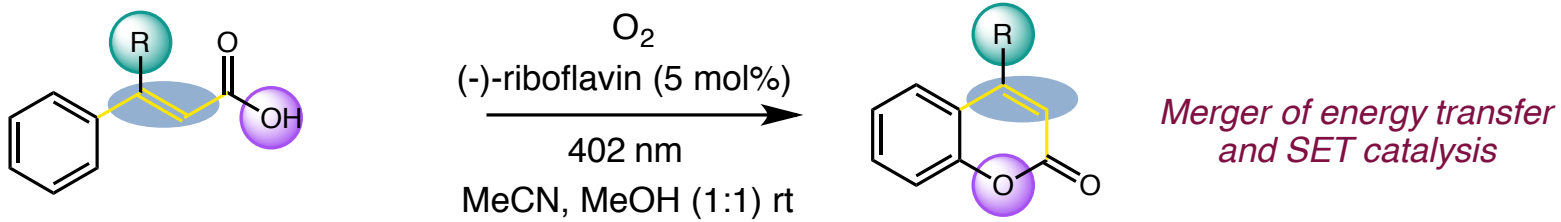
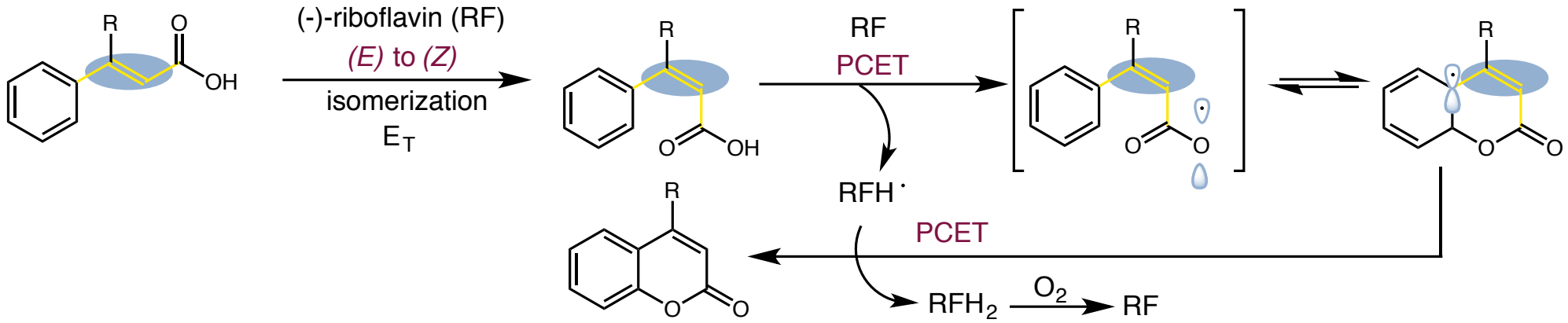


(*E*)-cinnamic acid **coumarin**

Merger of energy transfer and SET catalysis

mechanistic proposal



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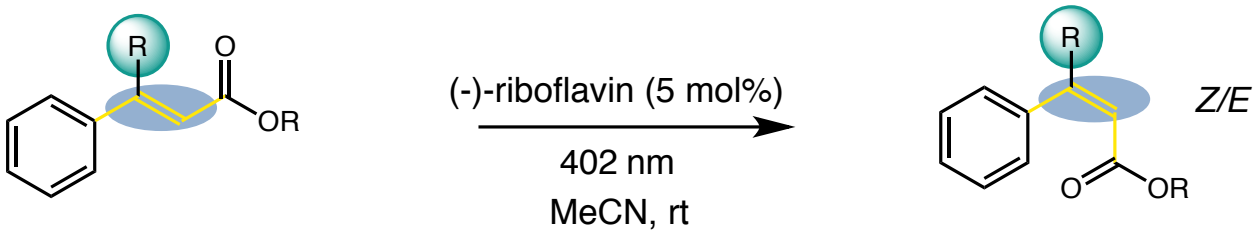
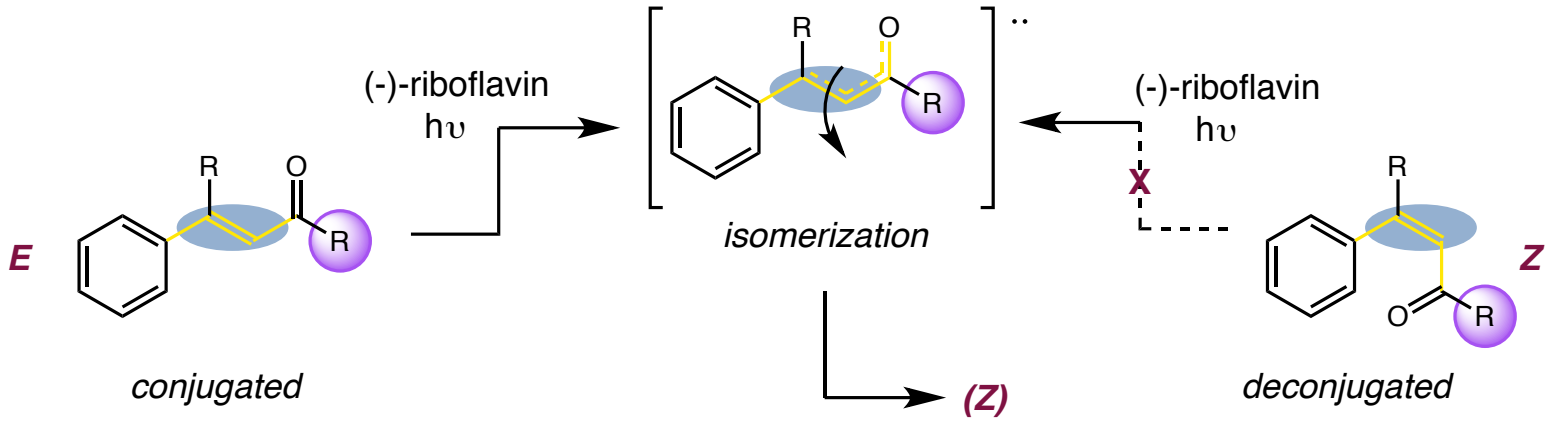


mechanistic hypothesis



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Flavins: A Bio-Inspired Approach to Photocatalysis

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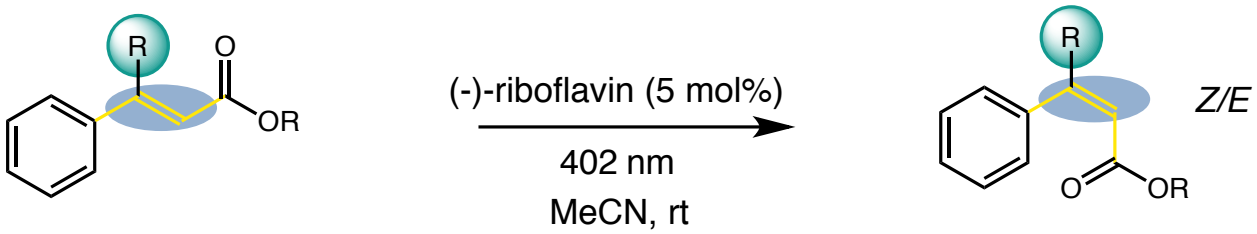
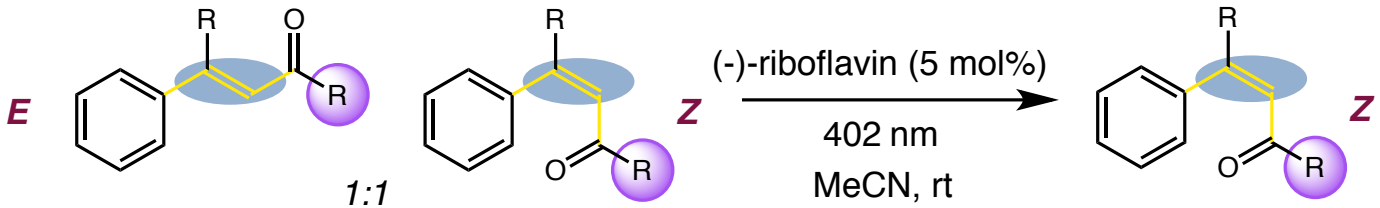


mechanistic hypothesis



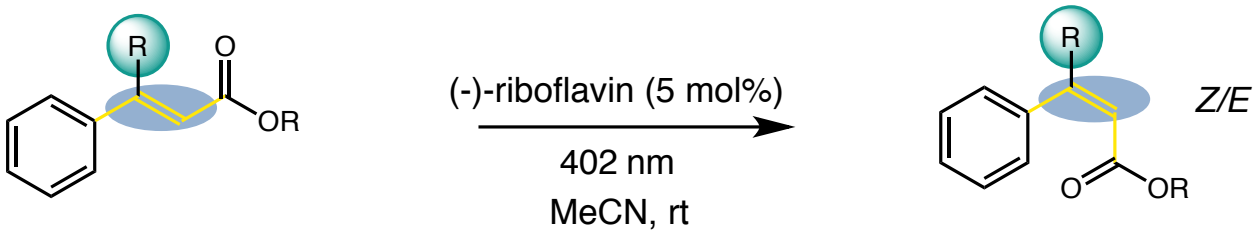
Stern Volmer quenching study

-(E) quenches 10x faster than (Z)

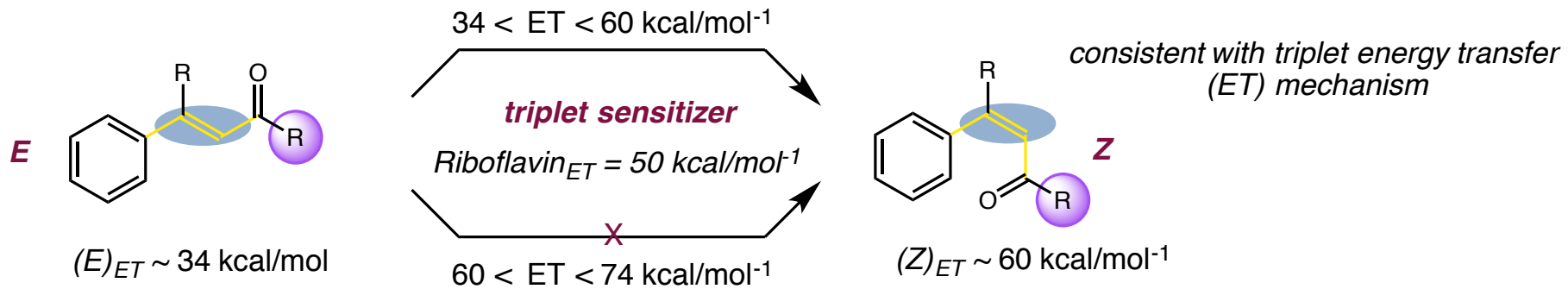
Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization



mechanistic hypothesis



Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

Flavins: A Bio-Inspired Approach to Photocatalysis

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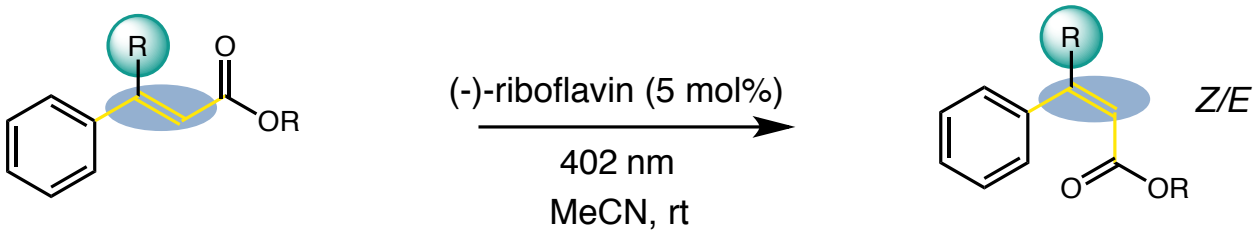
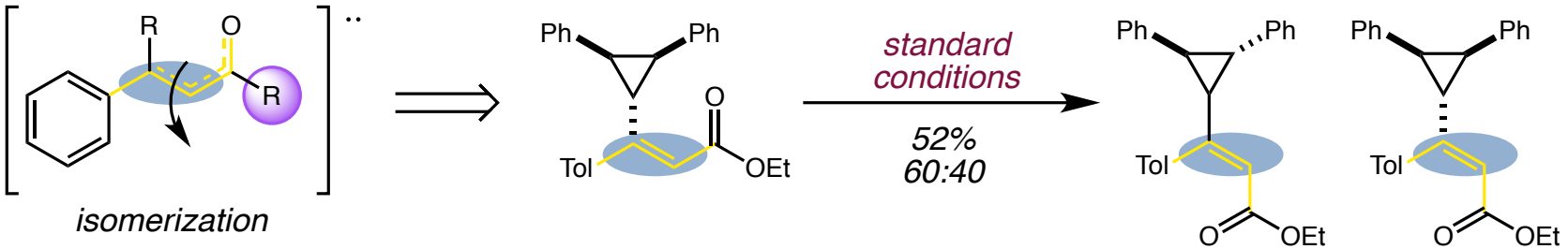


mechanistic hypothesis

* No reaction without photocatalyst



scrambled

Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

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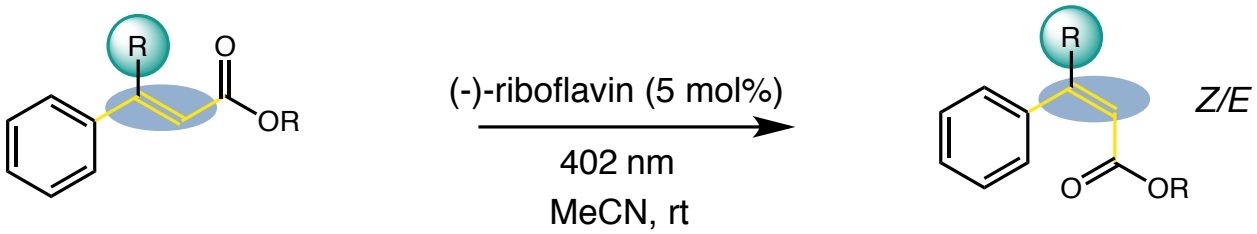
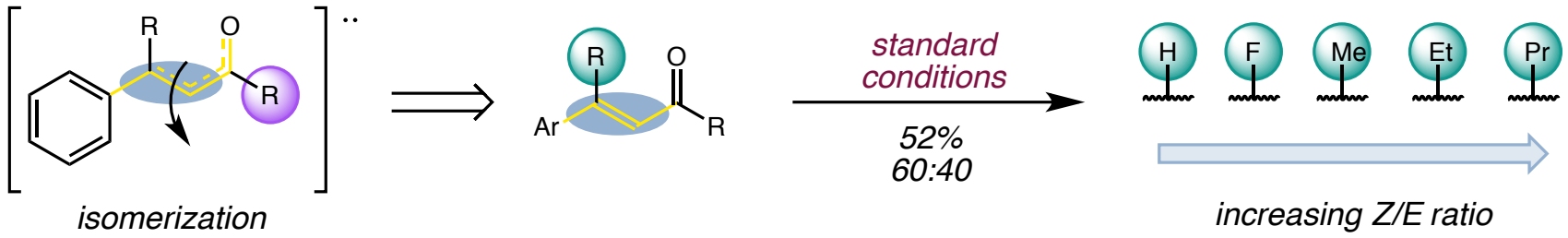


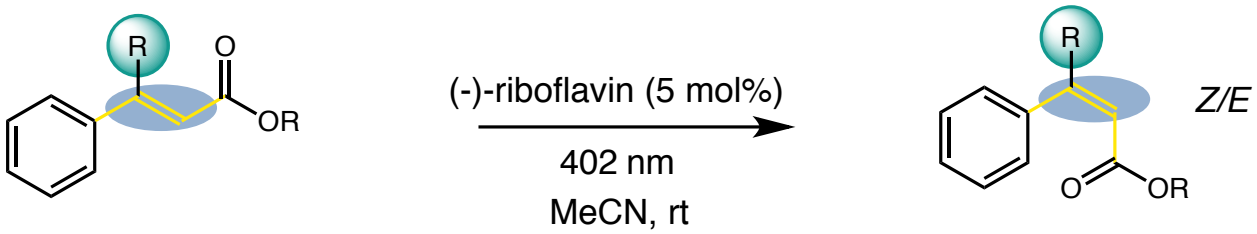
mechanistic hypothesis



Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

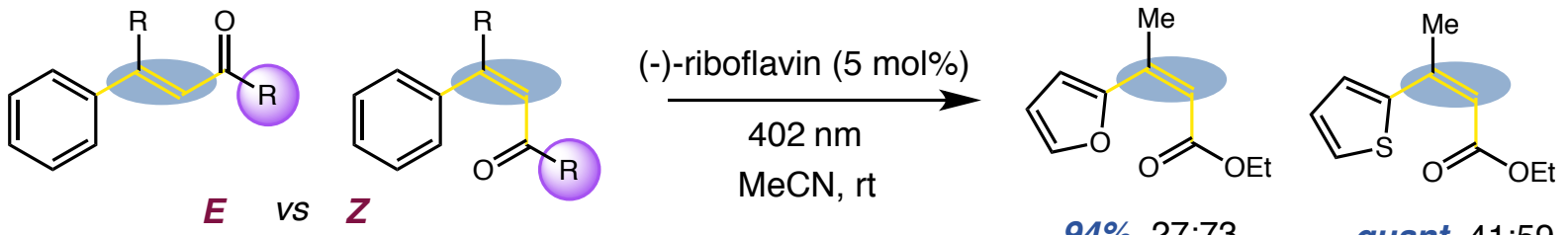
Flavins: A Bio-Inspired Approach to Photocatalysis

(E) to (Z) Isomerization



mechanistic hypothesis

reduced A1,3 strain in (Z)-products
(E) and (Z) are conjugated and planar



deconjugation induces selective excitation

Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

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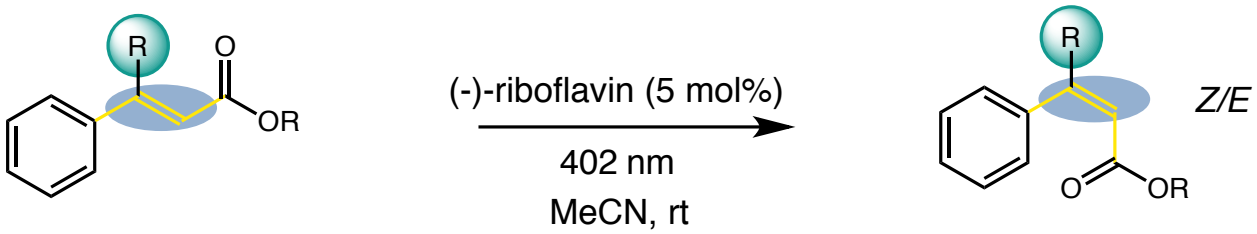
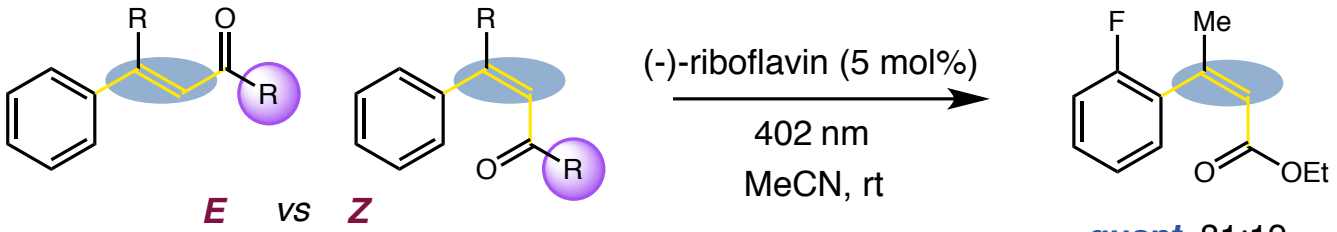
(E) to (Z) Isomerization



mechanistic hypothesis

introduction of allylic strain by ortho-fluoro



deconjugation induces selective excitation

quant, 81:19

Metternich, J. B.; Gilmour, R. *J. Am. Chem. Soc.* **2015**, *137*, 11254-11257.

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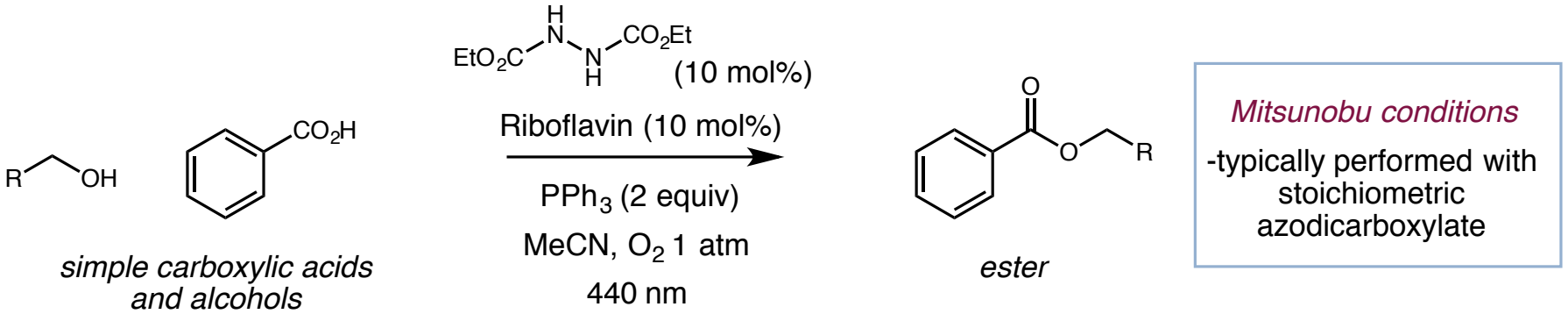
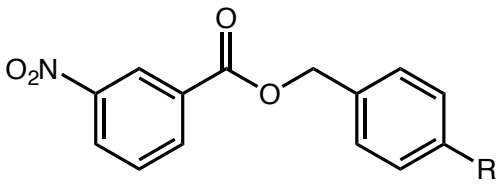
catalytic esterification

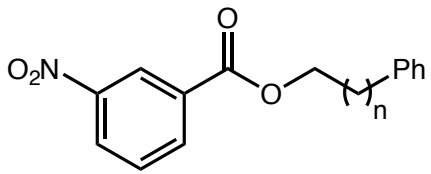


Mitsunobu conditions

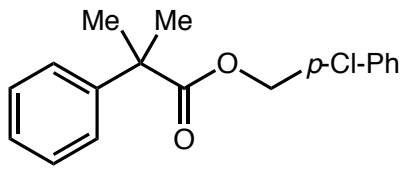
-typically performed with stoichiometric azodicarboxylate



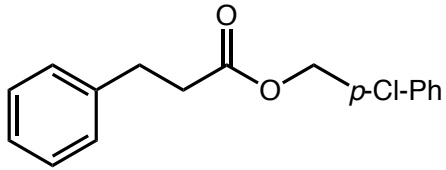
R = H, ***53%***
R = Me, ***54%***
R = NO_2, ***60%***
R = OMe, ***70%***



n = 1, ***80%***
n = 7, ***61%***



32%



58%

Marz, M.; Chudoba, J.; Kohout, M.; Cibulka, R. *Org. Biomol. Chem.* **2017.**

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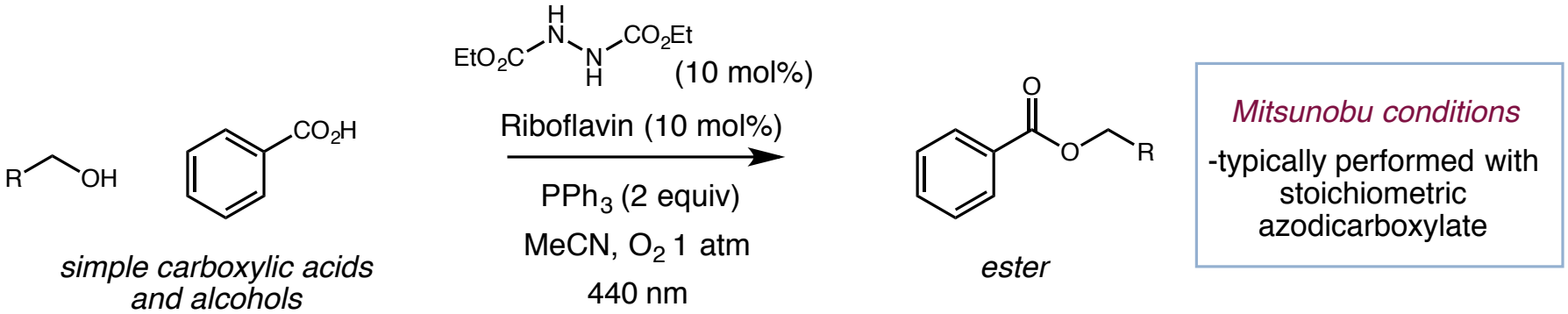
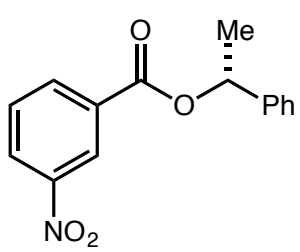
catalytic esterification

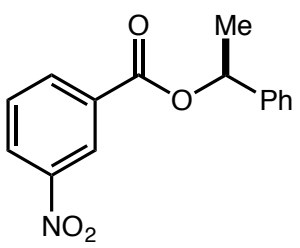


Mitsunobu conditions

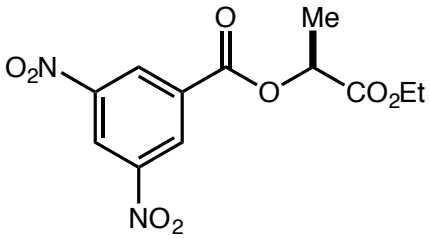
-typically performed with stoichiometric azodicarboxylate



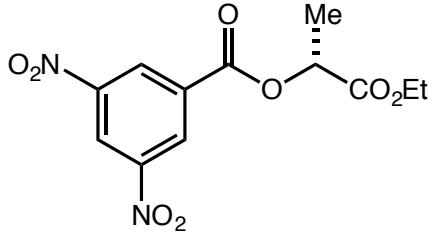
65% 99:1 er



59%, 99:1 er



50%, 98:2 er



48%, 98:2 er

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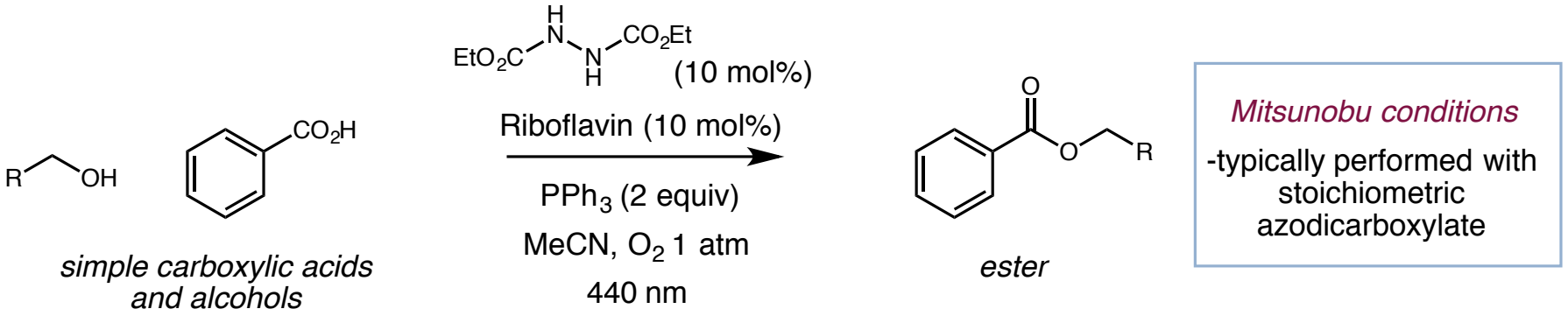
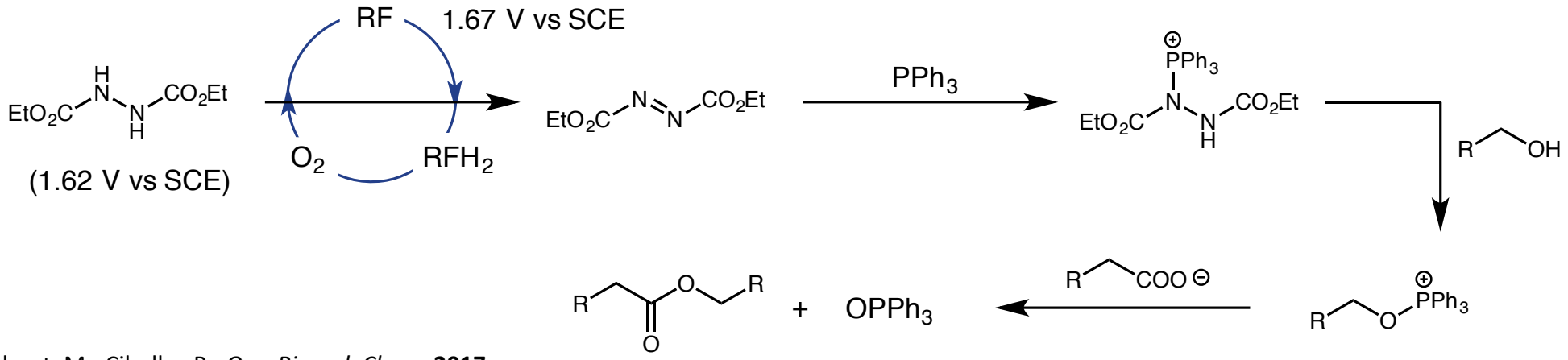
Flavins: A Bio-Inspired Approach to Photocatalysis

catalytic esterification



mechanistic proposal



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Concluding Remarks

- Flavins serve an essential role in biochemistry
- The unique photoredox properties of Flavins make them interesting photocatalyst
- Flavin photoredoxcatalysis is still under-ultized in synthetic organic chemistry
- Flavin photocatalysis is an emerging field