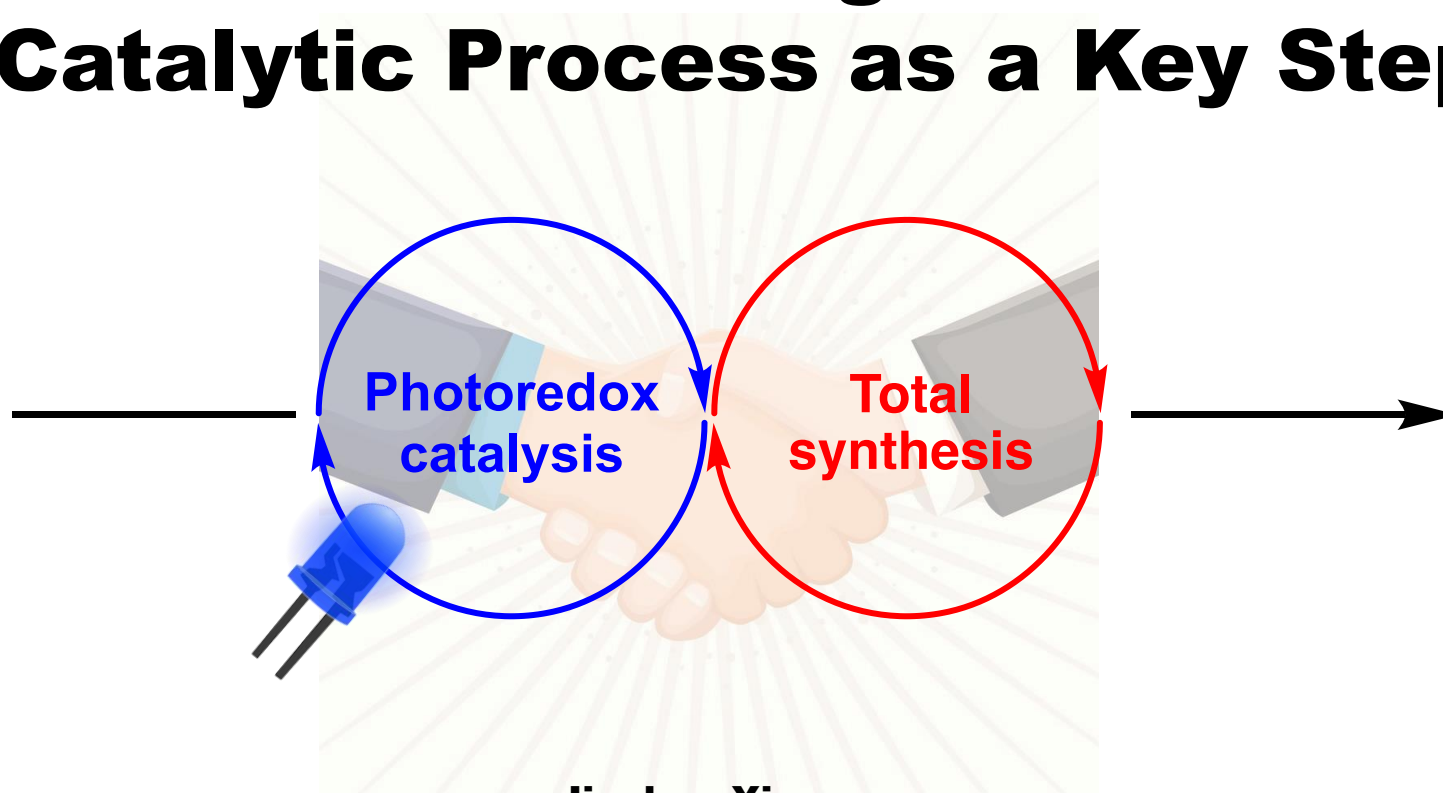


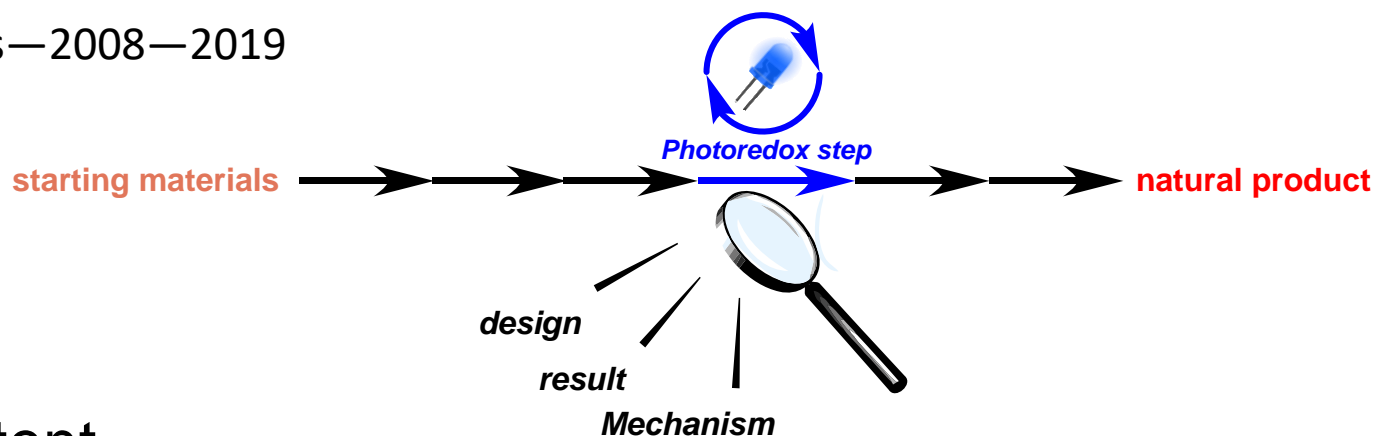
## Group Seminar

# Total Synthesis of Natural Products involving Photoredox Catalytic Process as a Key Step



**Jiachen Xiang**  
(Prof. Jieping Zhu's Lab)  
24-10-2019

1970s—2008—2019



## Content

1. Reductive Couplings
2. Photocycloadditions
3. N-centered radicals
4. Proton-coupled Electron Transfer (*PCET*)
5. Outlook

# 1. Reductive Couplings

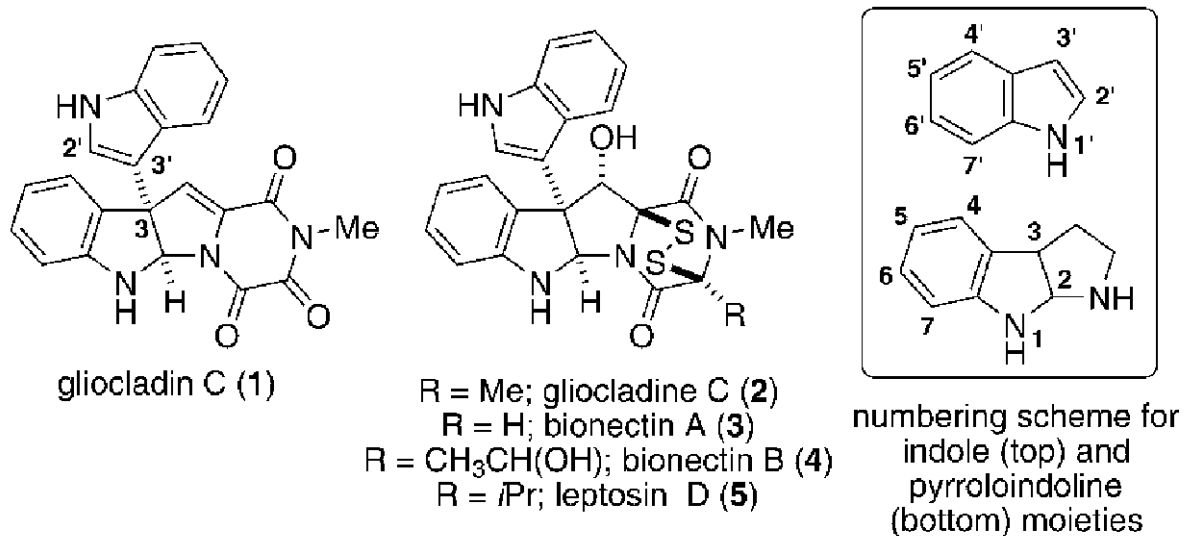
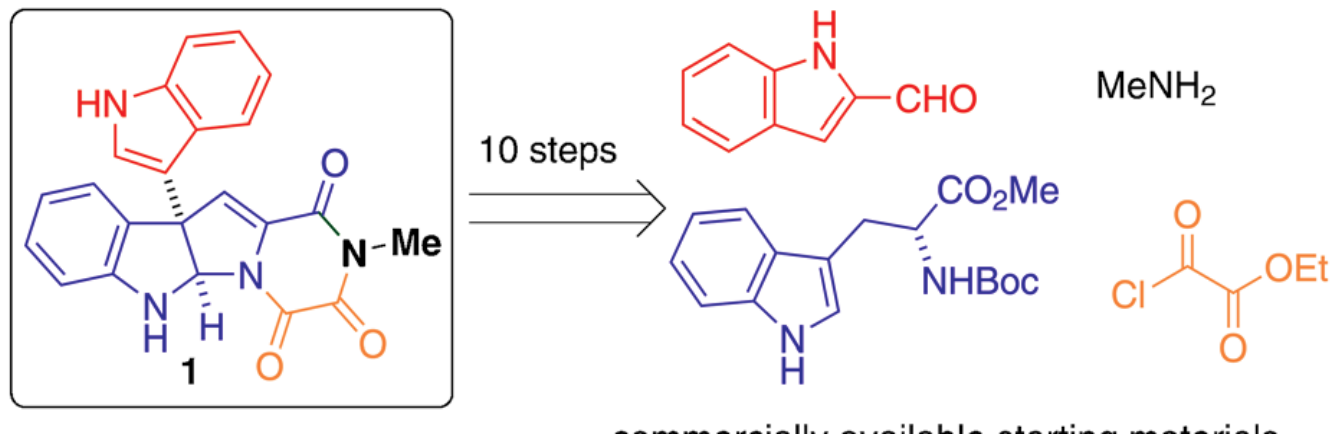
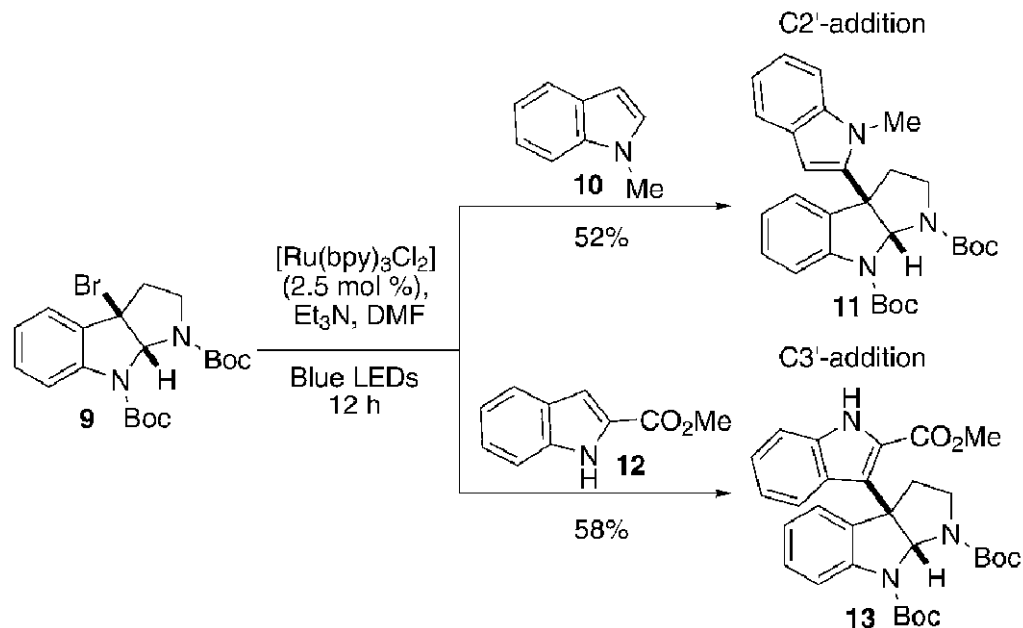


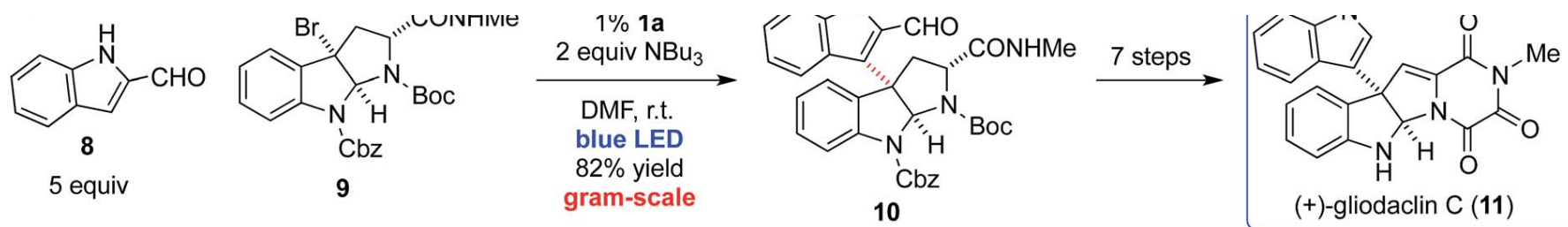
Figure 1. Representative examples of cytotoxic and antibiotic C3–C3' bisindole alkaloids.<sup>[6]</sup>



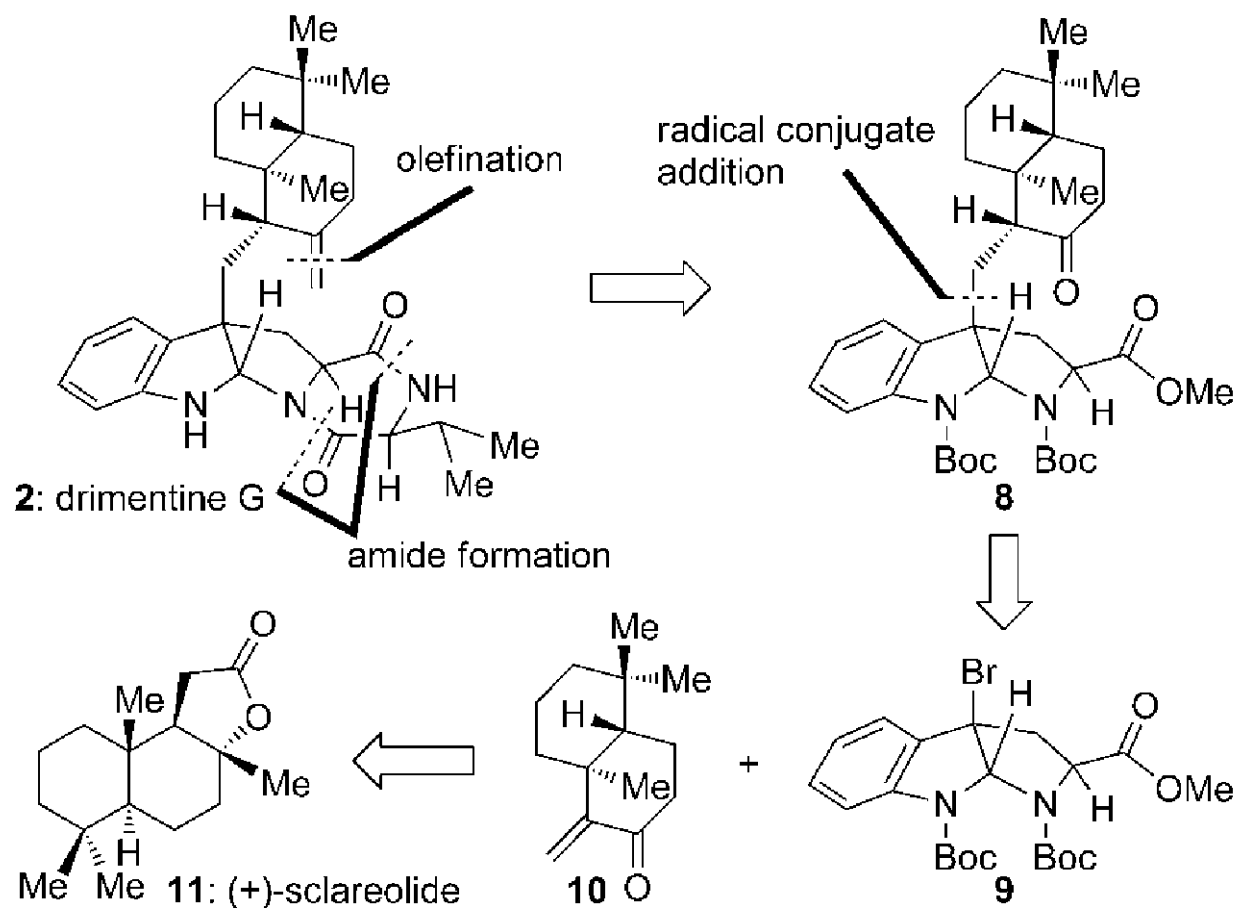
# 1. Reductive Couplings



Scheme 2. Visible-light-mediated coupling of bromopyrroloindoline **9** with indoles enables selective access to both C2'- and C3'-substituted bisindoles. Boc = tert-butyloxycarbonyl.



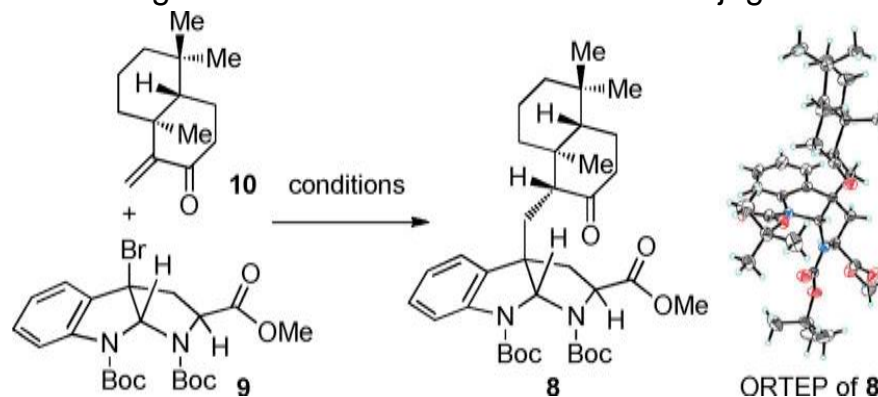
# 1. Reductive Couplings



**Scheme 2. Retrosynthetic analysis of drimentine G.**

# 1. Reductive Couplings

Table 1: Investigation of conditions for the radical conjugate addition.



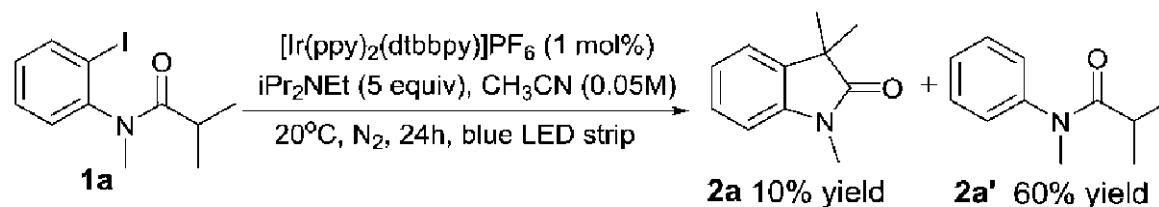
The success of this reaction is presumably due to the low concentration of the reductive species and the slow rate of side reactions such as the formation of debromo-**9**.

Entry	Conditions	Yield [%] <sup>[f]</sup>
1	AIBN, Bu <sub>3</sub> SnH, or (TMS) <sub>3</sub> SiH, toluene <sup>[a,b]</sup>	0
2	Et <sub>3</sub> B, O <sub>2</sub> , Bu <sub>3</sub> SnH, THF <sup>[a,c]</sup>	0
3	[Co(PPh <sub>3</sub> )Cl], acetone <sup>[a,c]</sup>	0
4	Bu <sub>3</sub> SnH (syringe pump), benzene <sup>[b,d]</sup>	58
5	[Ru(bpy) <sub>3</sub> Cl <sub>2</sub> ] $\cdot$ 6H <sub>2</sub> O (2.5%), blue LED, Et <sub>3</sub> N <sup>[a,c,e]</sup>	51
6	blue LED, Et <sub>3</sub> N <sup>[a,c,e]</sup>	12
7	[Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub> (2.5%), blue LED, Et <sub>3</sub> N <sup>[a,c,e]</sup>	89 (87) <sup>[h]</sup>
8	[Ir(ppy) <sub>2</sub> (dtbbpy)]PF <sub>6</sub> (2.5%), blue LED, Et <sub>3</sub> N 10/9 = 1:1.5 <sup>[c,e]</sup>	91 (86) <sup>[g,h]</sup>

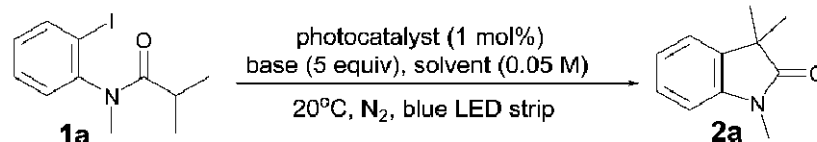
complete debromination of **9**  
**10** was fully recovered

[a] 4.0 equiv of **10**. [b] 80 **8C**. [c] 22 **8C**. [d] 10.0 equiv of **10**. [e] 2.0 equiv of Et<sub>3</sub>N in DMF (0.5 M in **9** or **10**). [f] Based on **9**. [g] Based on **10**. [h] Yields in parentheses obtained from gram-scale reactions. AIBN = azobisisobutyronitrile, bpy = bipyridine, dtbbpy = 4,4'-di-tert-butyl-2,2'-bipyridine, ppy = 2-phenylpyridine, TMS = trimethylsilyl.

# 1. Reductive Couplings

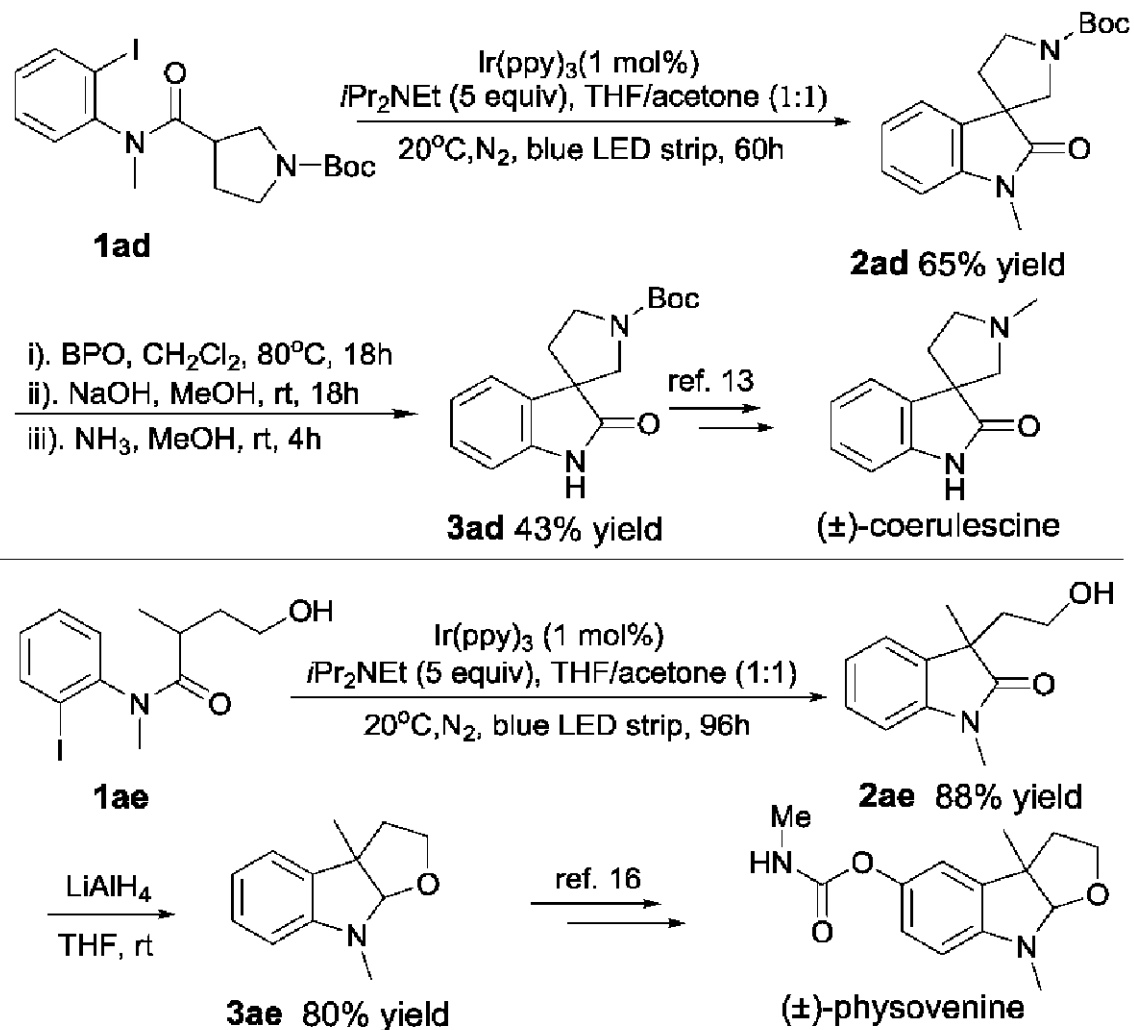


Scheme 2  $[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$  was used as the photocatalyst.



Entry	Catalyst	Base	Solvent (v/v)	Time	Yield <sup>b</sup> (%)
1	$\text{Ru}(\text{bpy})_3\text{Cl}_2$	$\text{iPr}_2\text{NEt}$	$\text{MeCN}$	24 h	0
2	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{MeCN}$	24 h	37
3	$[\text{Ir}(\text{ppy})_2(\text{dtbbpy})]\text{PF}_6$	$\text{iPr}_2\text{NEt}$	$\text{MeCN}$	24 h	10
4	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{CH}_2\text{Cl}_2$	24 h	57
5	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{THF}$	7 d	78
6	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{EA}$	5 d	46
7	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{DMSO}$	12 h	44
8	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{Acetone}$	36 h	67
9	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{MeOH}$	36 h	46
10	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{DMF}$	12 h	51
11	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{THF}/\text{H}_2\text{O}$ (7:1)	60 h	82
12	$\text{fac-Ir}(\text{ppy})_3$	$\text{iPr}_2\text{NEt}$	$\text{THF}/\text{acetone}$ (1:1)	60 h	87

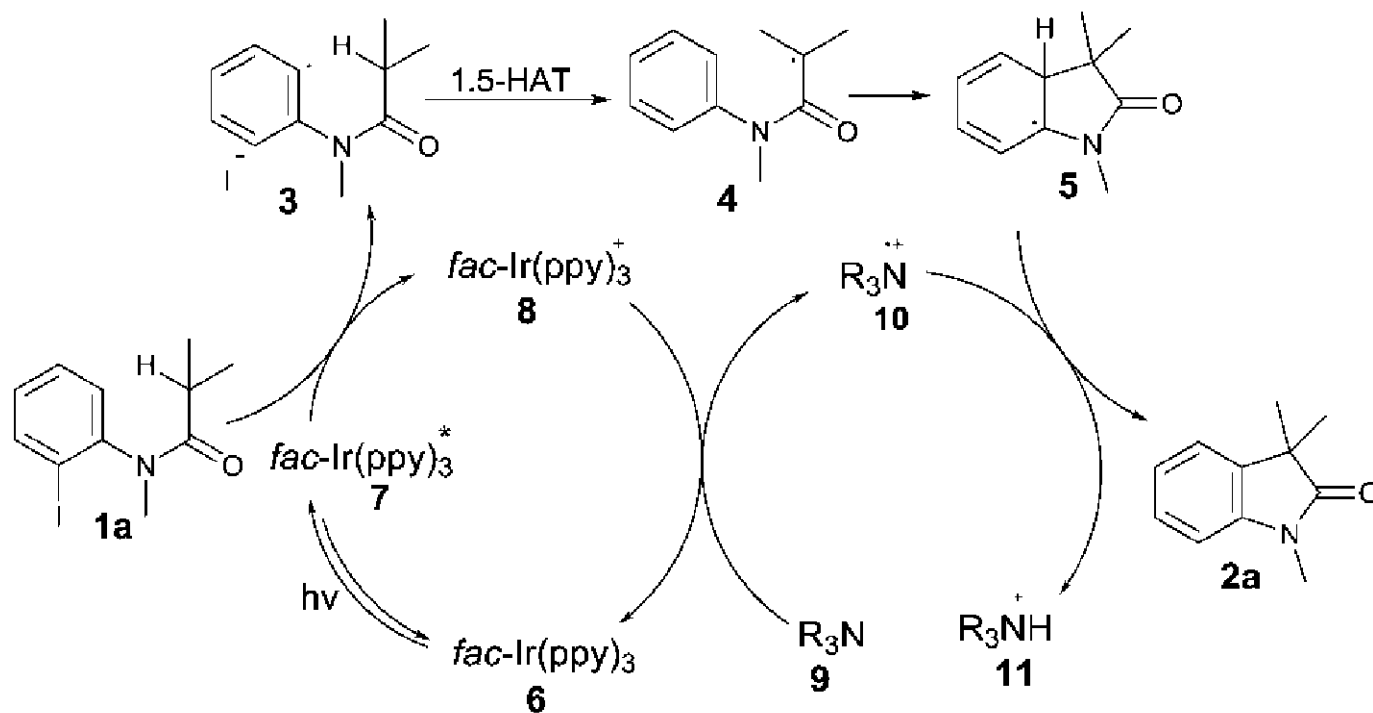
# 1. Reductive Couplings



Scheme 3 Formal synthesis of coerulescine and physovenine.



# 1. Reductive Couplings



Scheme 1 Proposed mechanism for the 1,5-HAT reaction.

## 2. Photocycloadditions

### [2 + 2] : photoredox process vs simple $h\nu$

The excited states of photoredox catalysts can **oxidise one of the reaction partners under mild conditions**, such reactions are **highly regio/stereo- selective and high-yielding**.

Daniele Leonori\* *Nat. Prod. Rep.*, 2016, 33, 1248–1254

### [4 + 2] : photoredox process vs thermal reactions

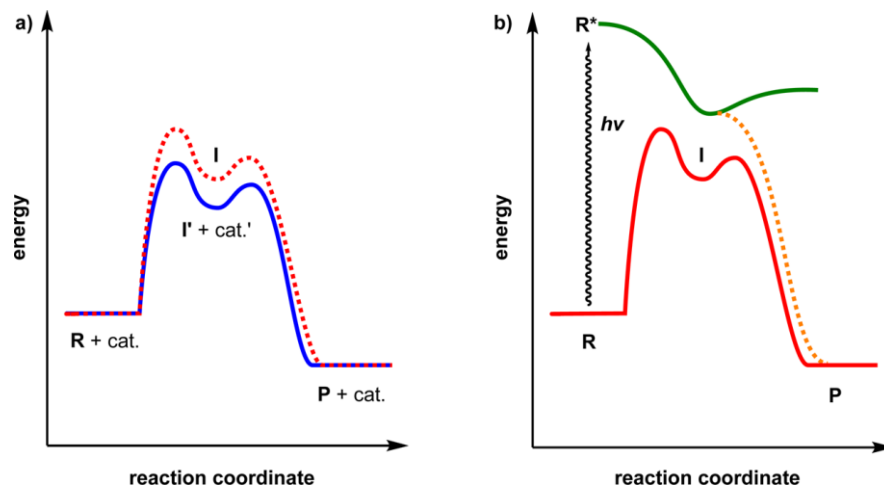
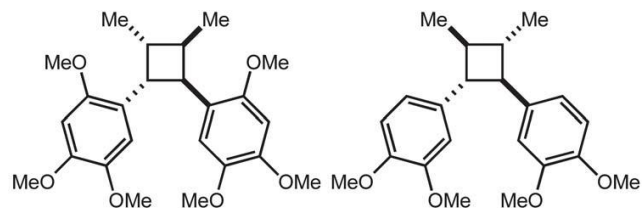


Figure 1. Reaction pathways in (a) a thermal reaction with reagent R yielding product P catalyzed by a catalyst (cat.) via intermediate I' and (b) in a photochemically induced reaction where the chemical reaction commences from the excited state of the reagent (R\*).

Stephenson\* *Chem. Rev.* 2016, 116, 9683–9747

## 2. Photocycloadditions: [2 + 2] *via* cation radical

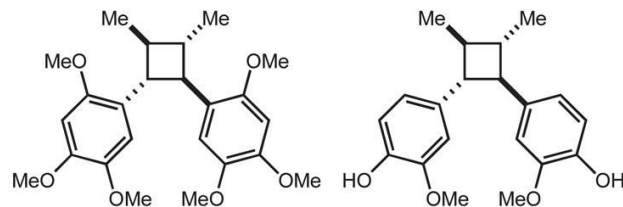


**andamanicin**

NOS inhibition  $IC_{50} = 53.5 \mu M$

**di-O-methylendiandrin A**

GR binding  $IC_{50} = 13 \mu M$



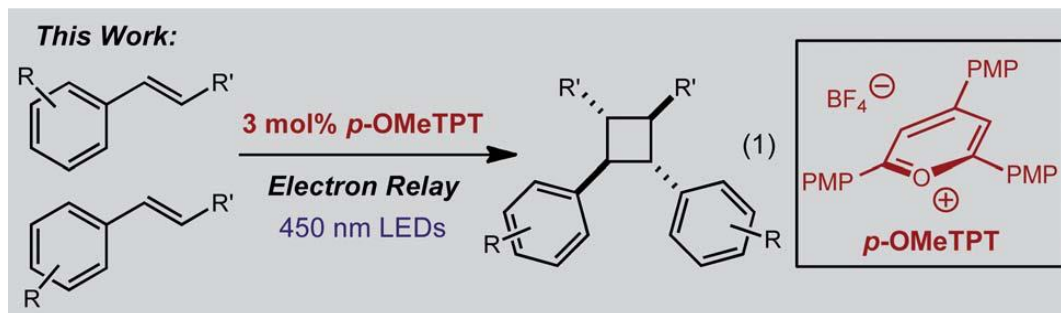
**magnosalin**

NOS inhibition  $IC_{50} = 5.9 \mu M$

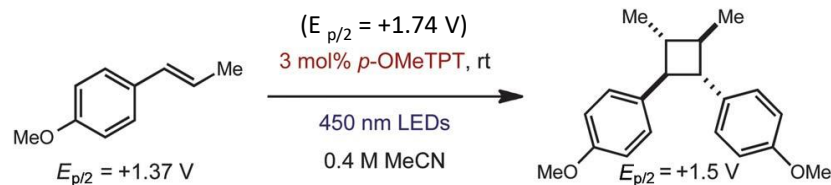
**endiandrin A**

GR binding  $IC_{50} = 0.9 \mu M$

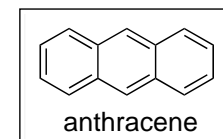
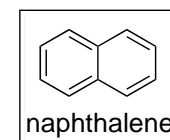
**Scheme 1** Several examples of bioactive cyclobutane lignan natural products and derivatives.



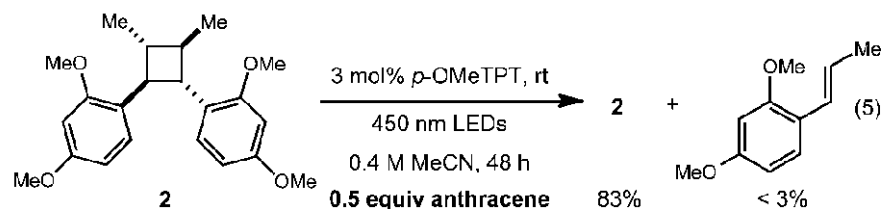
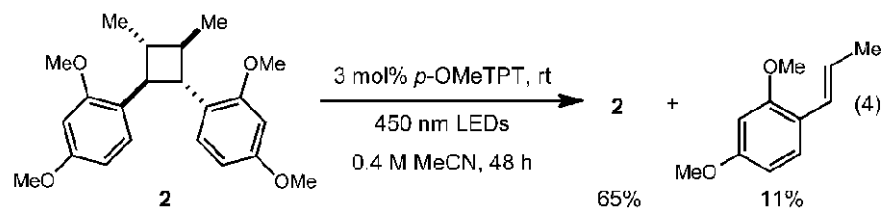
## 2. Photocycloadditions: [2 + 2] *via* cation radical



Entry	Electron relay <sup>b</sup>	Equivalents	Yield
1	None	None	0%
2	Anthracene (+1.21 V)	0.25	13%
3	Naphthalene (+1.61 V)	0.25	16%
4	Naphthalene	0.5	18%
5 <sup>c</sup>	<b>Naphthalene</b>	<b>0.5</b>	<b>54%</b>
6	NPh <sub>3</sub> (+0.91 V)	0.25	0%
7 <sup>d</sup>	Naphthalene	0.5	0%
8 <sup>e</sup>	Naphthalene	0.5	0%



<sup>a</sup> Reactions were carried out for 24 h, unless otherwise noted. <sup>1</sup>H NMR yields are reported. <sup>b</sup> Peak potentials of electron relay in parenthesis. <sup>c</sup> Reaction time was 5 days. <sup>d</sup> Reaction in the dark. <sup>e</sup> Reaction in the absence of *p*-OMeTPT.



## 2. Photocycloadditions: [2 + 2] *via* cation radical

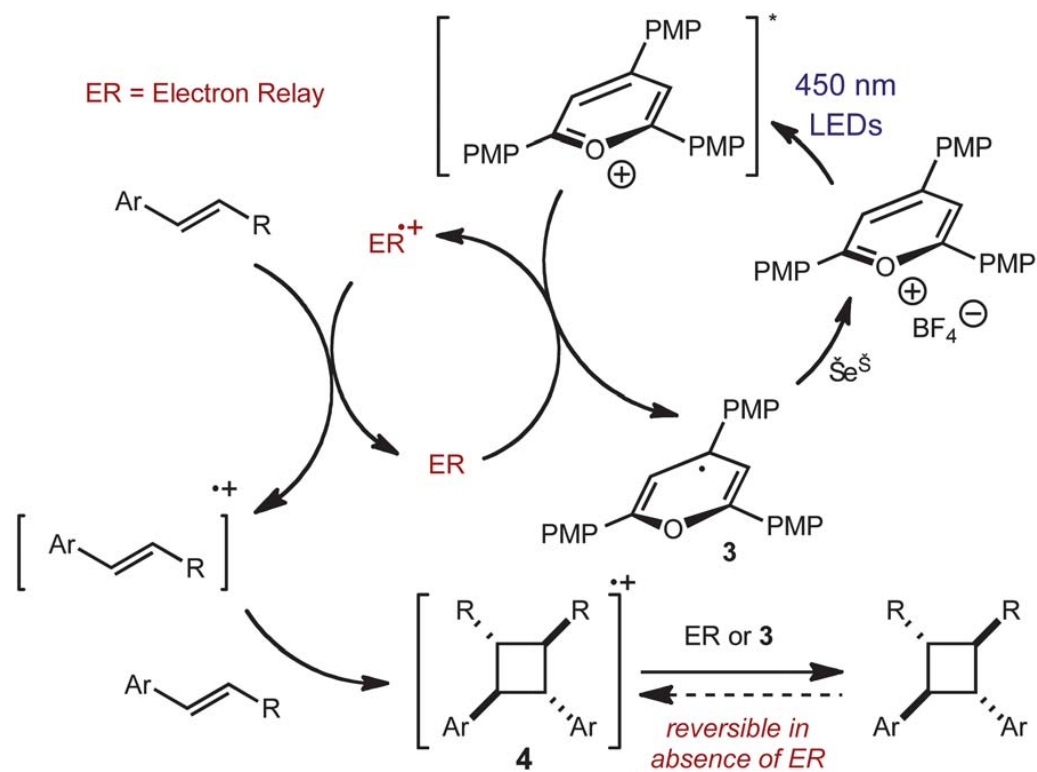
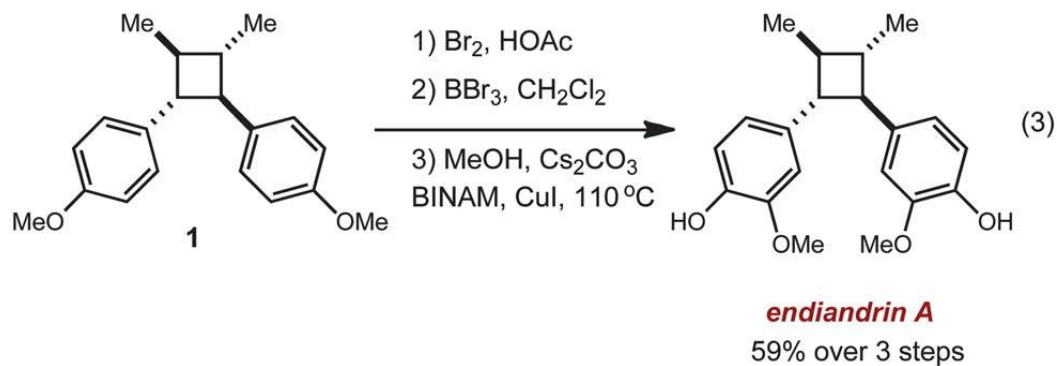
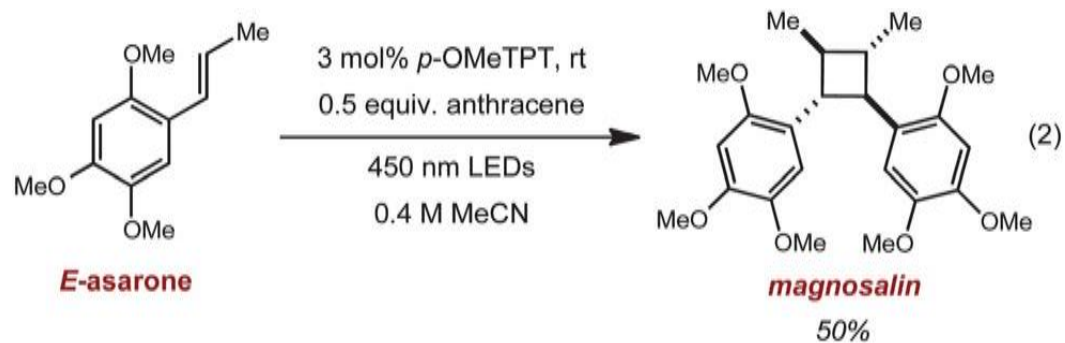
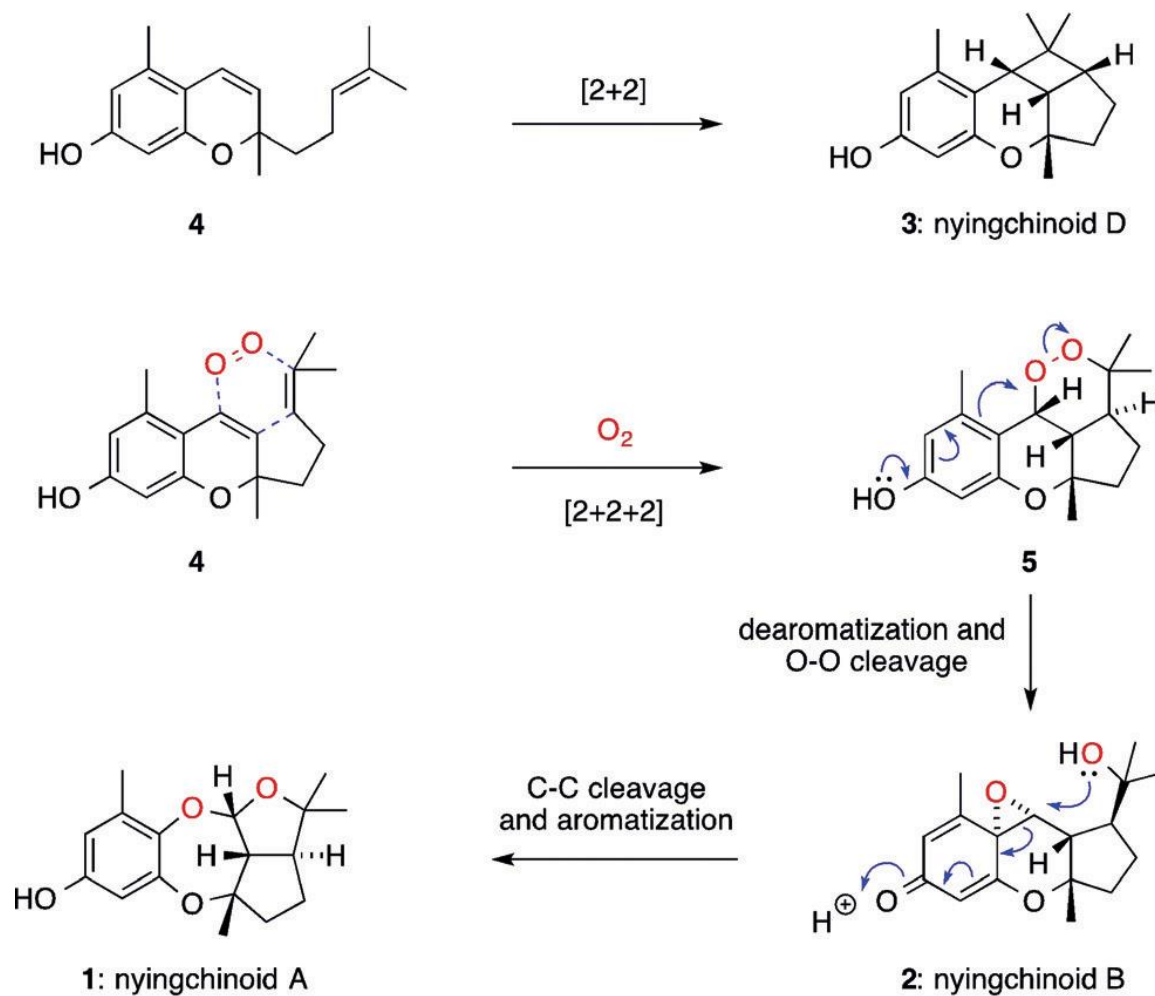


Fig. 2 Working mechanism for the alkene cyclodimerization reaction.

## 2. Photocycloadditions: [2 + 2] *via* cation radical

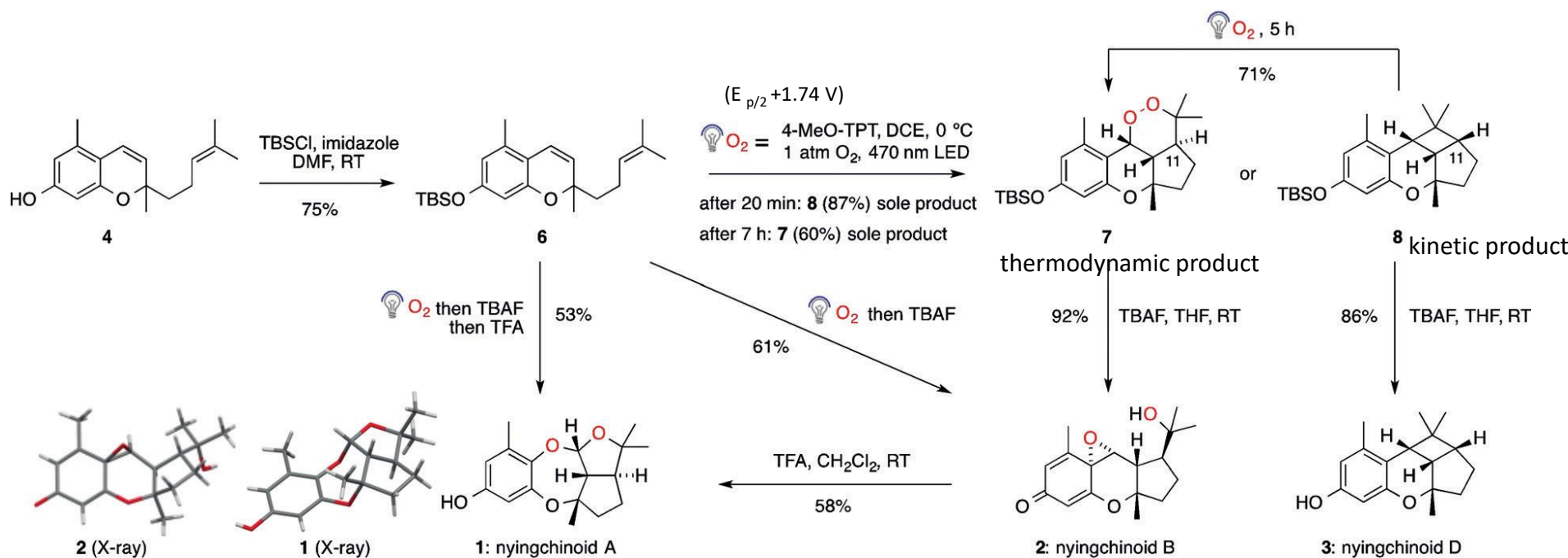


## 2. Photocycloadditions: [2 + 2] *via* cation radical



Scheme 1. Proposed biosynthesis of nyingchinoids A, B, and D.

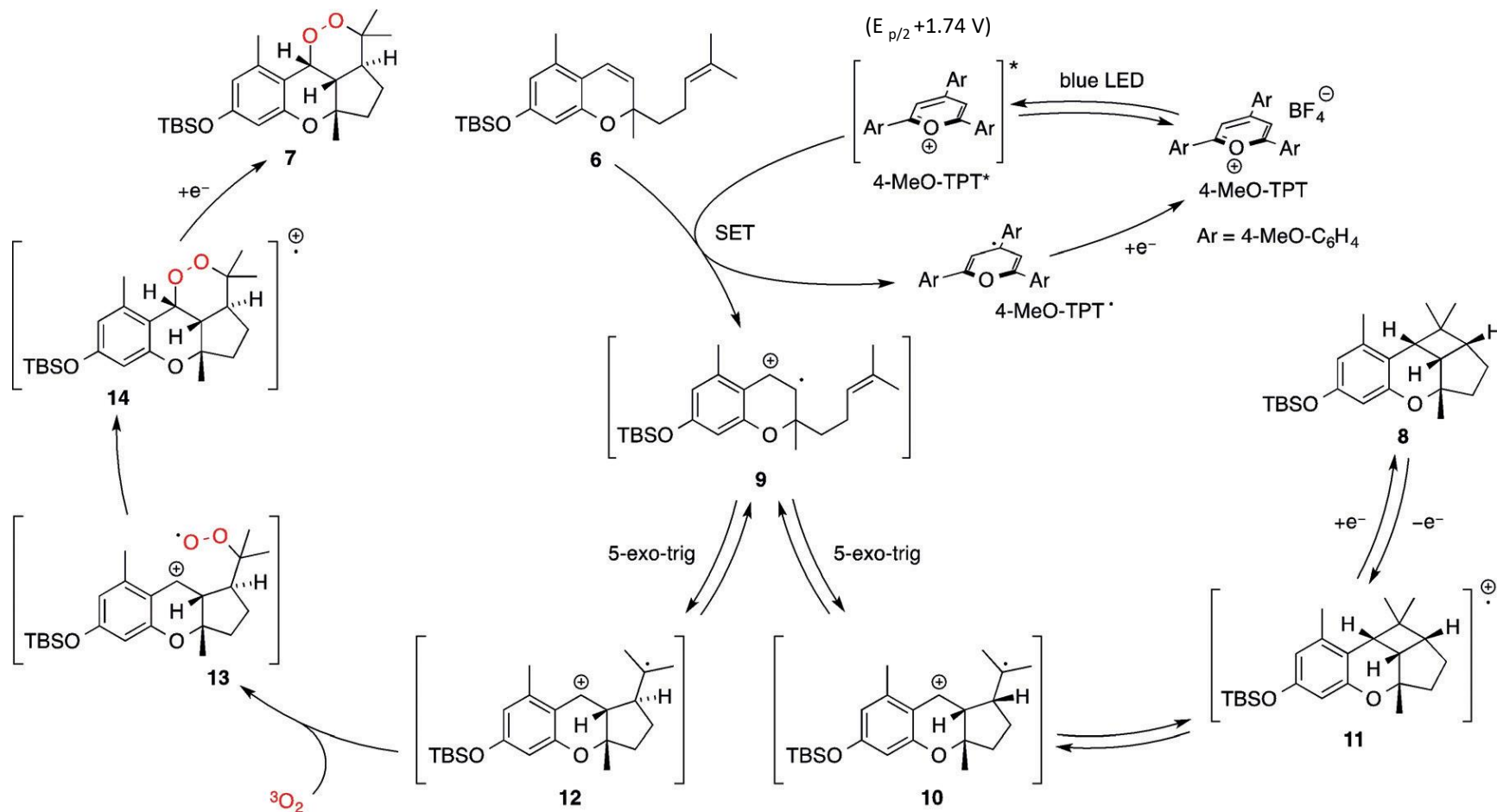
## 2. Photocycloadditions: [2 + 2] *via* cation radical





## 2. Photocycloadditions: [2 + 2] *via* cation radical

7 as the **thermodynamic product**

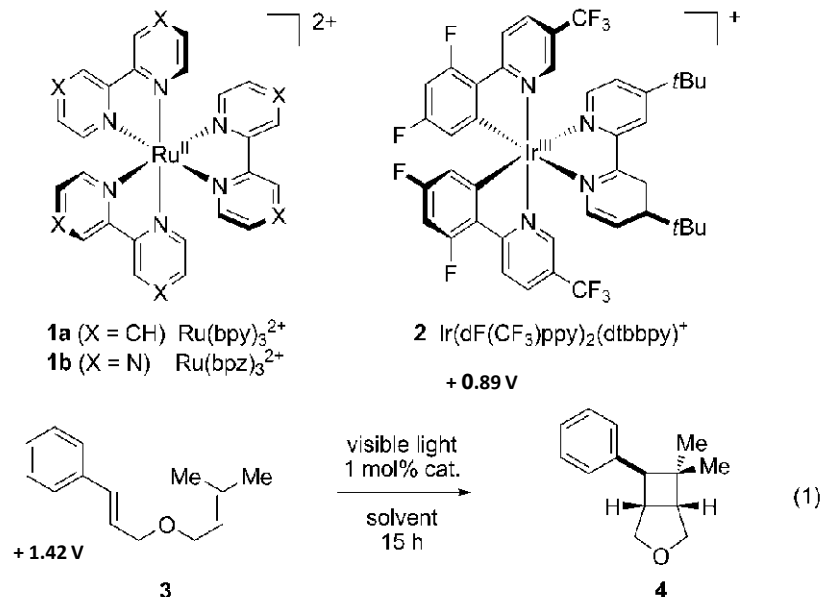


kinetically trapped as 11 instead of forming 12

biomimetic process

## 2. Photocycloadditions: [2 + 2] *via* triplet energy transfer

Table 1: Optimization and control studies for photocatalytic [2+2] cycloaddition.

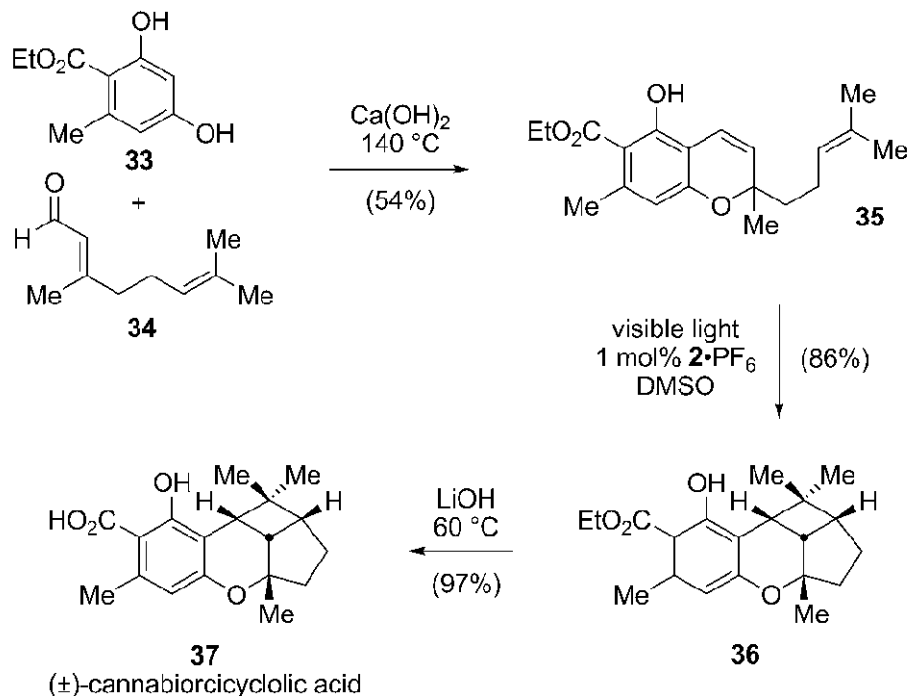


Entry <sup>[a]</sup>	Catalyst	Solvent	Conc. [m]	Yield <sup>[b]</sup> [%]
1	2-PF <sub>6</sub>	CHCl <sub>3</sub>	0.05	22
2	2-PF <sub>6</sub>	CH <sub>2</sub> Cl <sub>2</sub>	0.05	26
3	2-PF <sub>6</sub>	THF	0.05	21
4	2-PF <sub>6</sub>	acetone	0.05	24
5	2-PF <sub>6</sub>	MeOH	0.05	21
6	2-PF <sub>6</sub>	MeCN	0.05	13
7	2-PF <sub>6</sub>	DMSO	0.05	33
8	2-PF <sub>6</sub>	DMSO	0.01	89 (83) <sup>[c]</sup>
9	1a-(PF <sub>6</sub> ) <sub>2</sub>	DMSO	0.01	0
10	1b-(PF <sub>6</sub> ) <sub>2</sub>	DMSO	0.01	0
11	none	DMSO	0.01	0
12 <sup>[d]</sup>	2-PF <sub>6</sub>	DMSO	0.01	0

[a] Reactions irradiated using a 23 W compact fluorescent light bulb.

[b] Yields determined by <sup>1</sup>H NMR analysis against a calibrated internal standard unless noted. [c] Yield of the isolated product in parenthesis.

[d] Control reaction conducted in the dark.

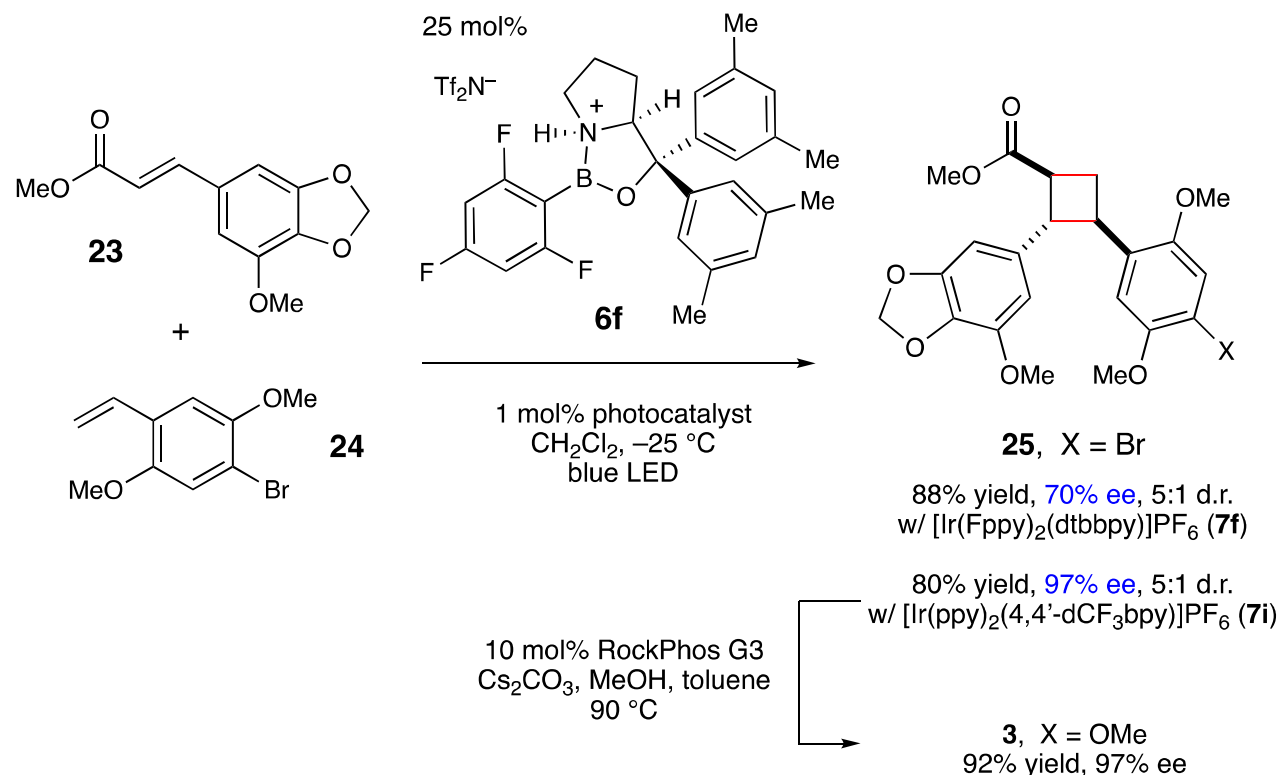


Scheme 2 Synthesis of cannabiorcicycloic acid.

Tehshik P. Yoon\* *Angew. Chem. Int. Ed.* **2012**, *51*, 10329–10332

## 2. Photocycloadditions: [2 + 2] *via* triplet energy transfer

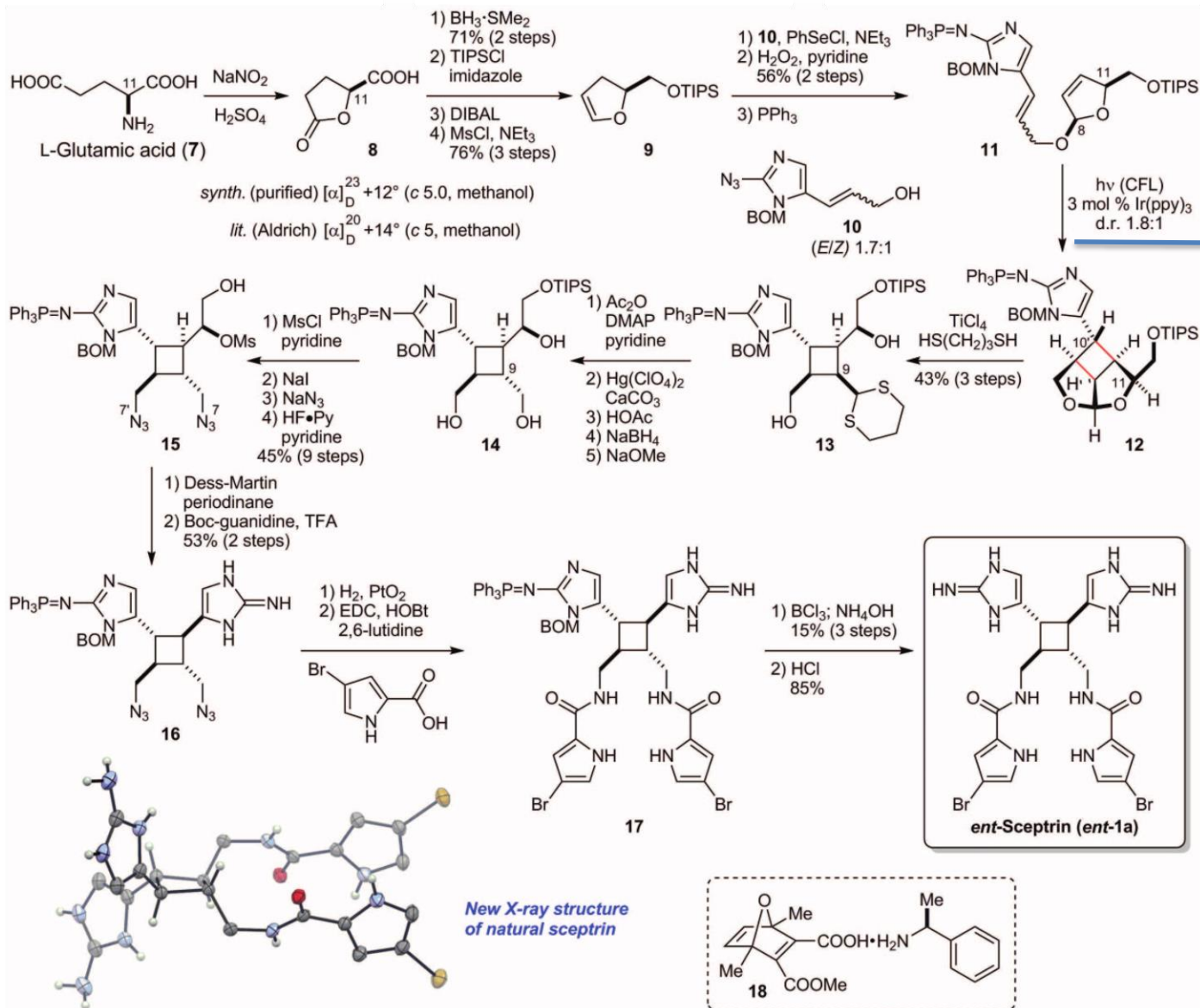
### Scheme 1. Streamlined Synthesis of Norlignan 3



**Influence of Lewis acids on the singlet-triplet gap:**

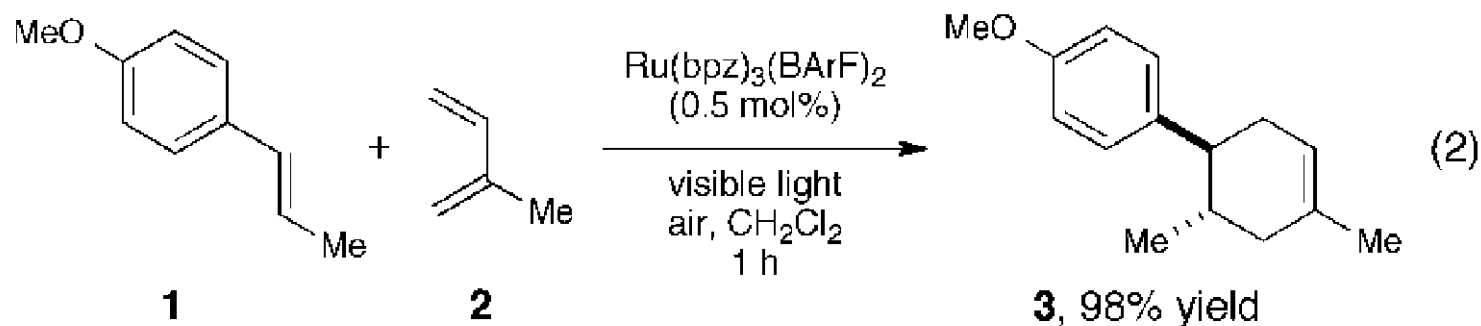
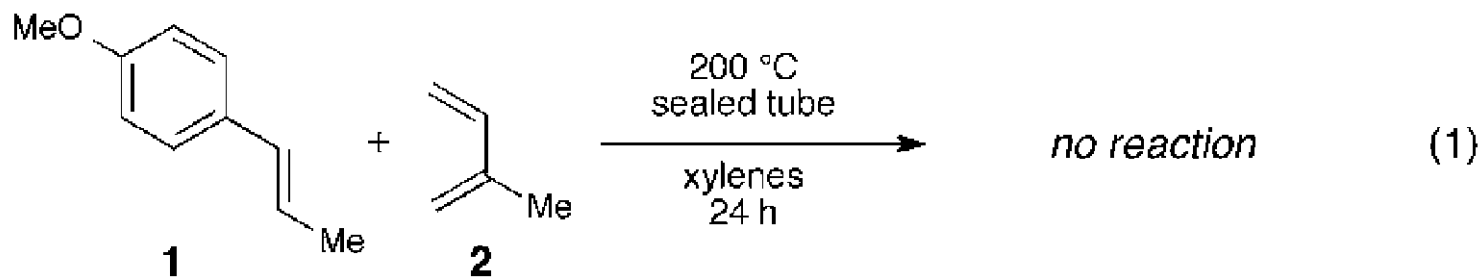
**Lewis acids can accelerate energy transfer by stabilizing the triplet state of the organic substrate**

## 2. Photocycloadditions: [2 + 2] *via* triplet energy transfer



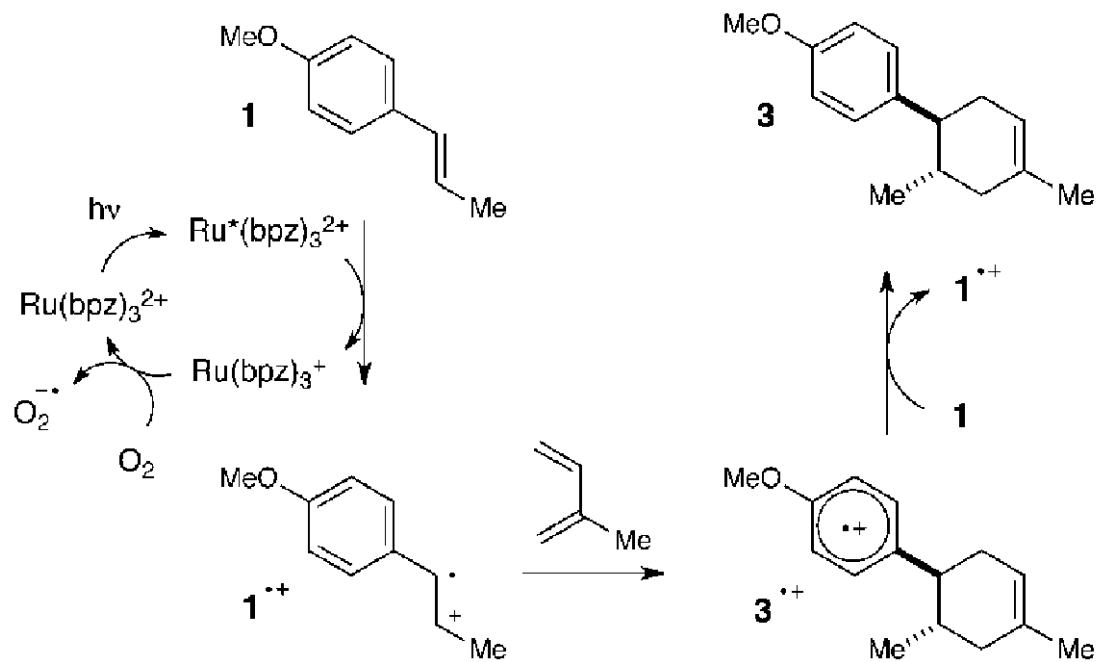
## 2. Photocycloadditions: [4 + 2] *via* Radical Cation Diels Alder Cycloaddition

Electronically mismatched Diels Alder reactions between two electron-rich components

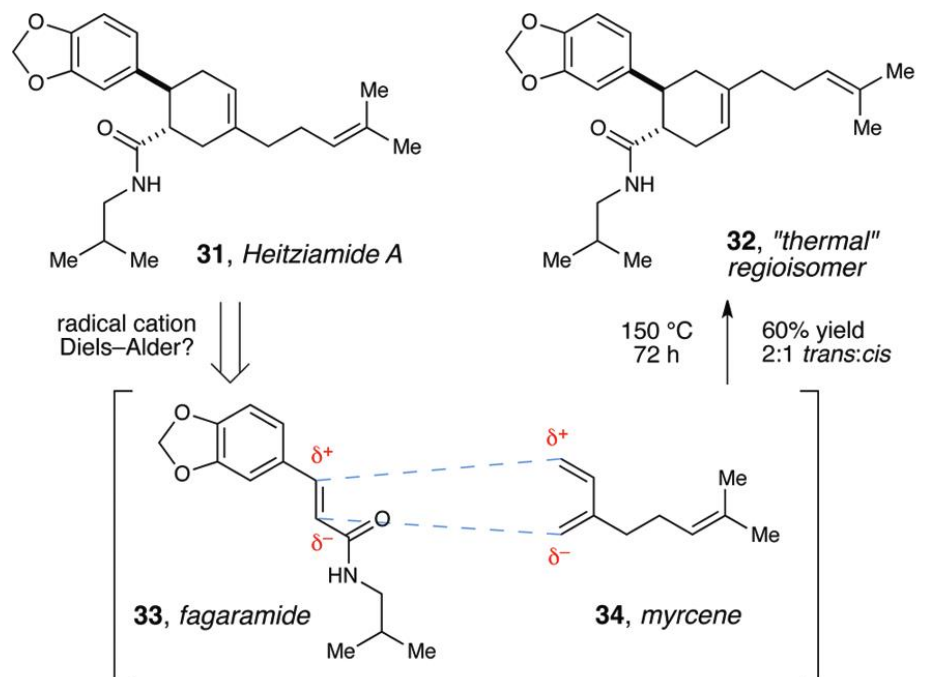


## 2. Photocycloadditions: [4 + 2] *via* Radical Cation Diels Alder Cycloaddition

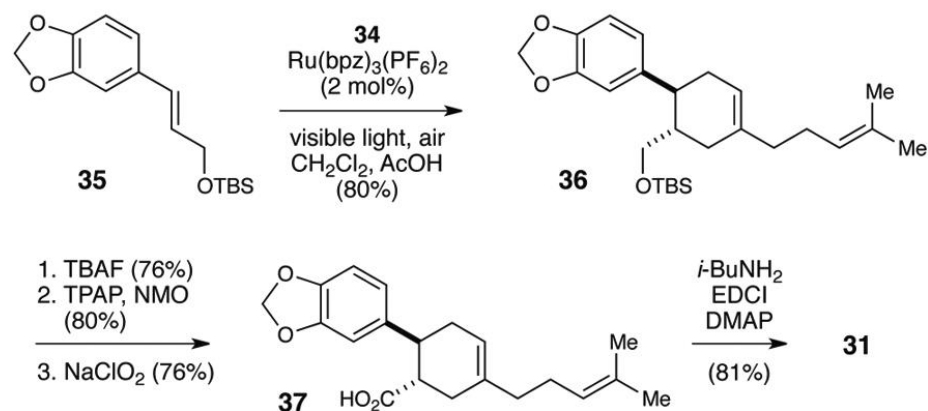
Scheme 1. Proposed Mechanism



## 2. Photocycloadditions: [4 + 2] *via* Radical Cation Diels Alder Cycloaddition



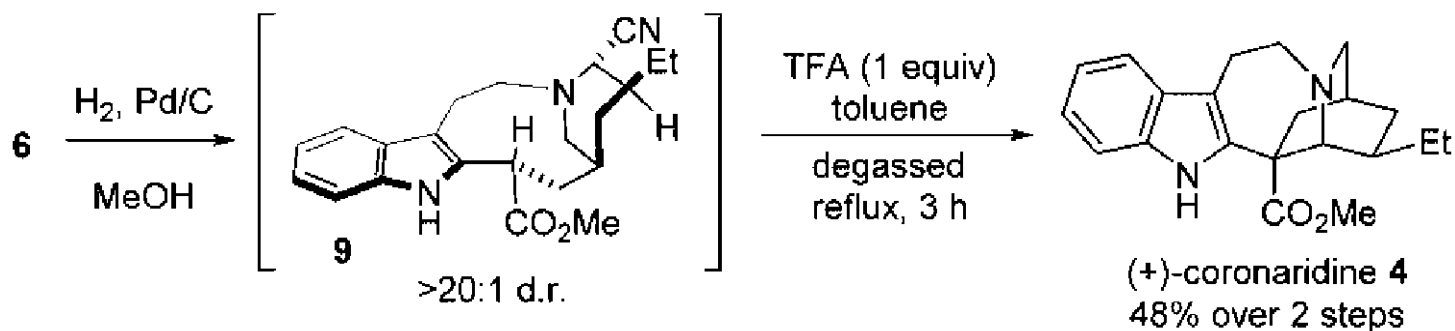
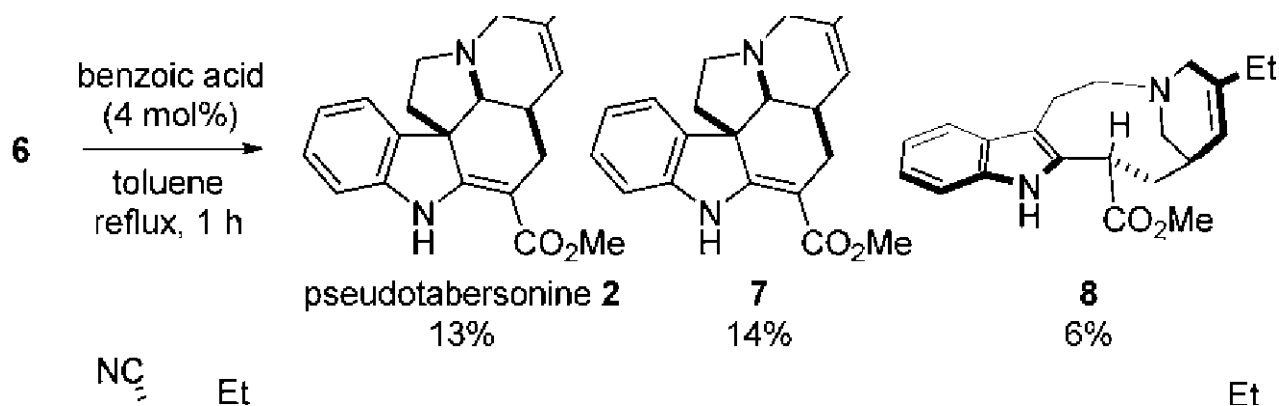
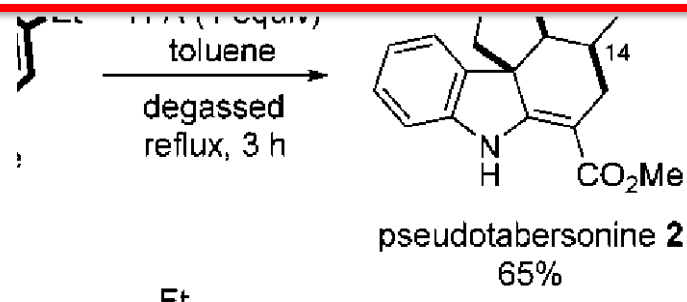
the polarization of the diene and dienophile  $\pi$  bonds suggests that the regiochemistry expected from the thermal Diels Alder reaction would afford the isomeric cycloadduct **32**







### 3. N-centered radicals



### 3. N-centered radicals

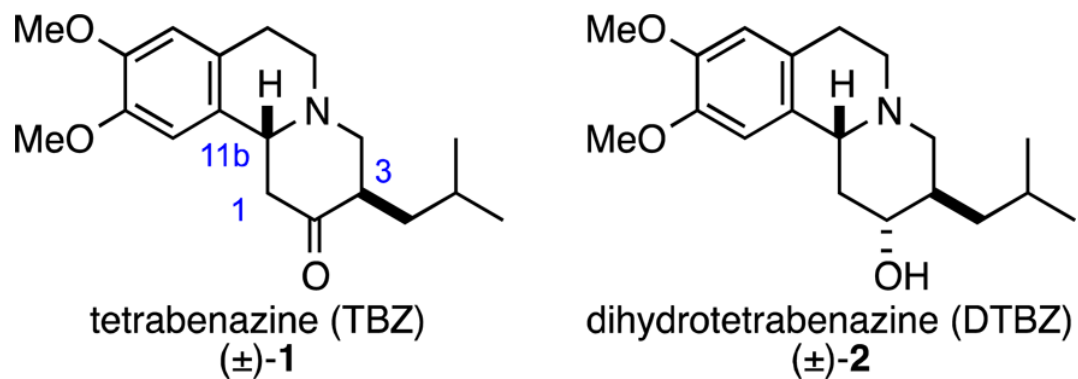
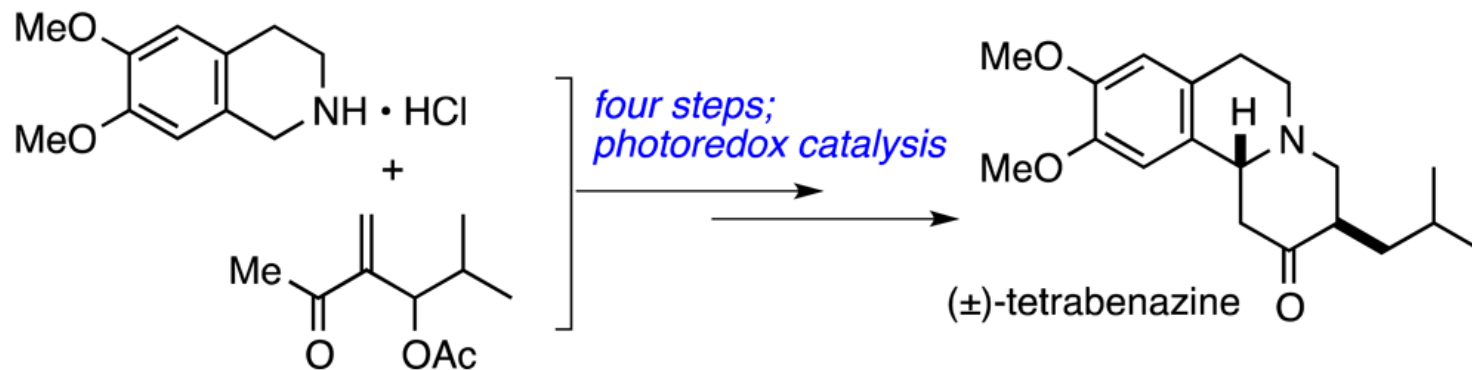
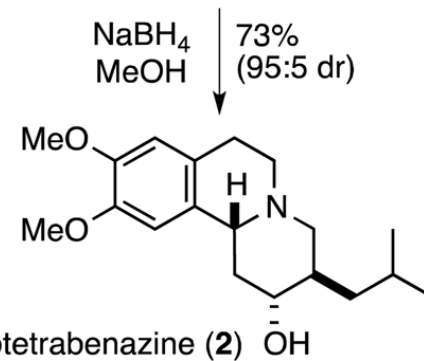
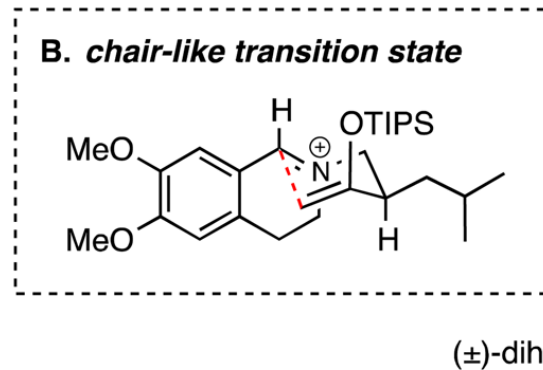
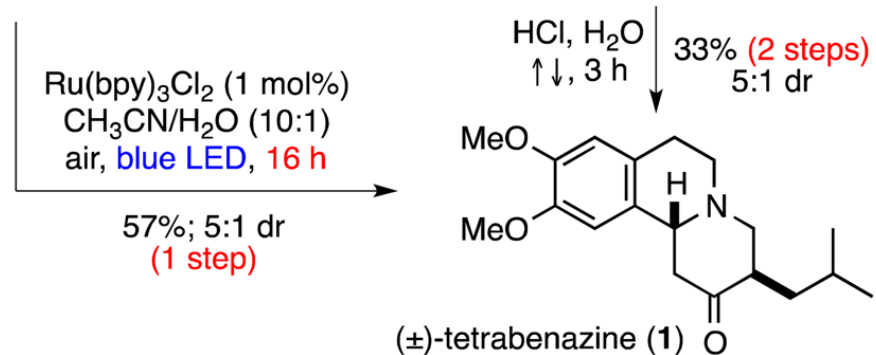
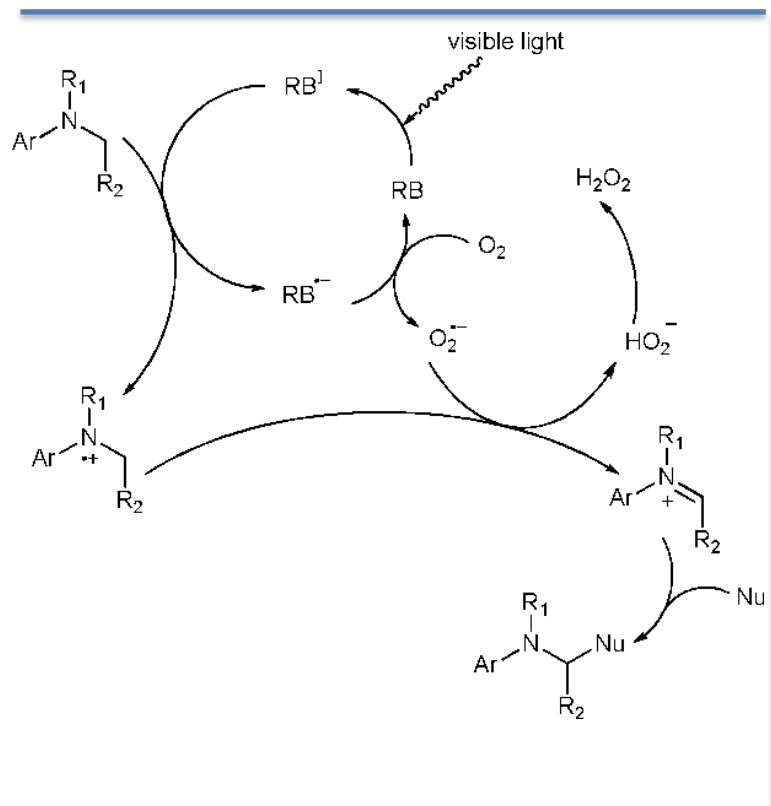
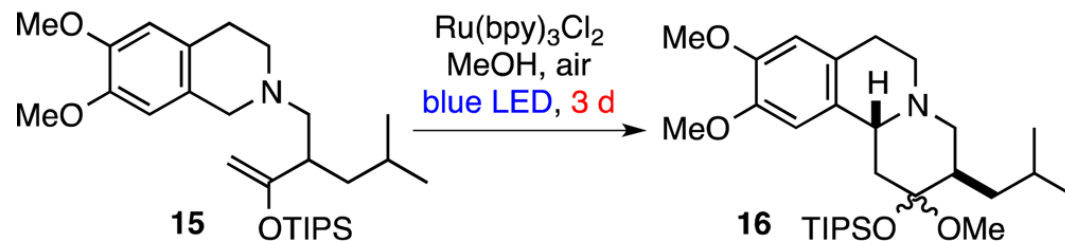
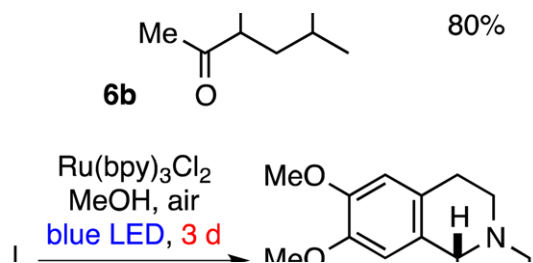


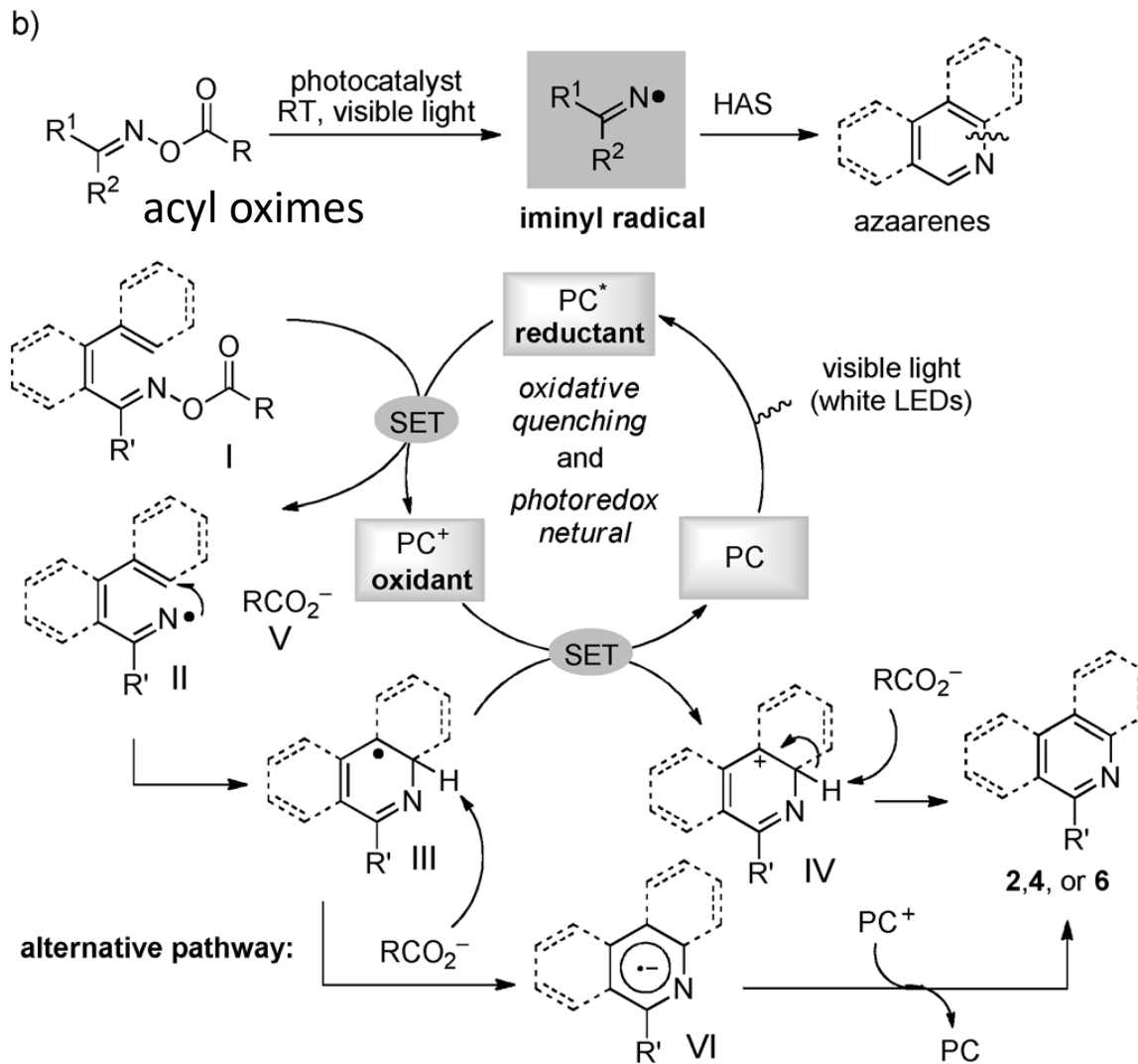
Figure 1. Tetrabenazine and dihydrotetrabenazine.



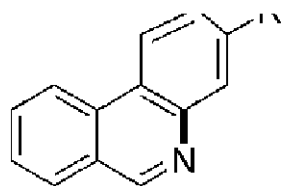
### 3. N-centered radicals



### 3. N-centered radicals



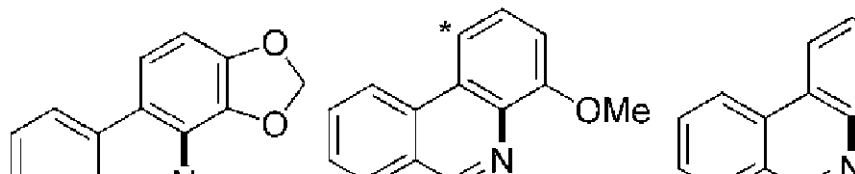
### 3. N-centered radicals



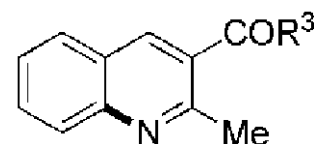
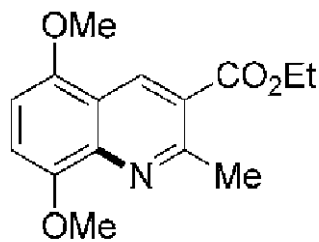
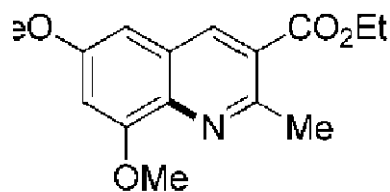
$R^1$   
**2i**,  $R^1 = \text{Et}$ , 95%  
**2j**,  $R^1 = \text{Bn}$ , 87%

$\text{Ar}$   
**2l**,  $\text{Ar} = p\text{-OMeC}_6\text{H}_4$   
**2m**,  $\text{Ar} = p\text{-CF}_3\text{C}_6\text{H}_4$   
**2n**,  $\text{Ar} = p\text{-ClC}_6\text{H}_4$

**2o**,  $R^3 = \text{H}$ , 91%  
**2p**,  $R^3 = \text{Me}$ , 88%  
**2q**,  $R^3 = \text{CF}_3$ , 93%

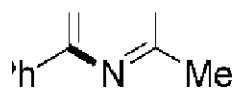


phenanthridines

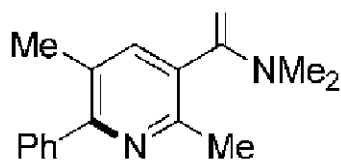


**4n**,  $R^3 = \text{OBn}$ , 74%  
**4o**,  $R^3 = \text{NMe}_2$ , 71%

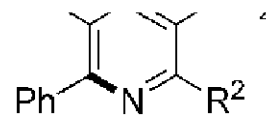
quinolines



**a**,  $R^1 = \text{OEt}$ , 89%  
**b**,  $R^1 = \text{OBn}$ , 82%  
**c**,  $R^1 = \text{OAllyl}$ , 84%



**6d**, 78%

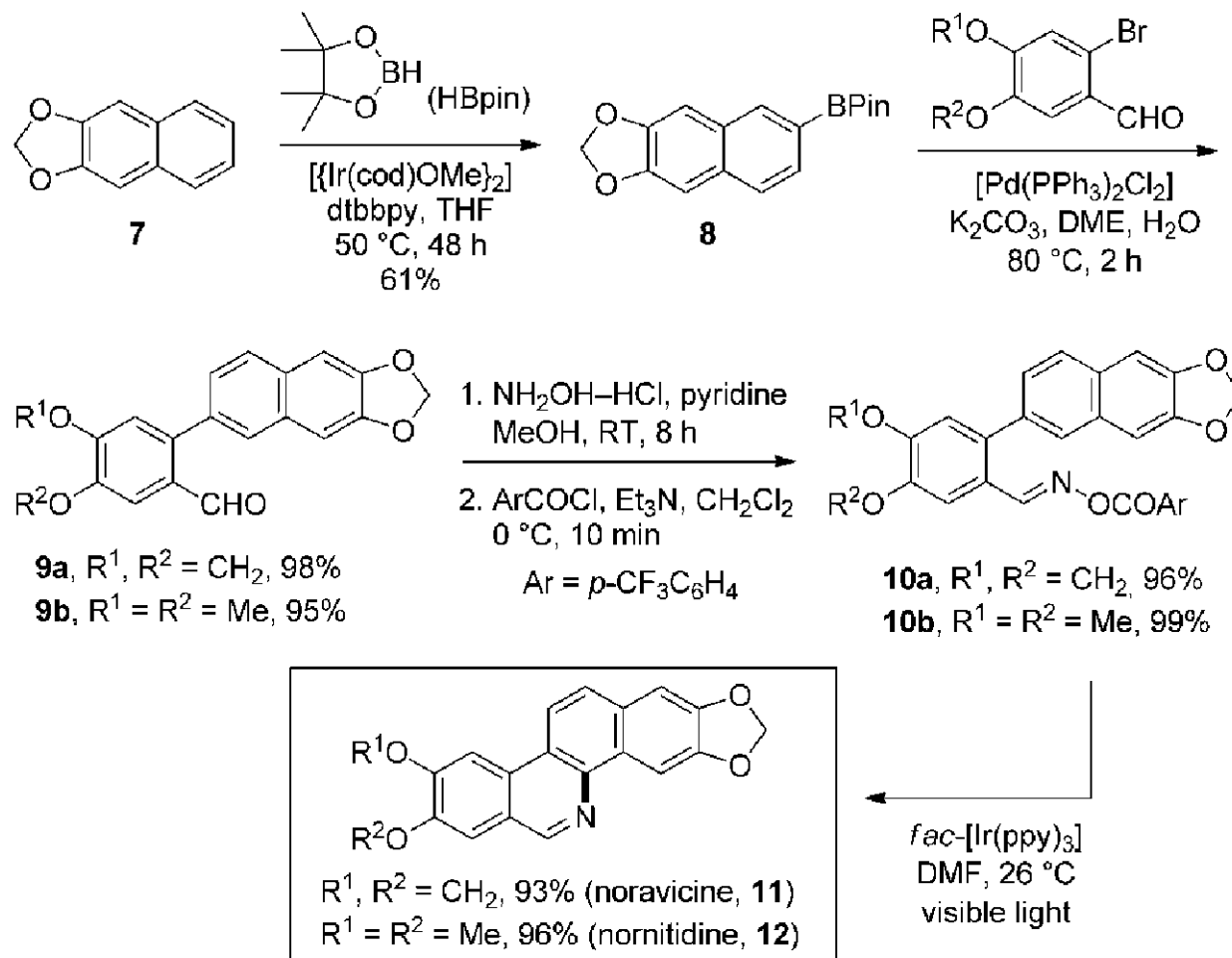


**6e**,  $R^2 = n\text{Pr}$ , 91%  
**6f**,  $R^2 = \text{Bn}$ , 87%

pyridines

### 3. N-centered radicals

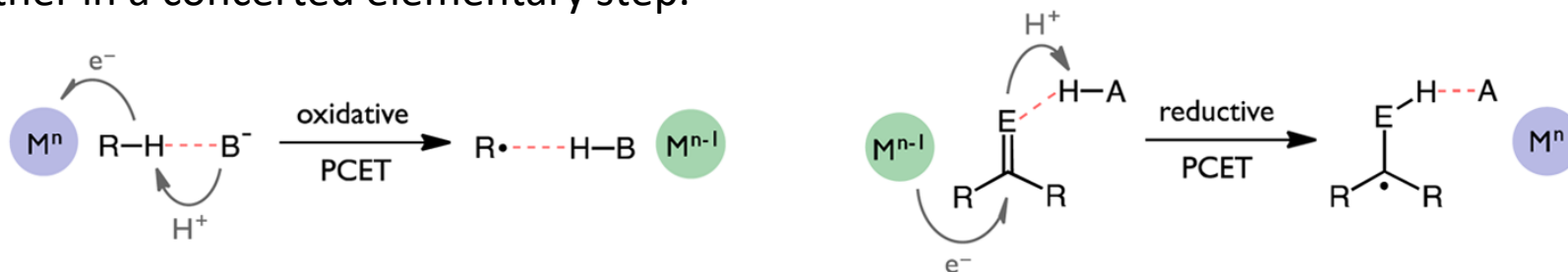
Previously reported routes to 11 and 12 required 11 steps and provided the products in about 20 % overall yield



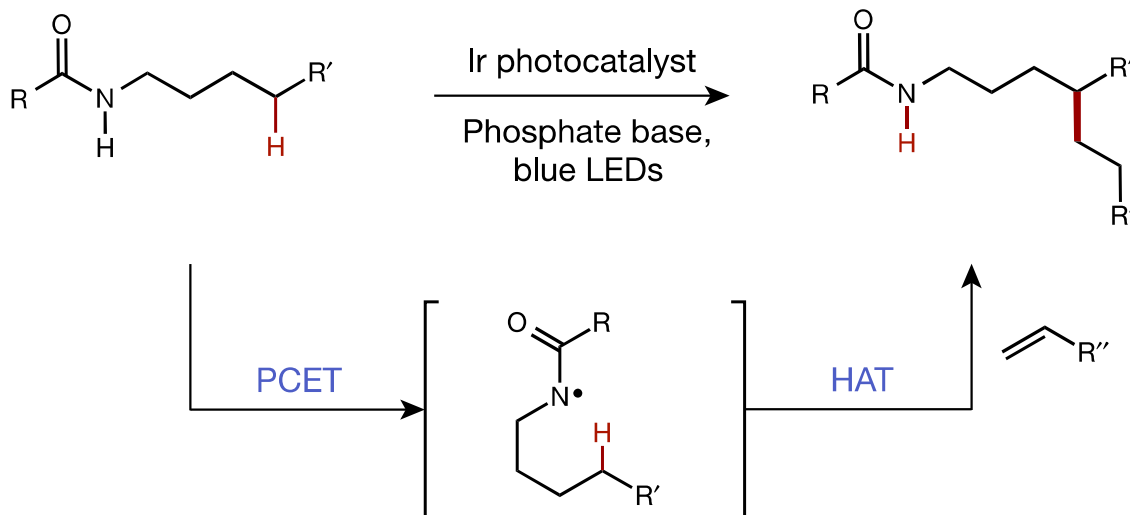
**Scheme 7.** Synthesis of benzo[*c*]phenanthridine alkaloids. cod = 1,5-cyclooctadiene, DME= dimethoxyethane, dtbbpy= 4,4'-di-*tert*-butyl-2,2'-bipyridine.

## 4. Proton-coupled Electron Transfer (PCET)

PCETs are unconventional redox processes in which an electron and proton are exchanged together in a concerted elementary step.

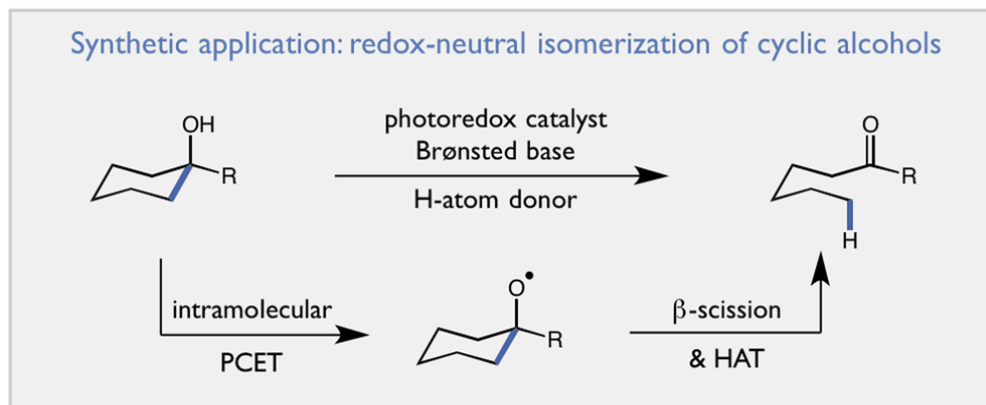


### c Catalytic C–H alkylation enabled by PCET

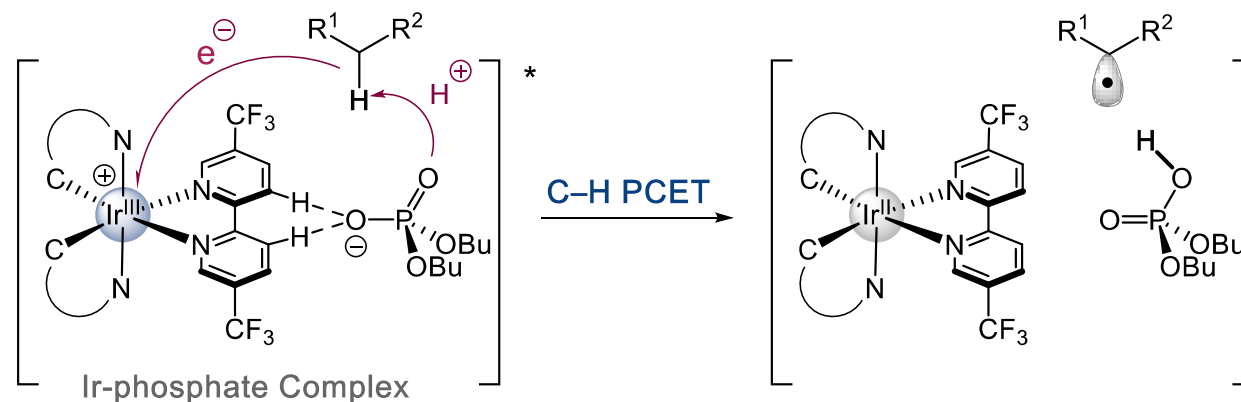


## 4. Proton-coupled Electron Transfer (PCET)

PCETs are unconventional redox processes in which an electron and proton are exchanged together in a concerted elementary step.



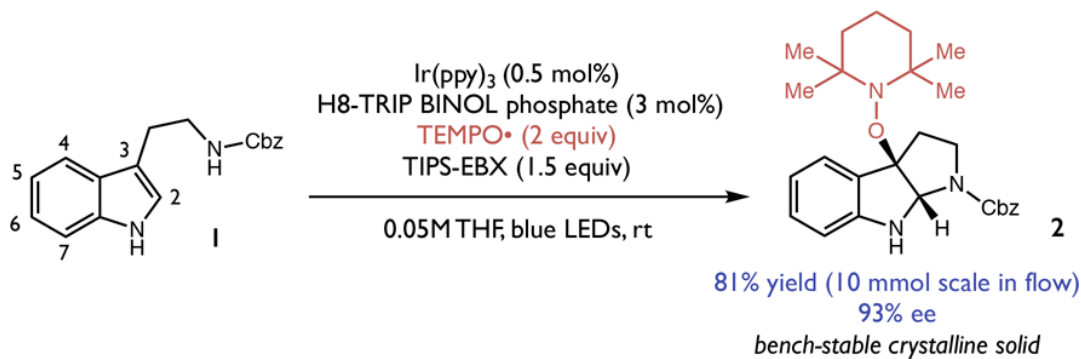
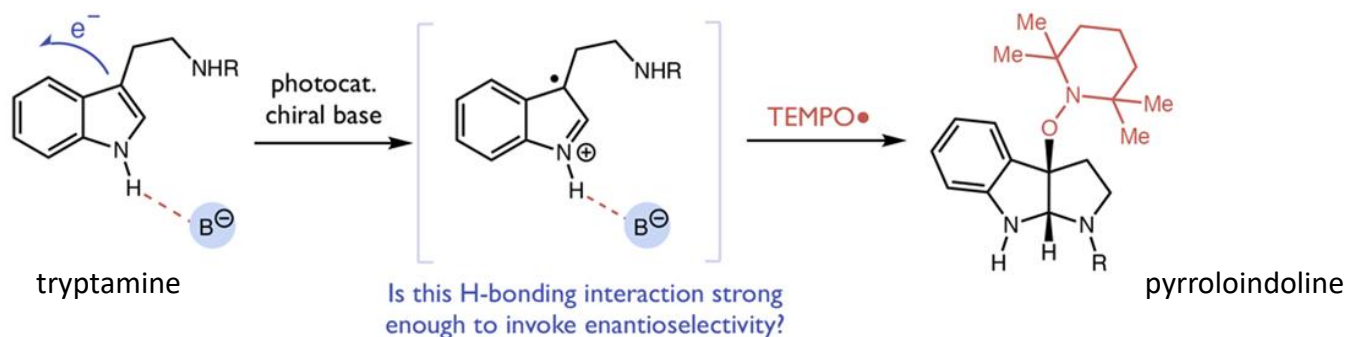
Robert R. Knowles\* *J. Am. Chem. Soc.* **2016**, *138*, 10794–10797



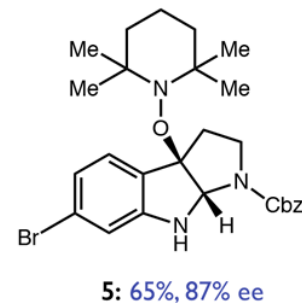
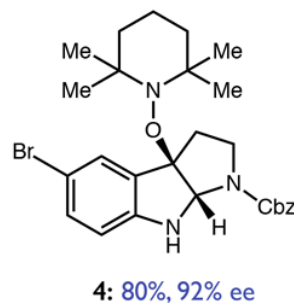
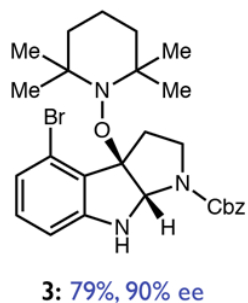
Robert R. Knowles\* *J. Am. Chem. Soc.* **2019**, *141*, 13253–13260



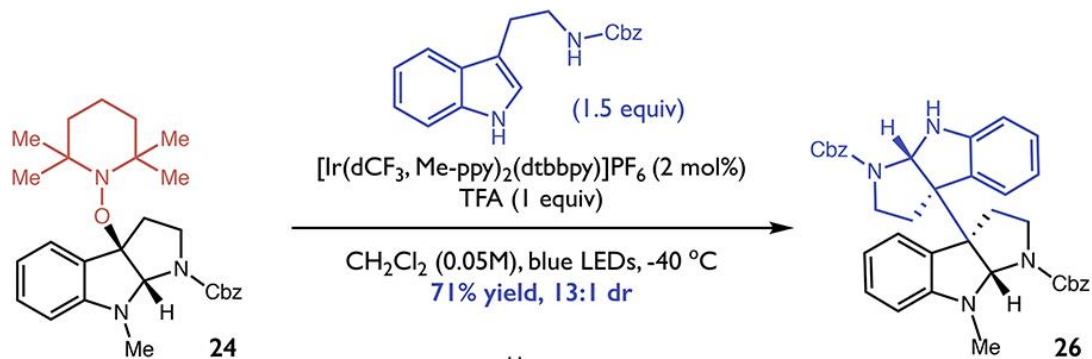
## 4. Proton-coupled Electron Transfer (PCET)



TEMPO-functionalized pyrroloindoline examples:

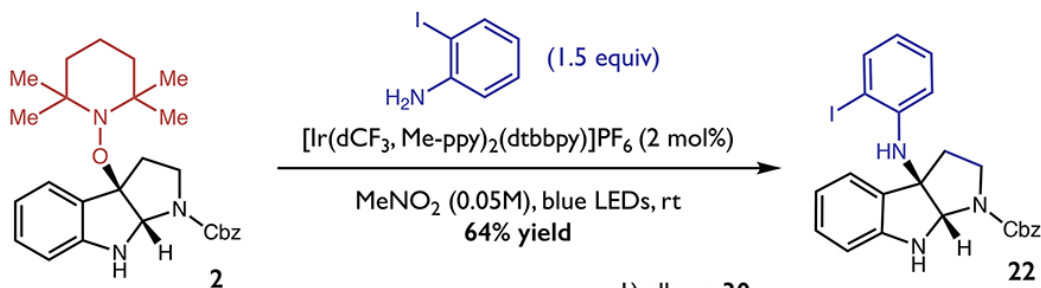


## 4. Proton-coupled Electron Transfer (PCET)



(-)-calycanthidine (27)  
4 steps from 1

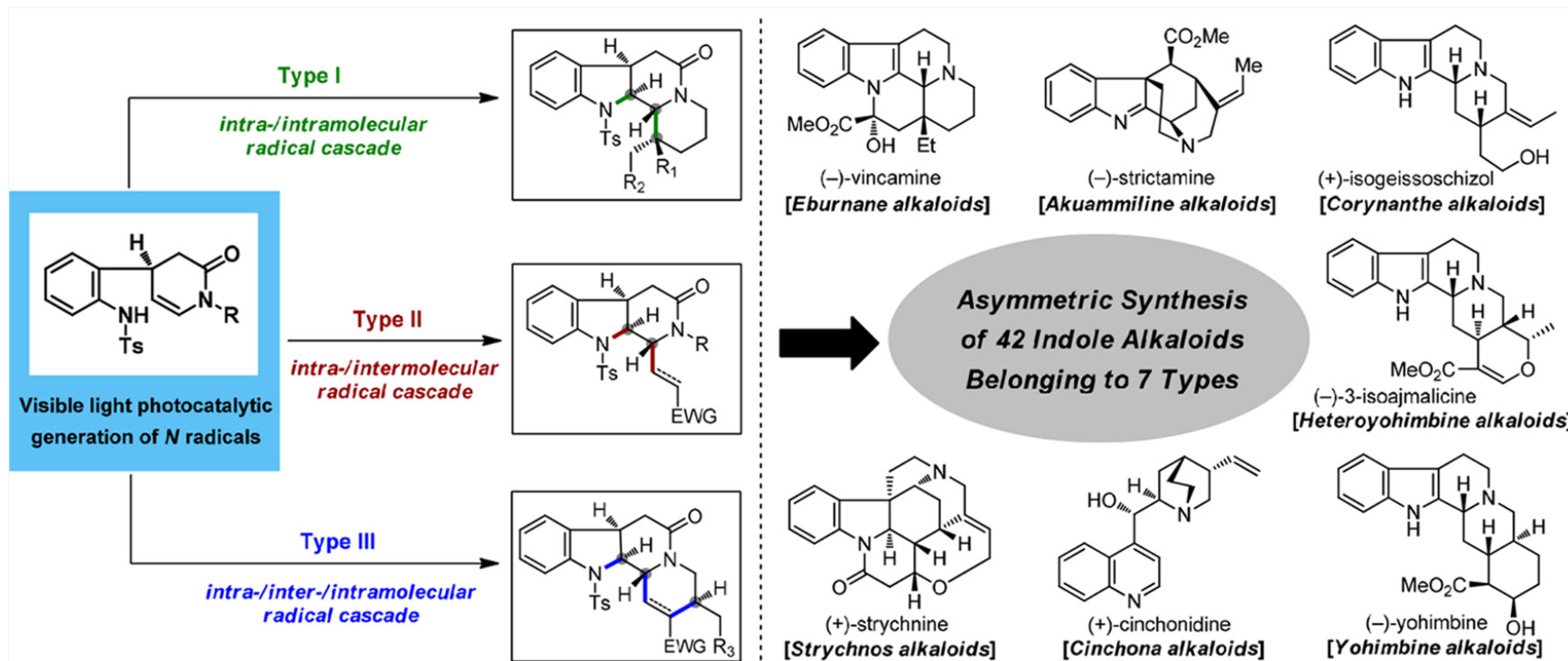
43% overall yield  
93% ee  
>13:1 dr



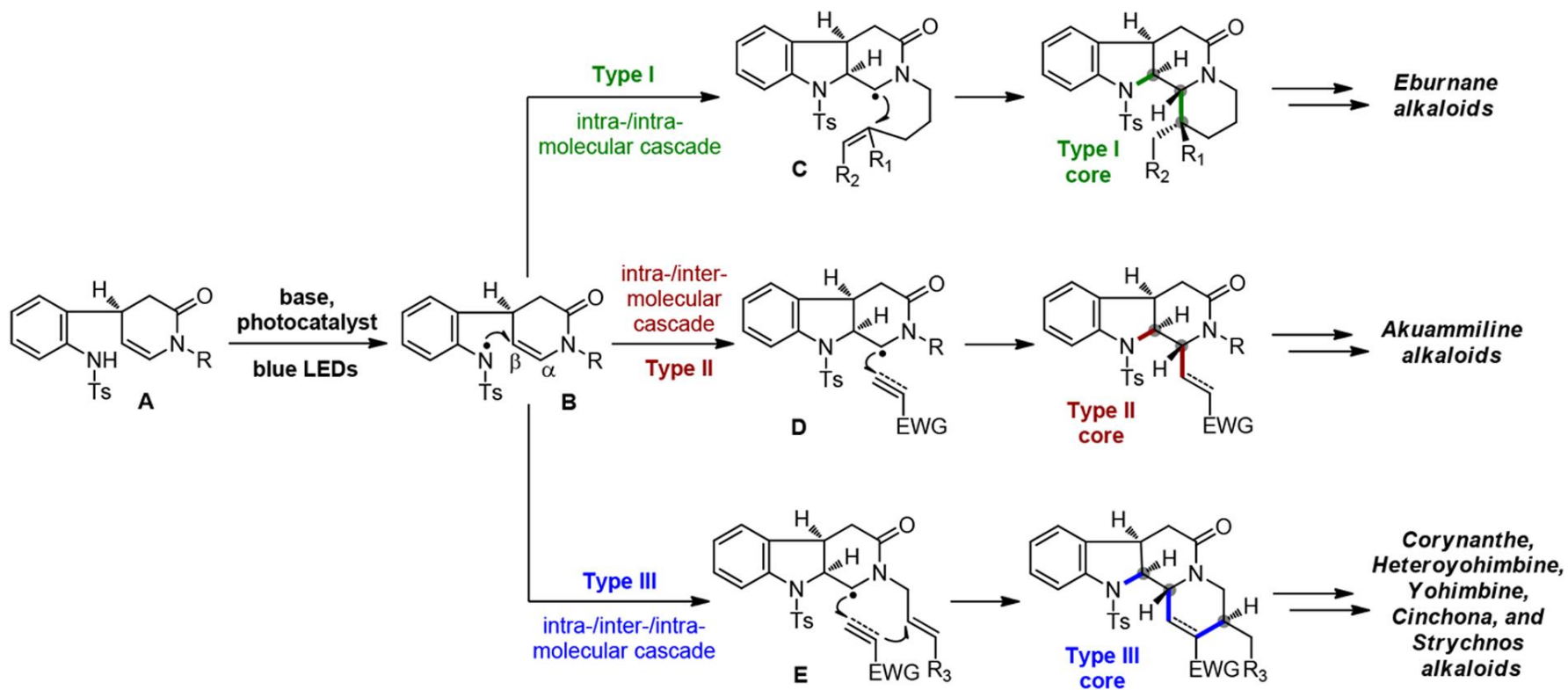
(-)-psychotriazine (31)

4 steps from 1  
38% overall yield  
93% ee

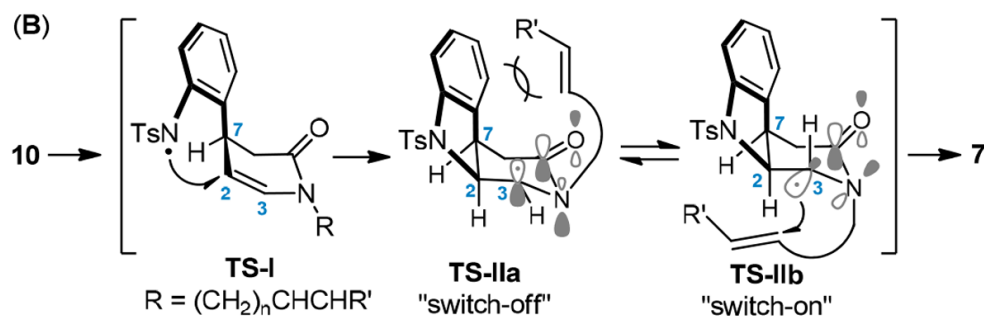
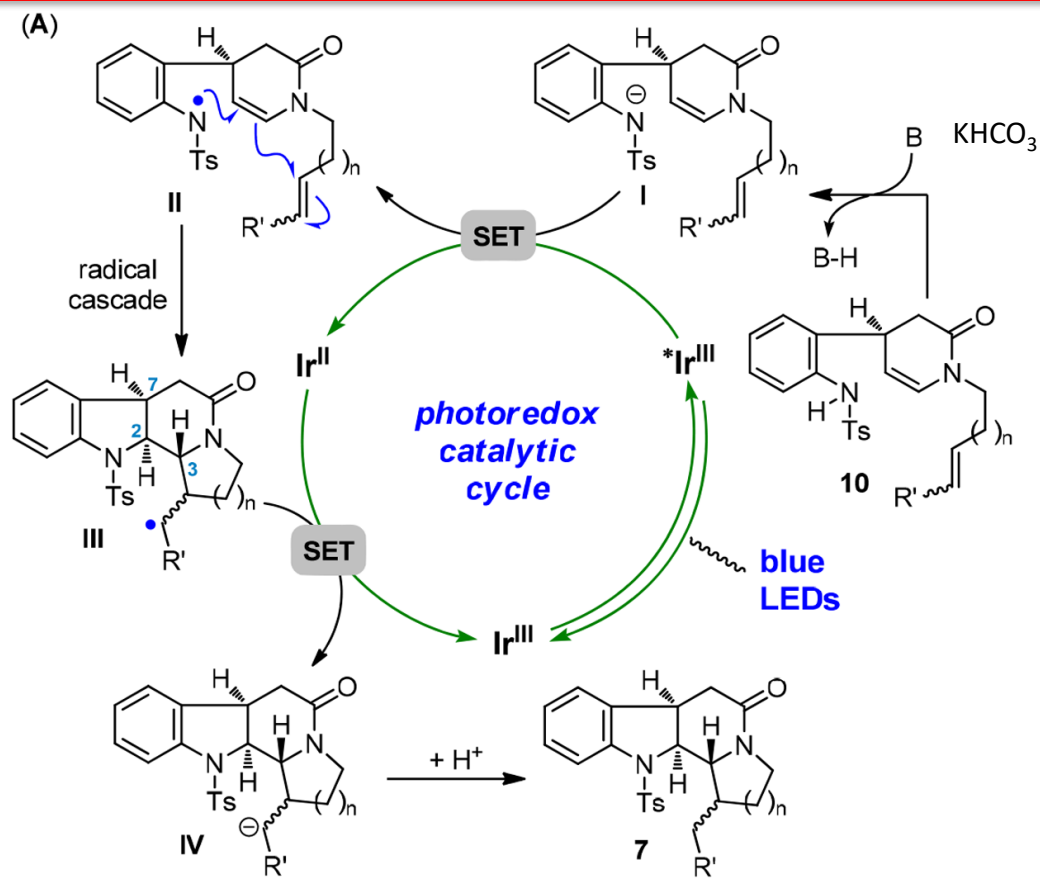
# 4. Proton-coupled Electron Transfer (PCET)



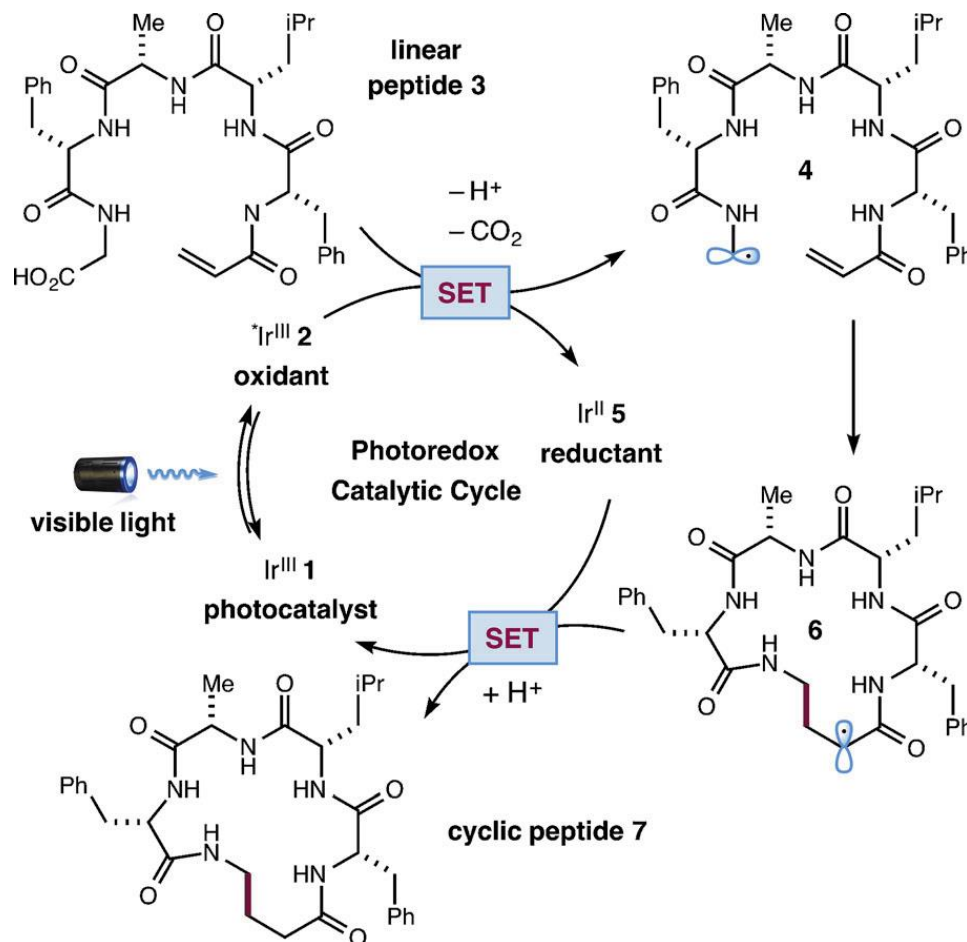
## 4. Proton-coupled Electron Transfer (PCET)



## 4. Proton-coupled Electron Transfer (PCET)

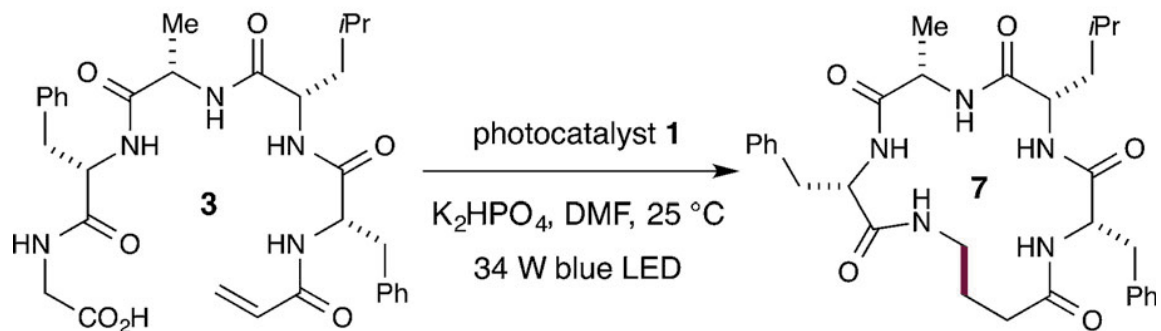


## 4. Proton-coupled Electron Transfer (PCET)



Scheme 2. Proposed mechanism for the decarboxylative peptide macrocyclization.

## 4. Proton-coupled Electron Transfer (PCET)

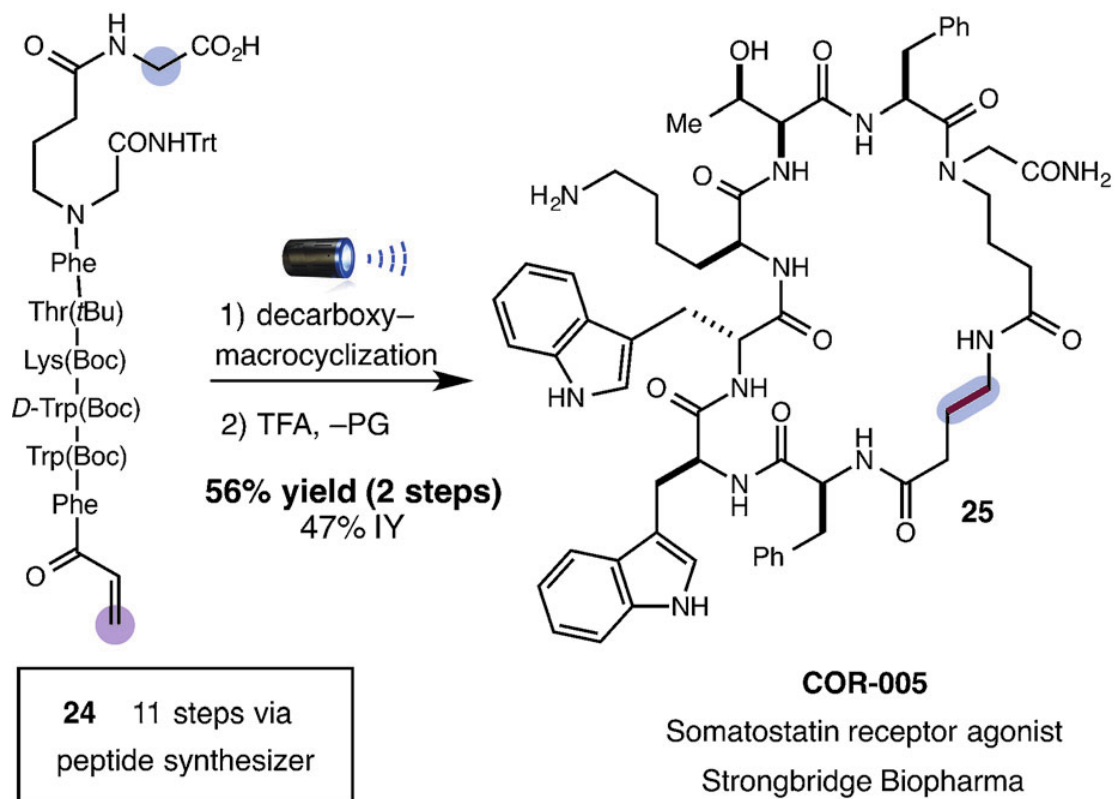


Entry	Conditions	Concentration	1 [mol %]	Yield [%] <sup>[a]</sup>
1	as shown	10 mM	8	33
2	as shown	5 mM	8	63
3	as shown	2.5 mM	8	72
4	as shown	2.5 mM	12	86
5	no base	2.5 mM	12	31
6	no photocatalyst	2.5 mM	0	0
7	no light	2.5 mM	12	0

[a] Yields determined by HPLC (see the Supporting Information).

DMF = N,N-dimethylformamide

## 4. Proton-coupled Electron Transfer (PCET)



Scheme 3. Photoredox macrocyclization to form the bioactive cyclic peptide COR-005.



### Advantages of photoredox process in total synthesis

- **Improved the efficiency of synthesis**
- **Low loading of photocat and mild conditions**
- **Special selectivity**
- **Give a chance to do the transformation in asymmetric version**
- **More biomimetic process**
- **.....**

**Not only a tool, but also a strategy!**

## 5. Outlook

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### For reviews:

- (1) X. Y. Liu, Y. Qin, Indole Alkaloid Synthesis Facilitated by Photoredox Catalytic Radical Radical Cascade Reactions, *Acc. Chem. Res.* **2019**, *52*, 1877–1891.
- (2) C. R. Jamison, L. E. Overman, Fragment Coupling with Tertiary Radicals Generated by Visible-Light Photocatalysis, *Acc. Chem. Res.* **2016**, *49*, 1578–1586.
- (3) T. P. Nicholls, D. Leonori, A. C. Bissember, Applications of visible light photoredox catalysis to the synthesis of natural products and related compounds, *Nat. Prod. Rep.*, **2016**, *33*, 1248–1254.
- (4) M. D. Kařkaš, J. A. Porco, Jr, C. R. J. Stephenson, Photochemical Approaches to Complex Chemotypes: Applications in Natural Product Synthesis, *Chem. Rev.* **2016**, *116*, 9683–9747

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- (1) M. H. Shaw, J. Twilton, D. W. C. MacMillan, Photoredox Catalysis in Organic Chemistry, *J. Org. Chem.* **2016**, *81*, 6898–6926.
- (2) N. A. Romero, D. A. Nicewicz, Organic Photoredox Catalysis, *Chem. Rev.* **2016**, *116*, 10075–10166.
- (3) K. L. Skubi, T. R. Blum, T. P. Yoon, Dual Catalysis Strategies in Photochemical Synthesis, *Chem. Rev.* **2016**, *116*, 10035–10074.