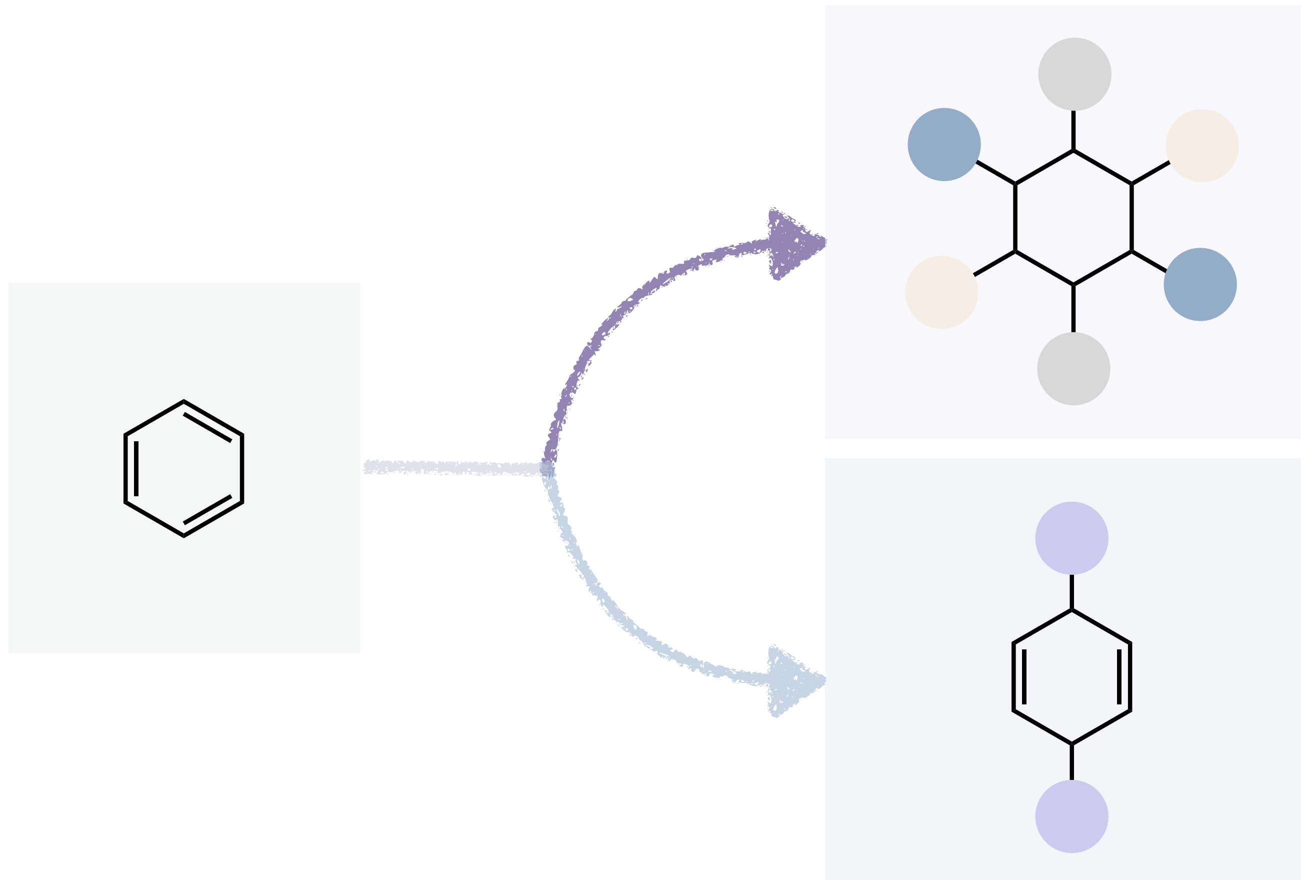
Dearomatization Strategies



Anna (Qinyan) Cai

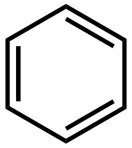
MacMillan Research Group

Literature talk

July 12th, 2024

Aromaticity

Aromaticity



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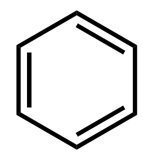
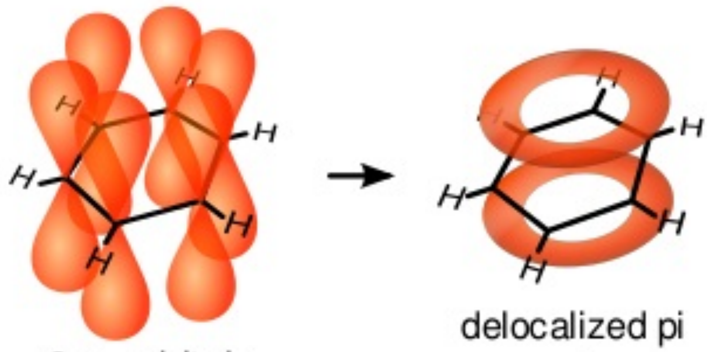
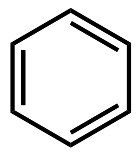


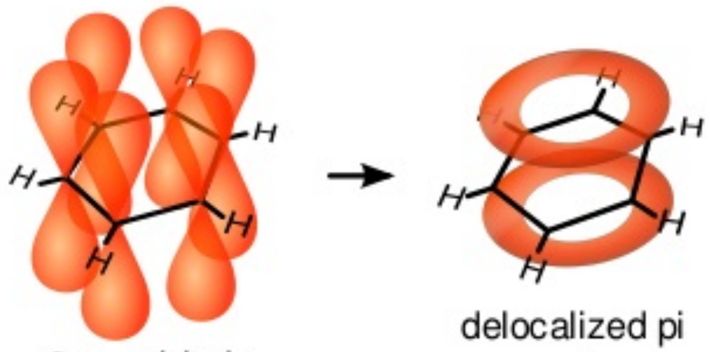


6 p_z orbitals

delocalized pi system

Aromaticity

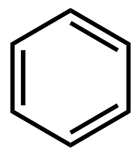


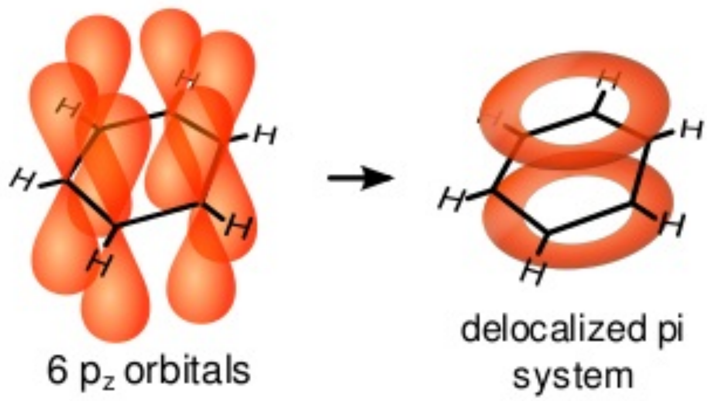


4 rules of aromaticity

- *Cyclic*
- *Planar*
- *Fully conjugated*
- *Hückel's Rule: 4n+2 π electrons*

Aromaticity





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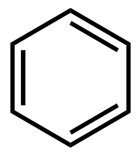
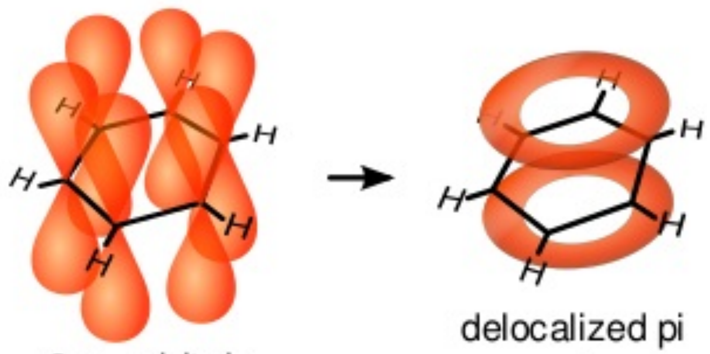
Stabilization from aromaticity

Aromaticity





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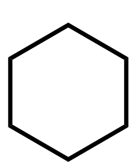
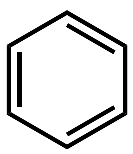
Stabilization from aromaticity

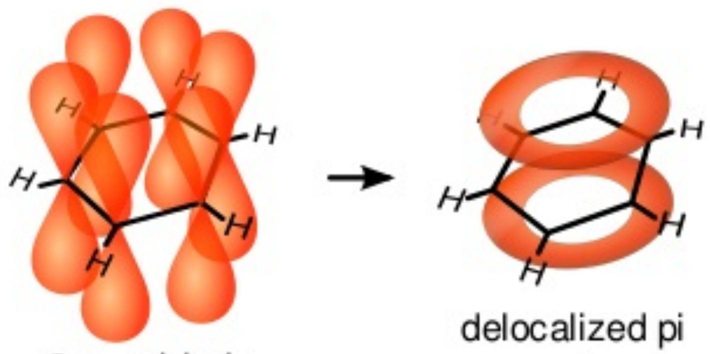
Cyclohexane



Kistiakowsky, G. B.; Ruhoff, J. R.; Smith, H. A.; Vaughan, W. E. *J. Am. Chem. Soc.* **1936**, *58*, 146.

Aromaticity





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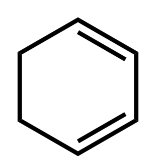
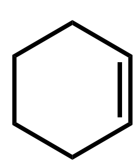
Stabilization from aromaticity

1,3-cyclohexadiene



Cyclohexene



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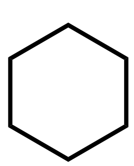

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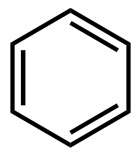

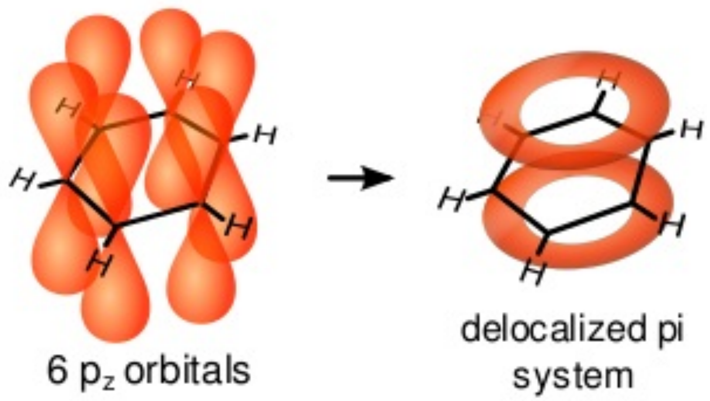

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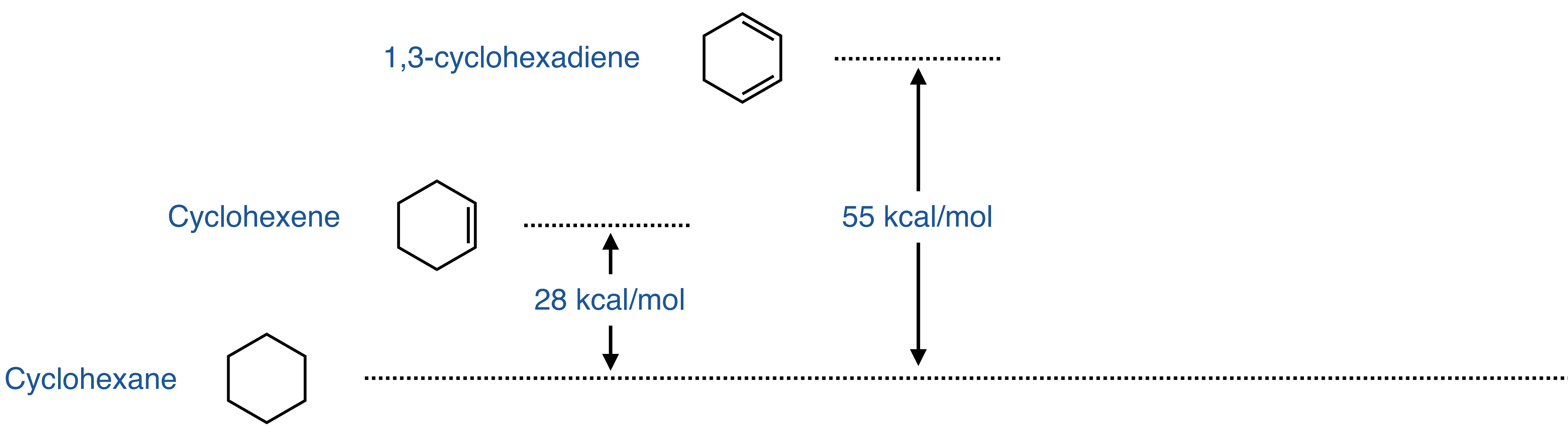

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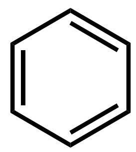

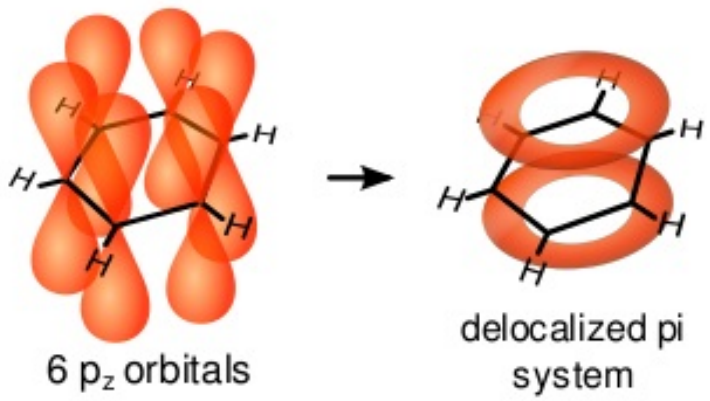

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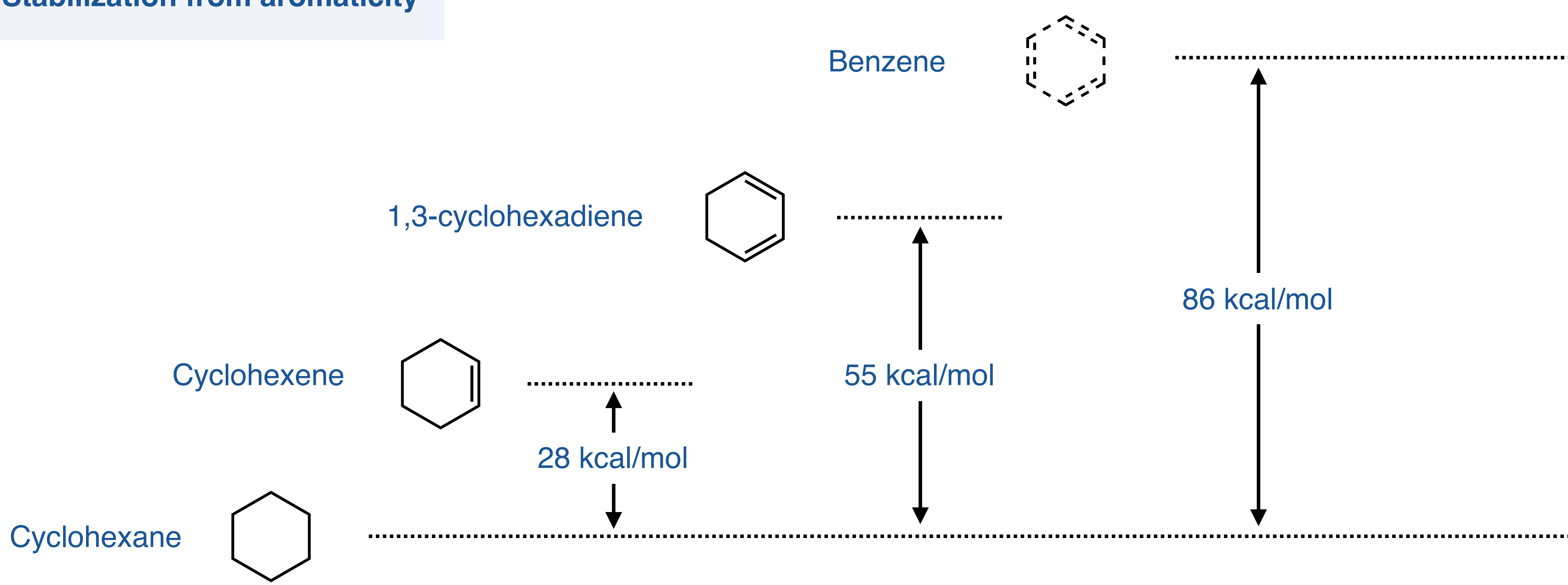

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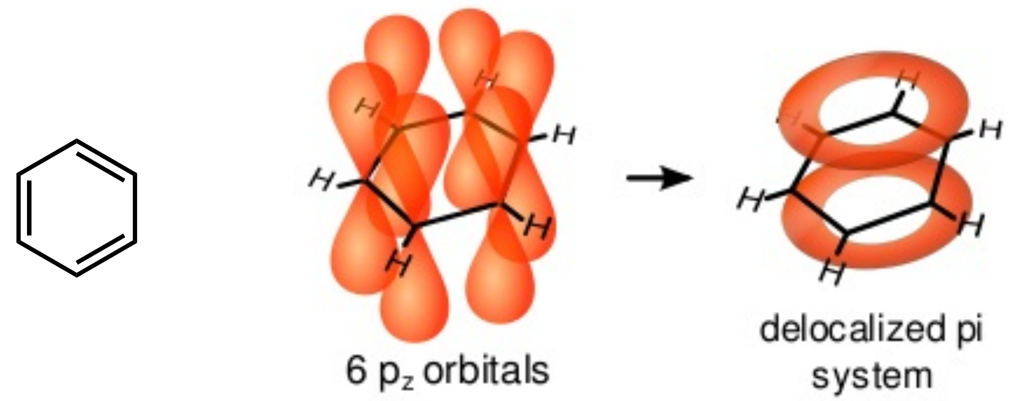

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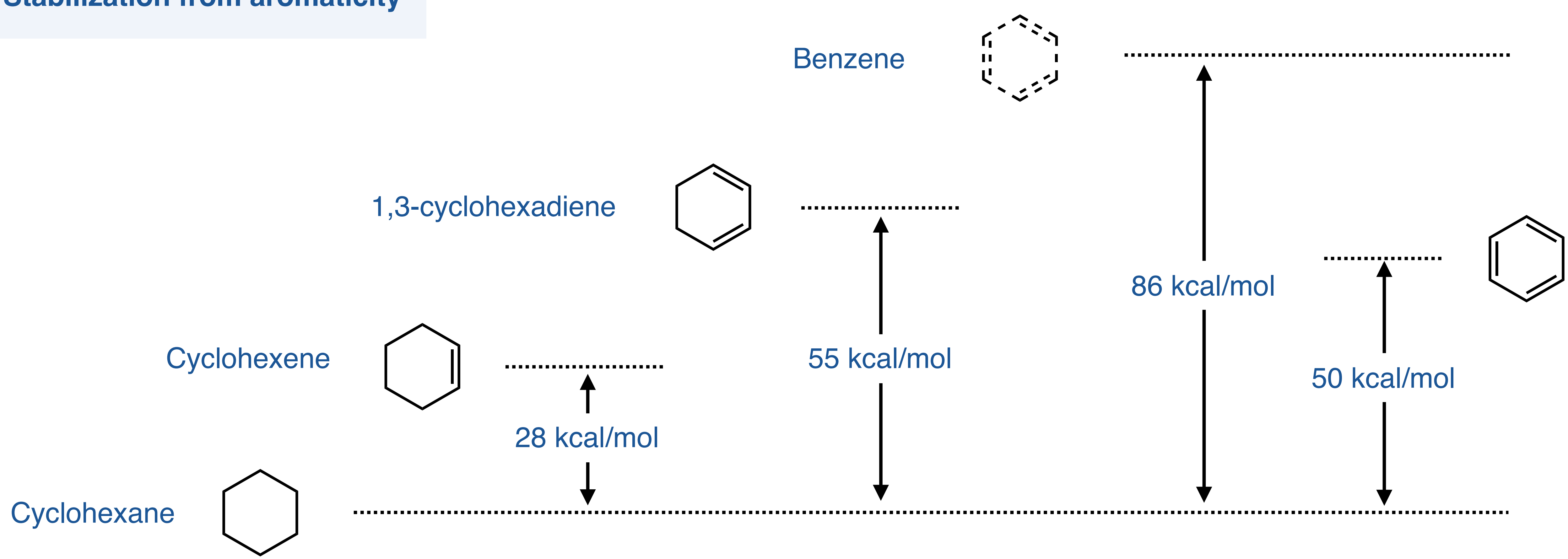

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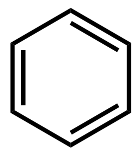

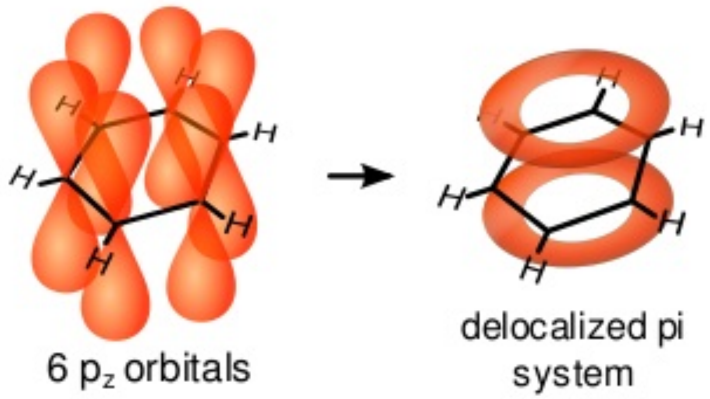

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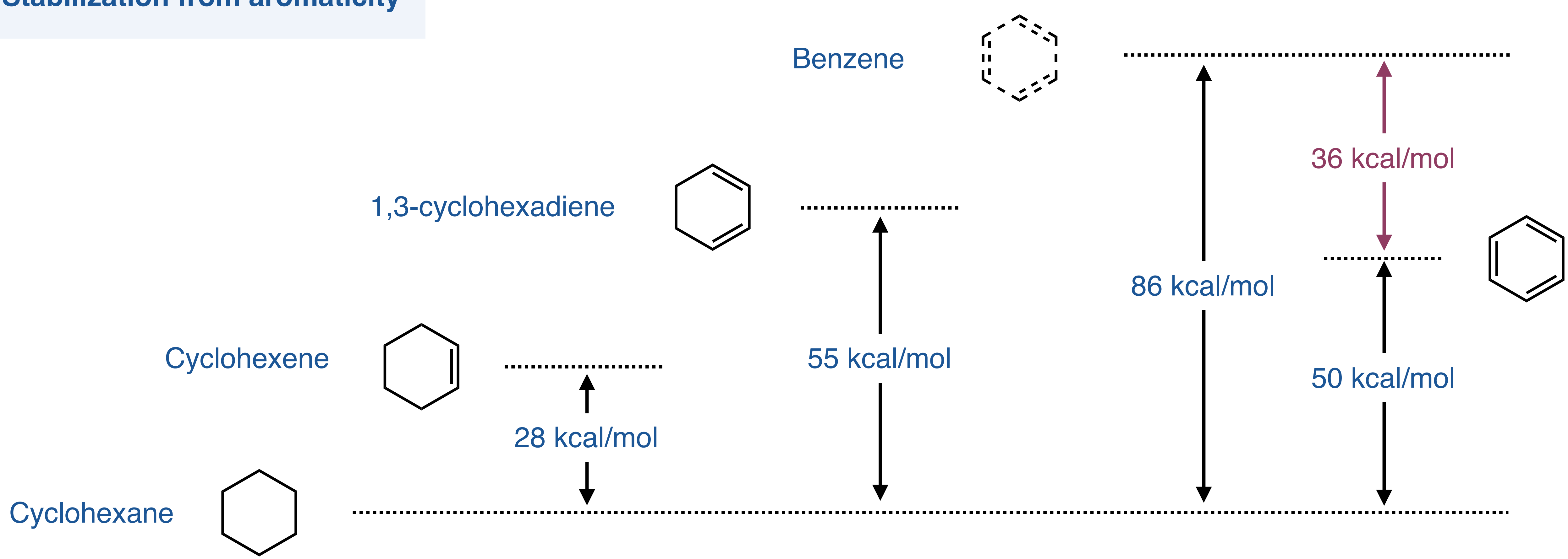

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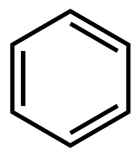
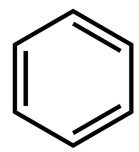
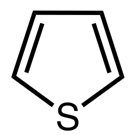
Diversity of Aromatic Compounds & Dearomatization

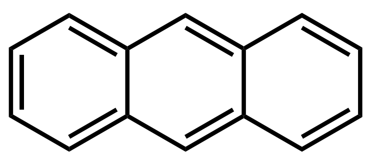


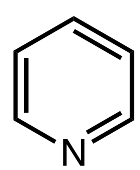
Wertjes, W. C.; Southgate, E. H.; Sarlah, D. *Chem Soc Rev* **2018**, *47* (21), 7996-8017.

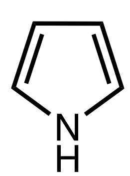
Diversity of Aromatic Compounds & Dearomatization

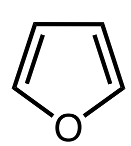












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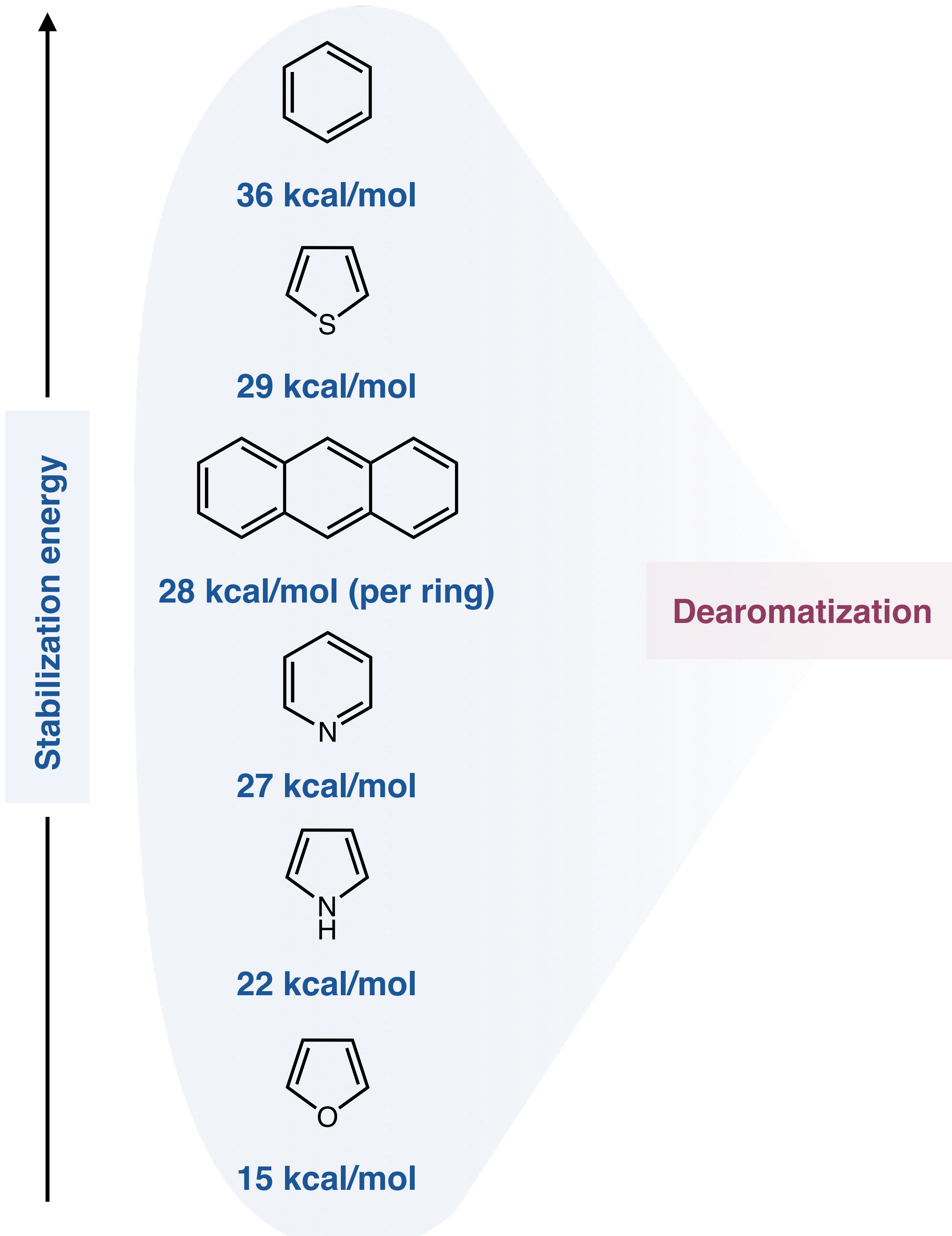

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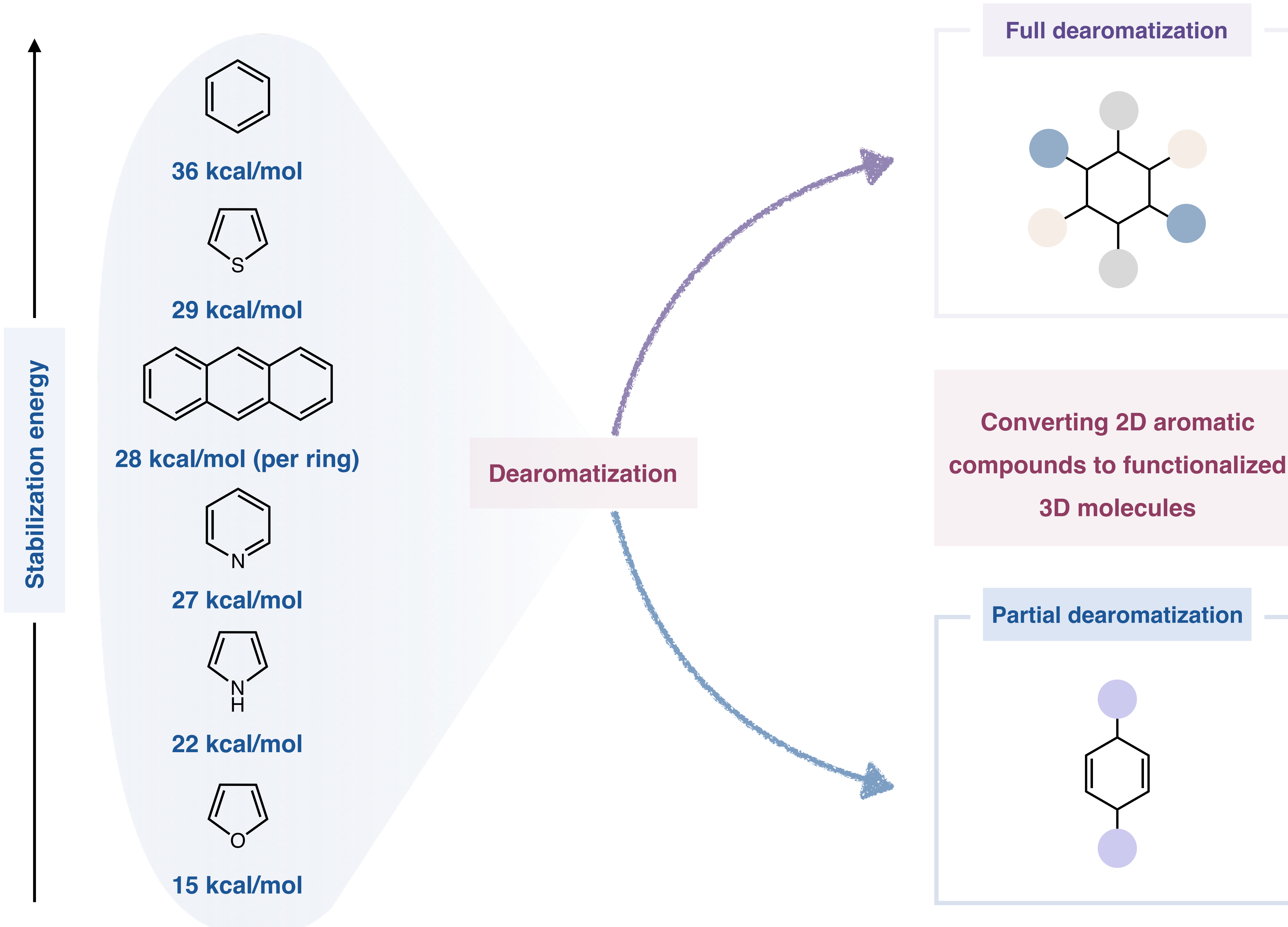

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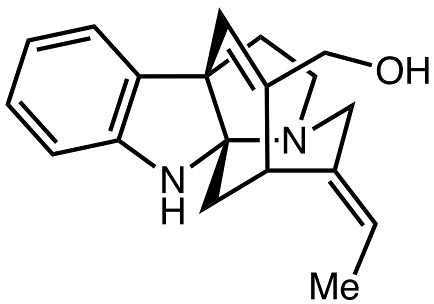
Applications of Dearomatization

Applications of Dearomatization

Total synthesis



(+)-minfiensine

S. B. Jones, B. Simmons, D.W. C. MacMillan, *J. Am. Chem. Soc.* **2009**, *131*, 13606 – 13607.

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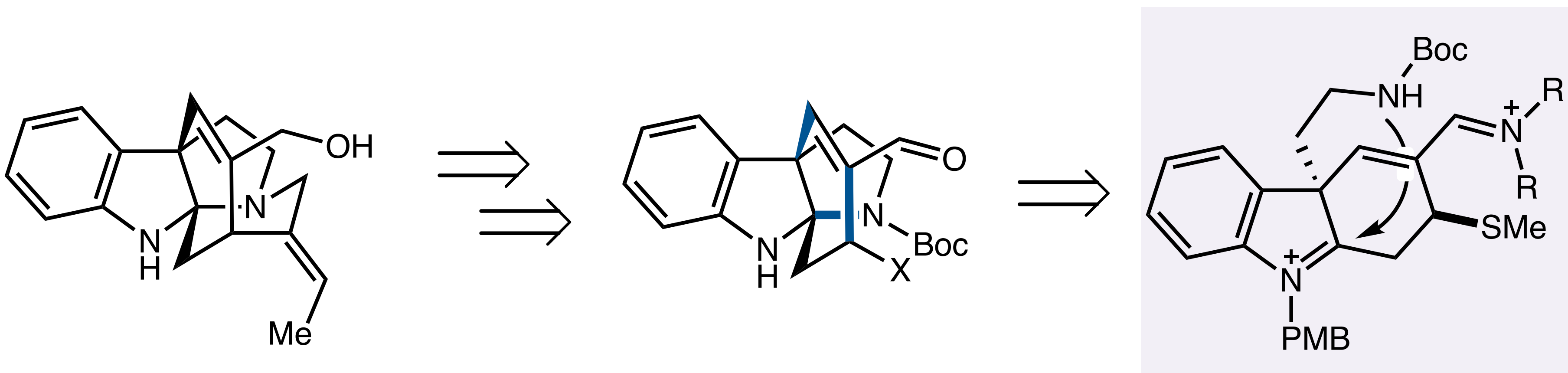

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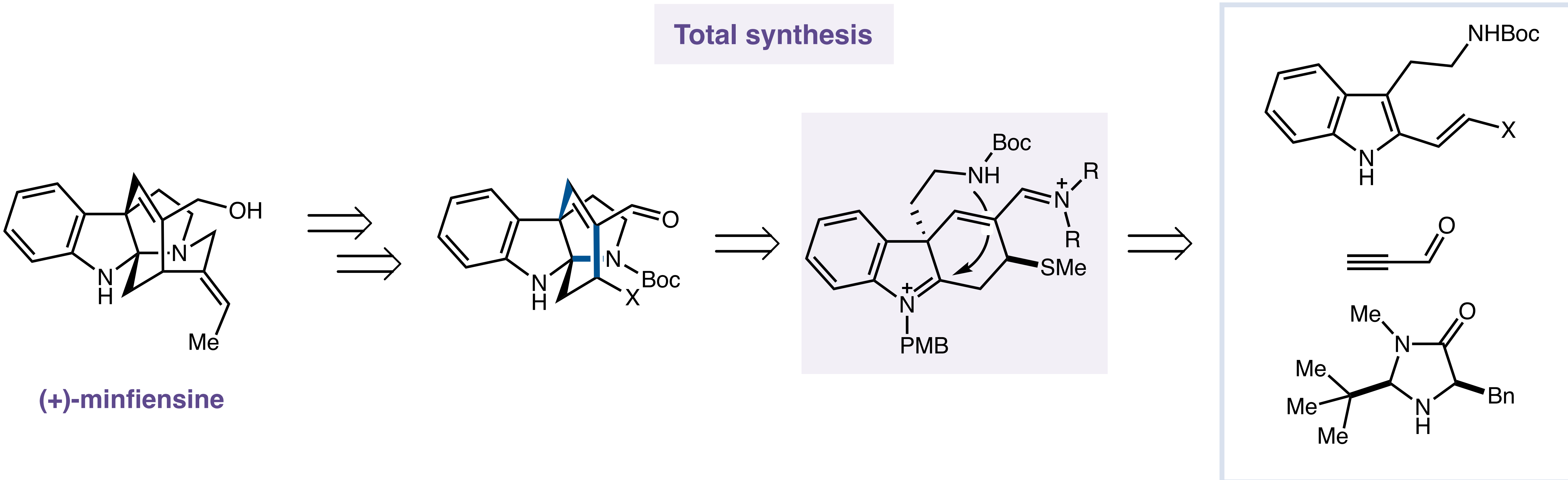

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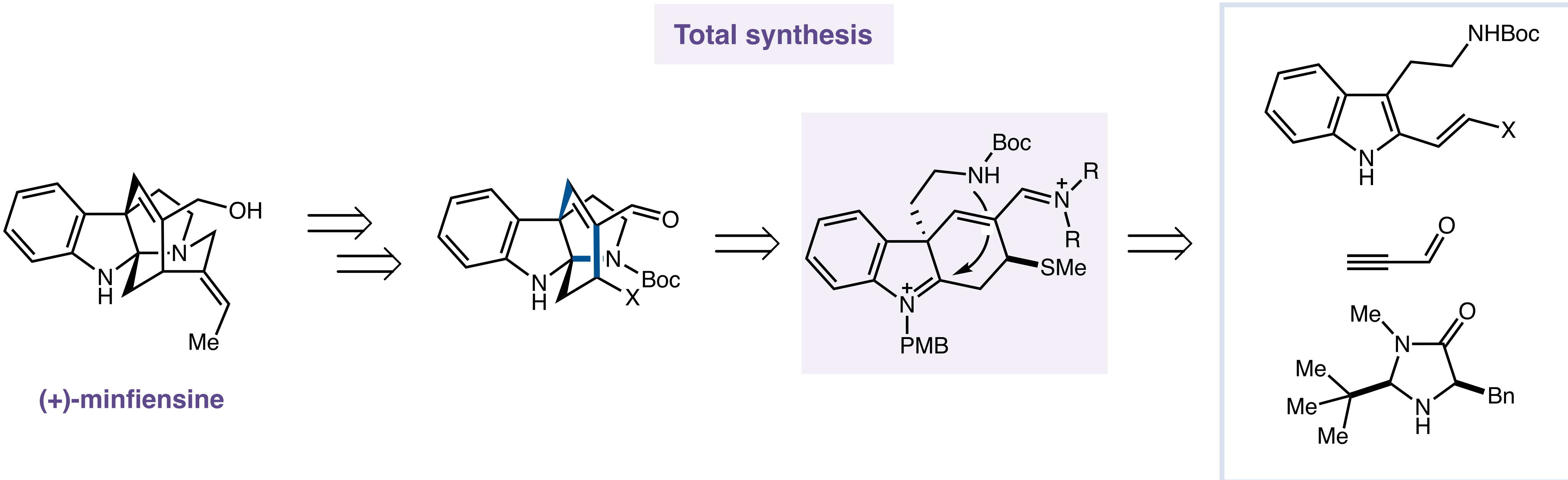

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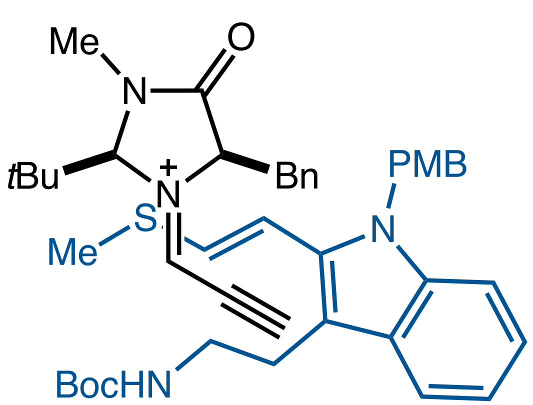

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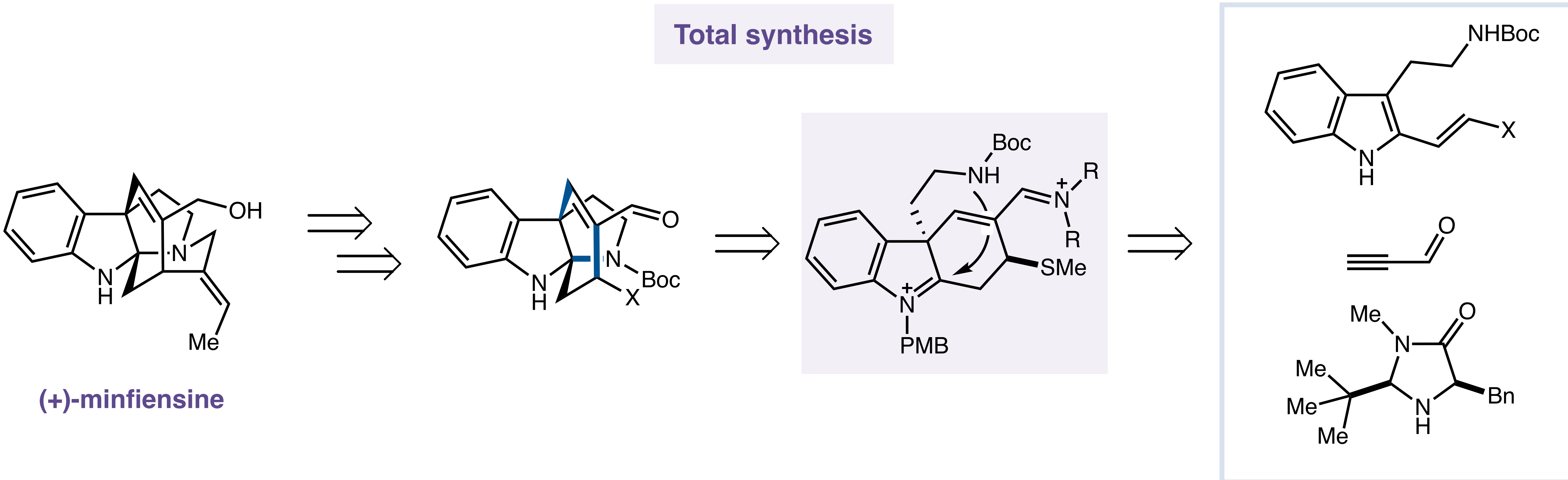
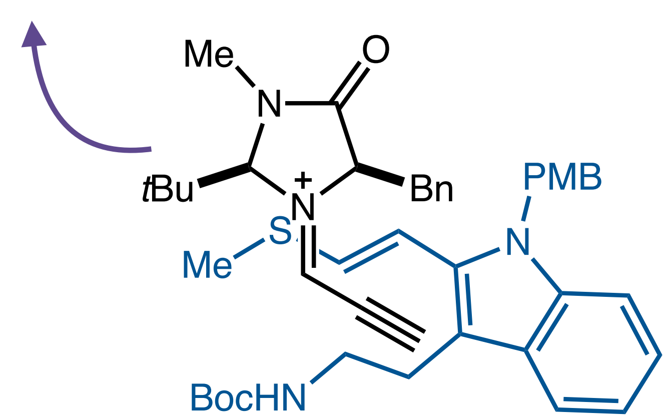


(+)-minfiensine

Lock *E*-configuration



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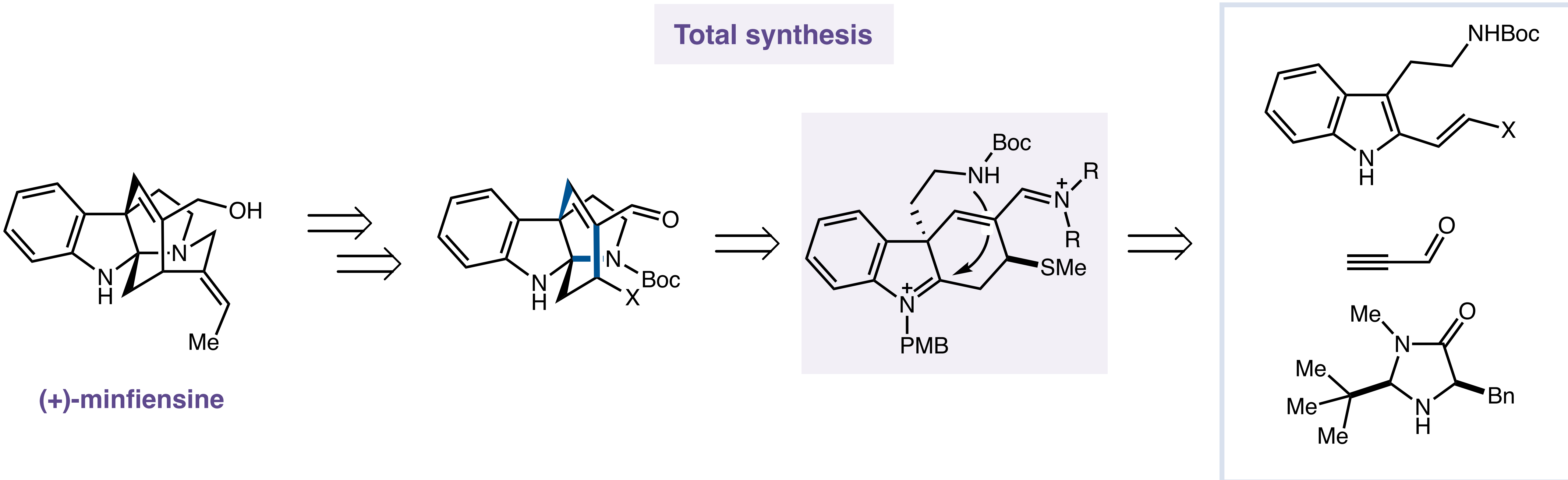

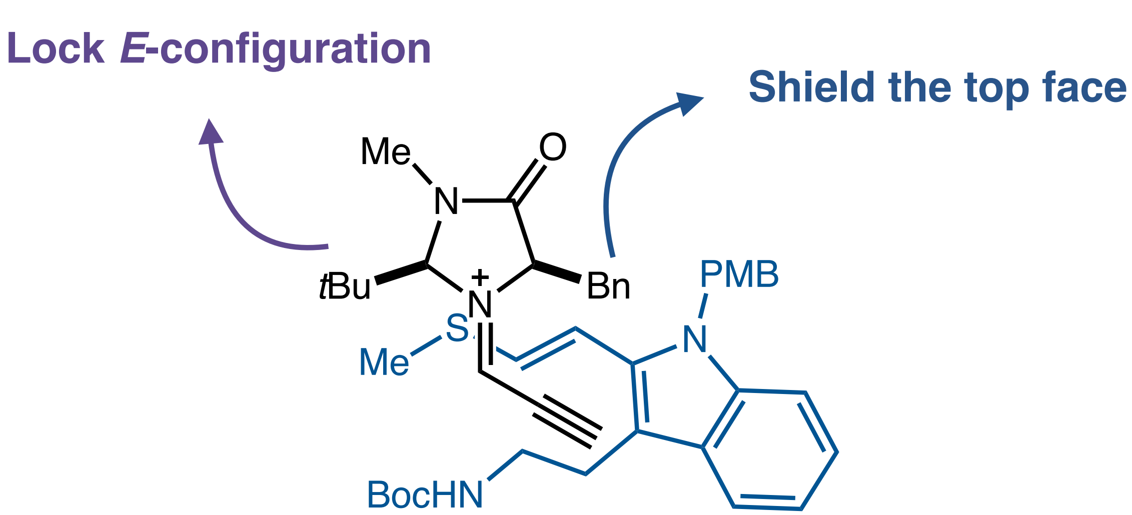

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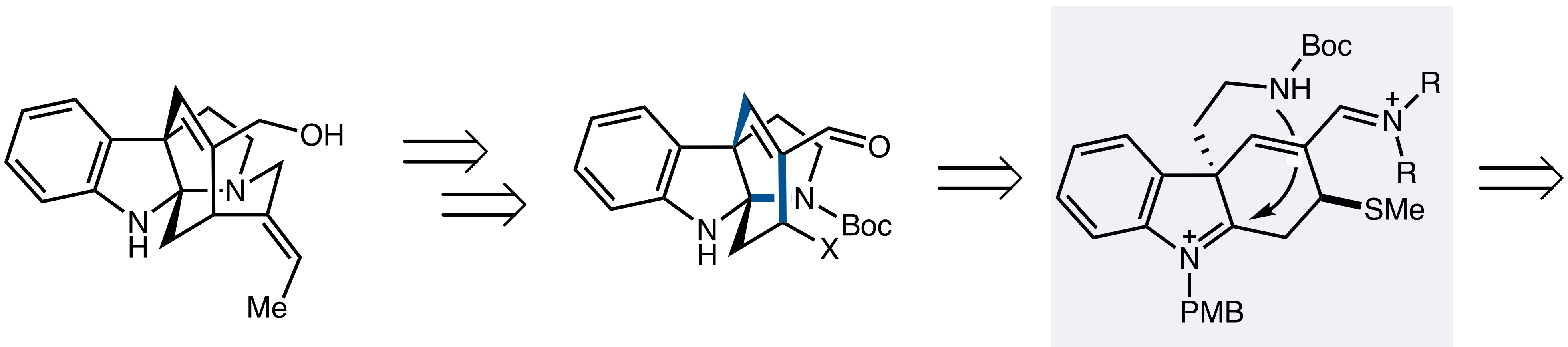

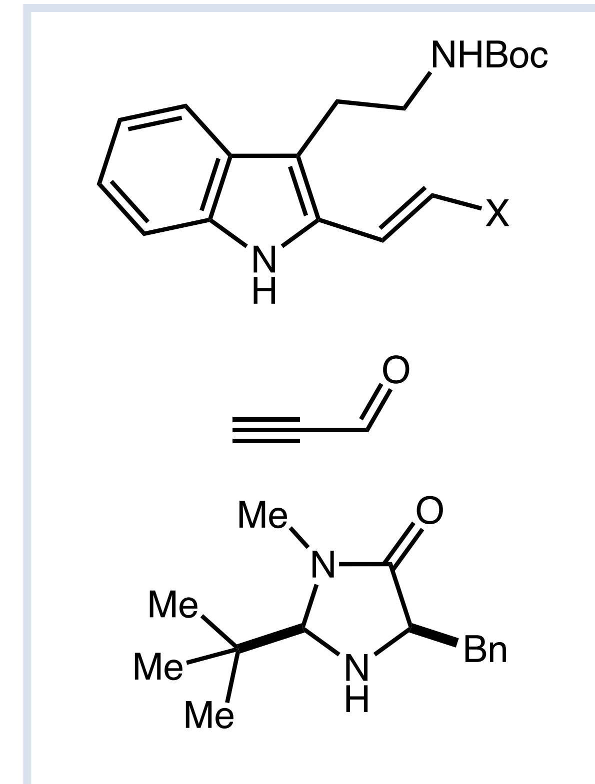

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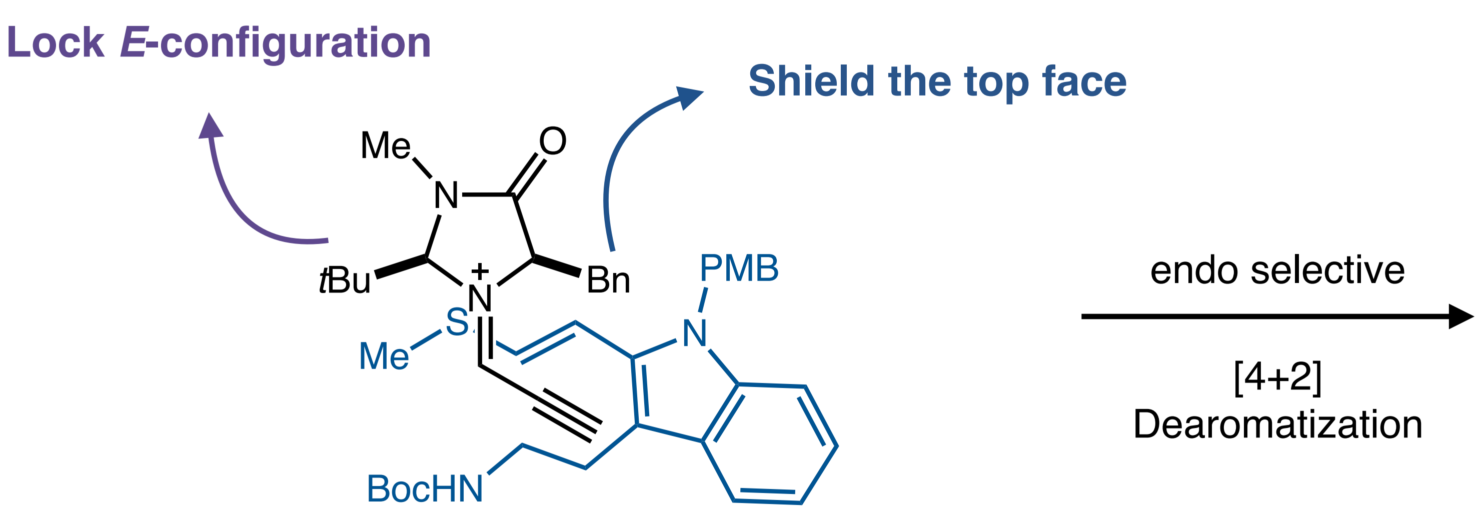

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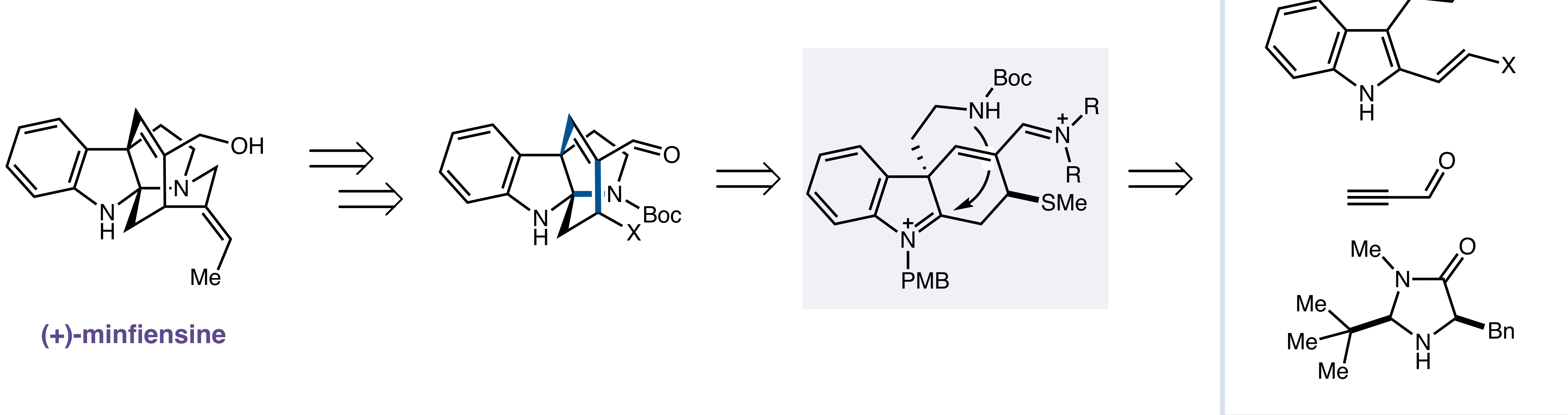

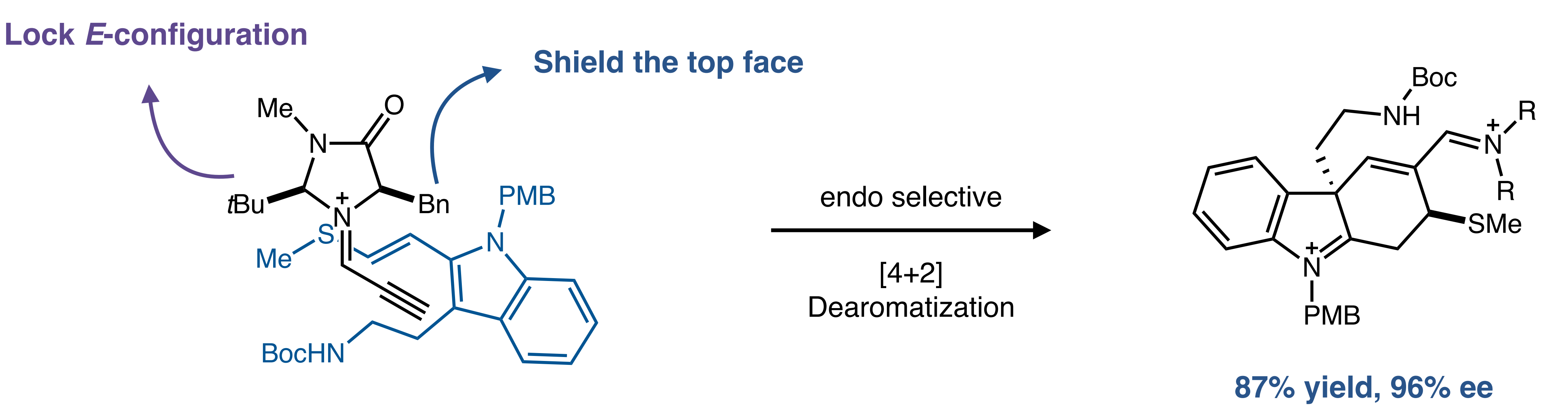

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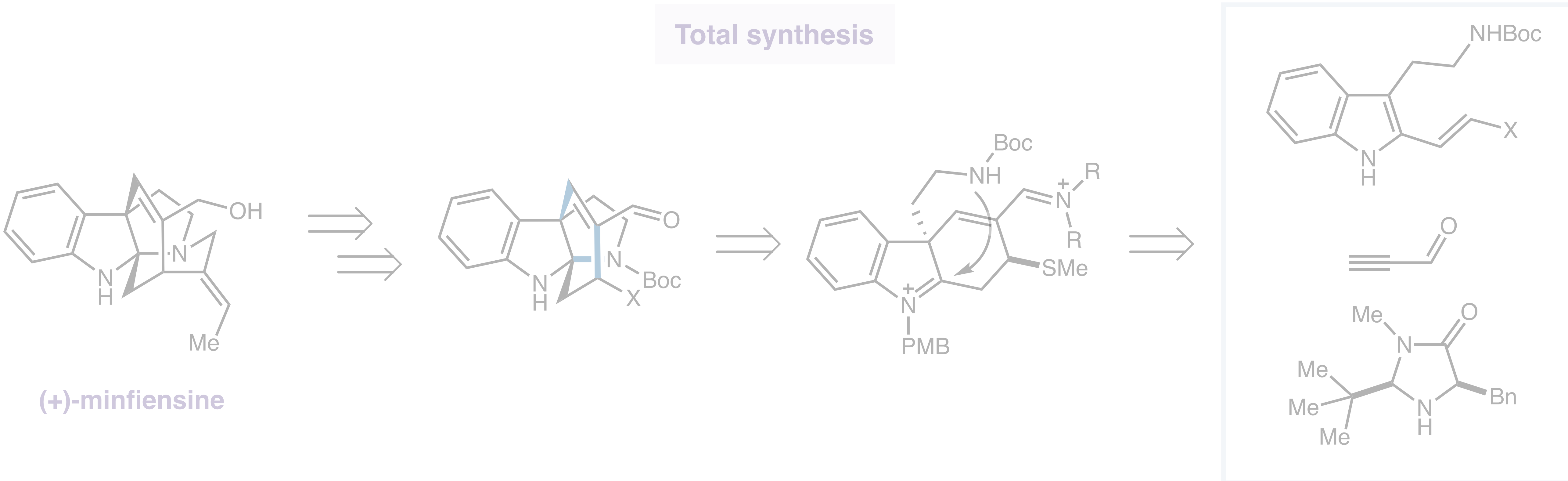

Drug synthesis

U. Zutter, H. Iding, P. Spurr and B. Wirz, *J. Org. Chem.*, **2008**, *73*, 4895–4902.

Applications of Dearomatization

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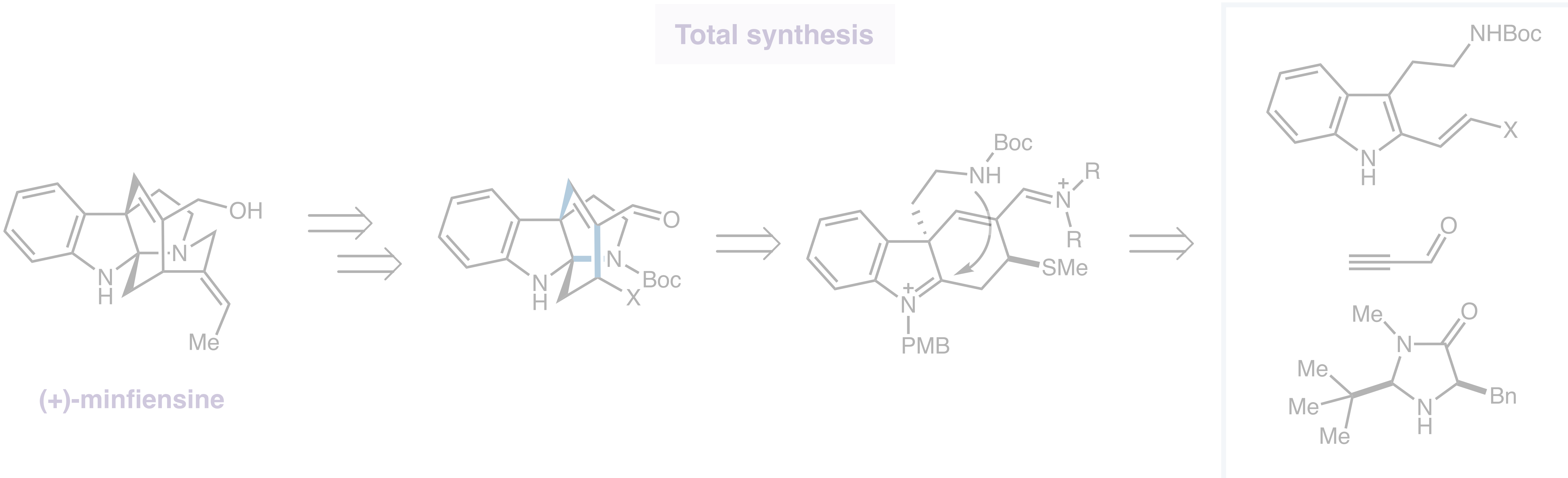

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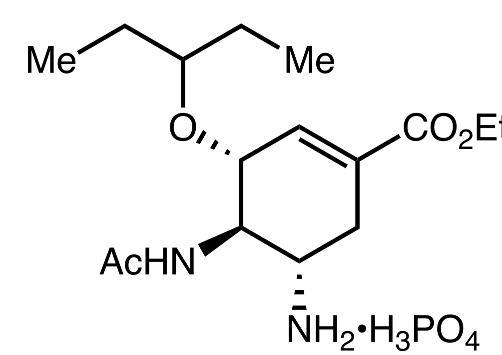

Tamiflu™

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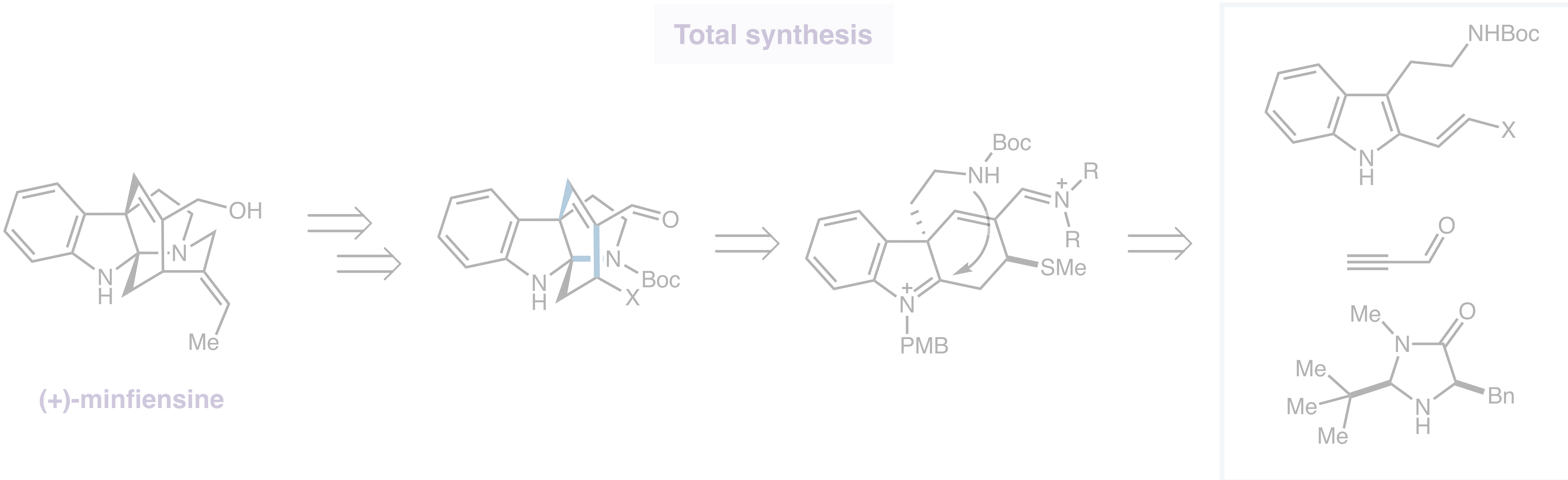

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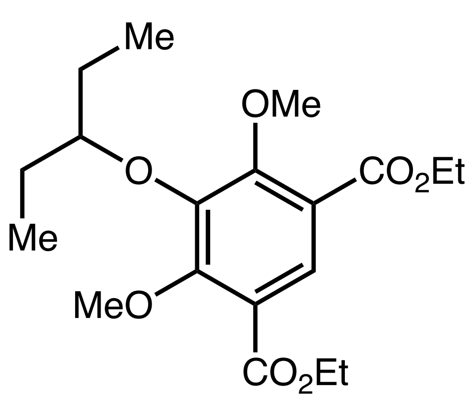

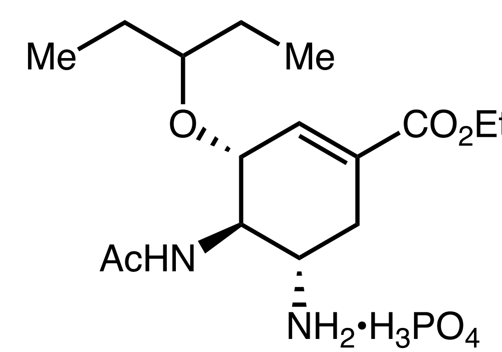

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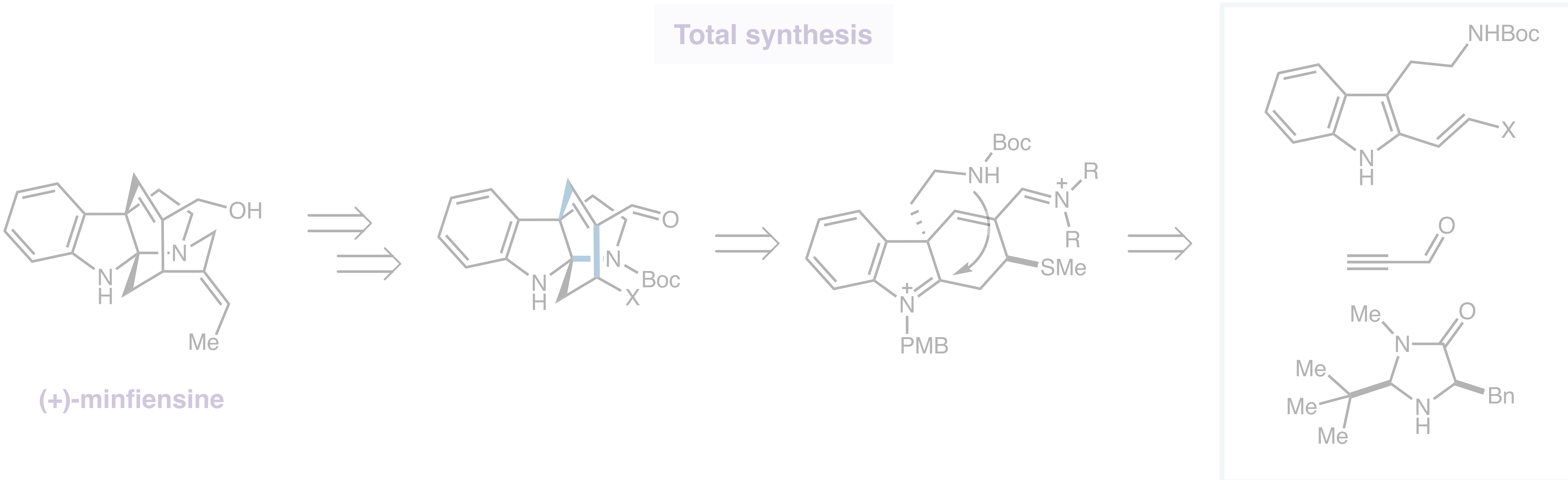

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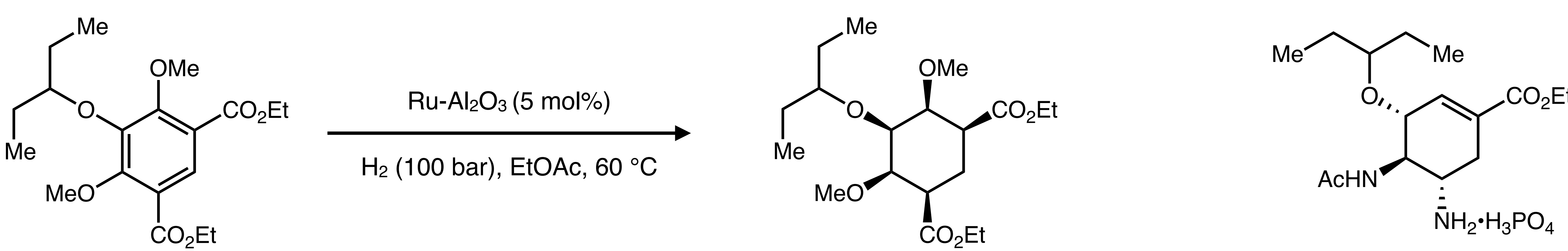

82% yield

***cis meso*-diester**

Tamiflu™

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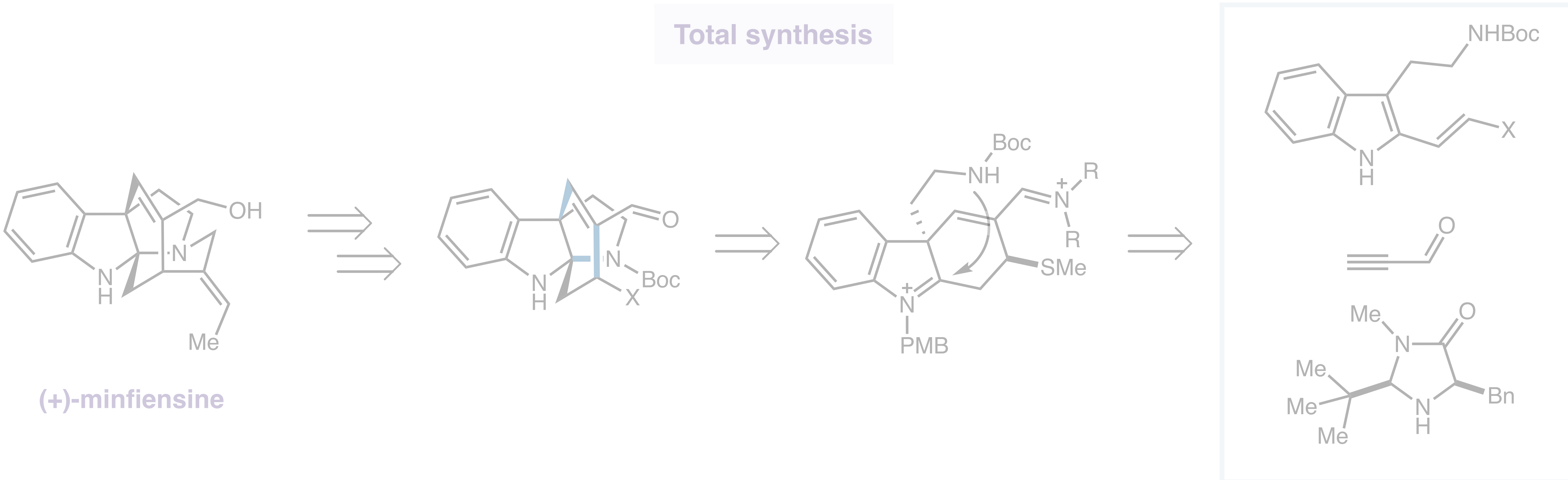

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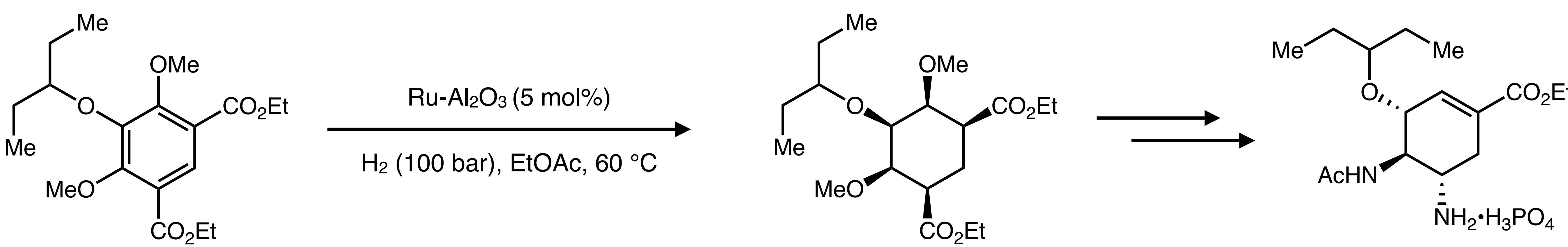

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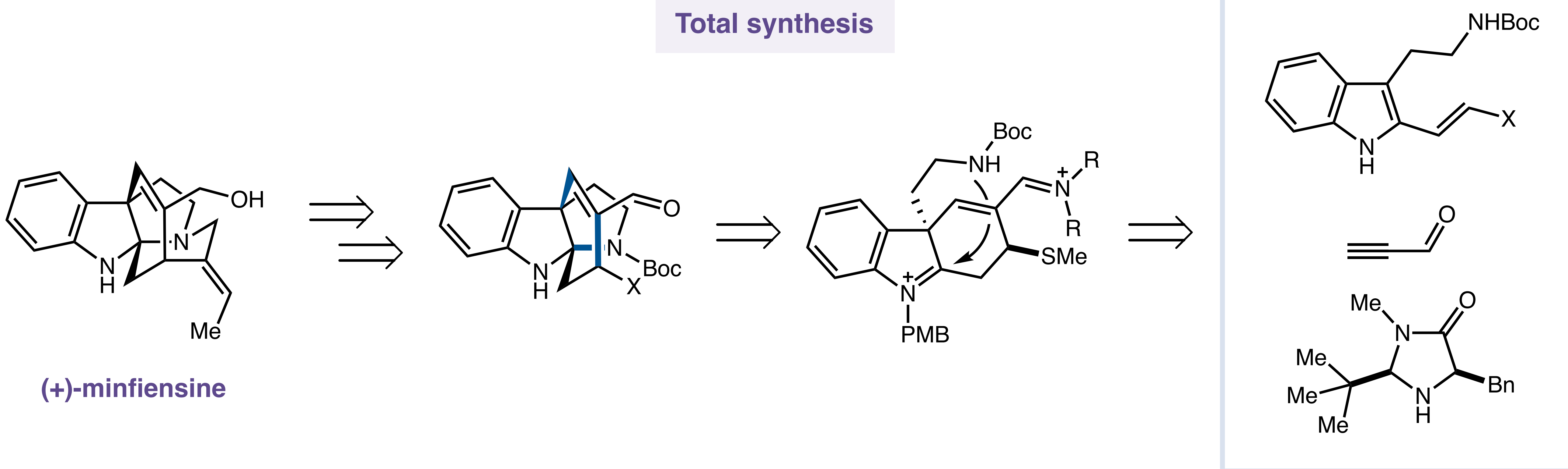
***cis meso*-diester**

Tamiflu™

U. Zutter, H. Iding, P. Spurr and B. Wirz, *J. Org. Chem.*, **2008**, *73*, 4895–4902.

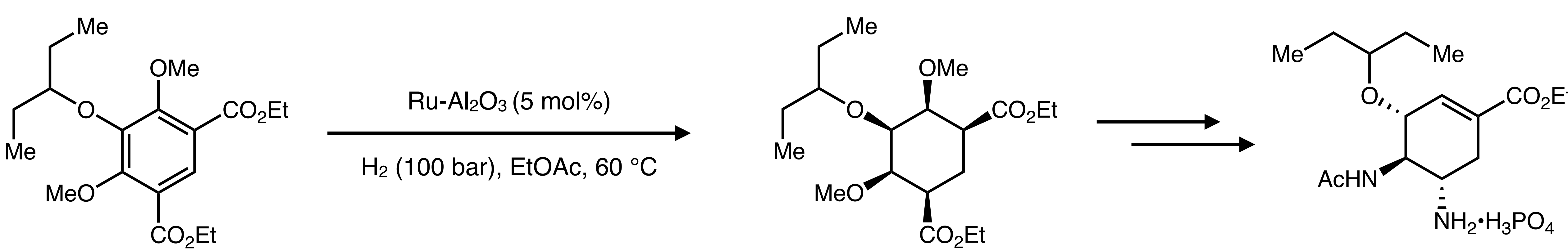
Applications of Dearomatization

Total synthesis



(+)-minfiensine

Drug synthesis



82% yield

***cis meso*-diester**

Tamiflu™

U. Zutter, H. Iding, P. Spurr and B. Wirz, *J. Org. Chem.*, **2008**, *73*, 4895–4902.

Fundamental Logic of Dearomatization Strategies

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How to disturb the aromaticity

Fundamental Logic of Dearomatization Strategies

How to disturb the aromaticity

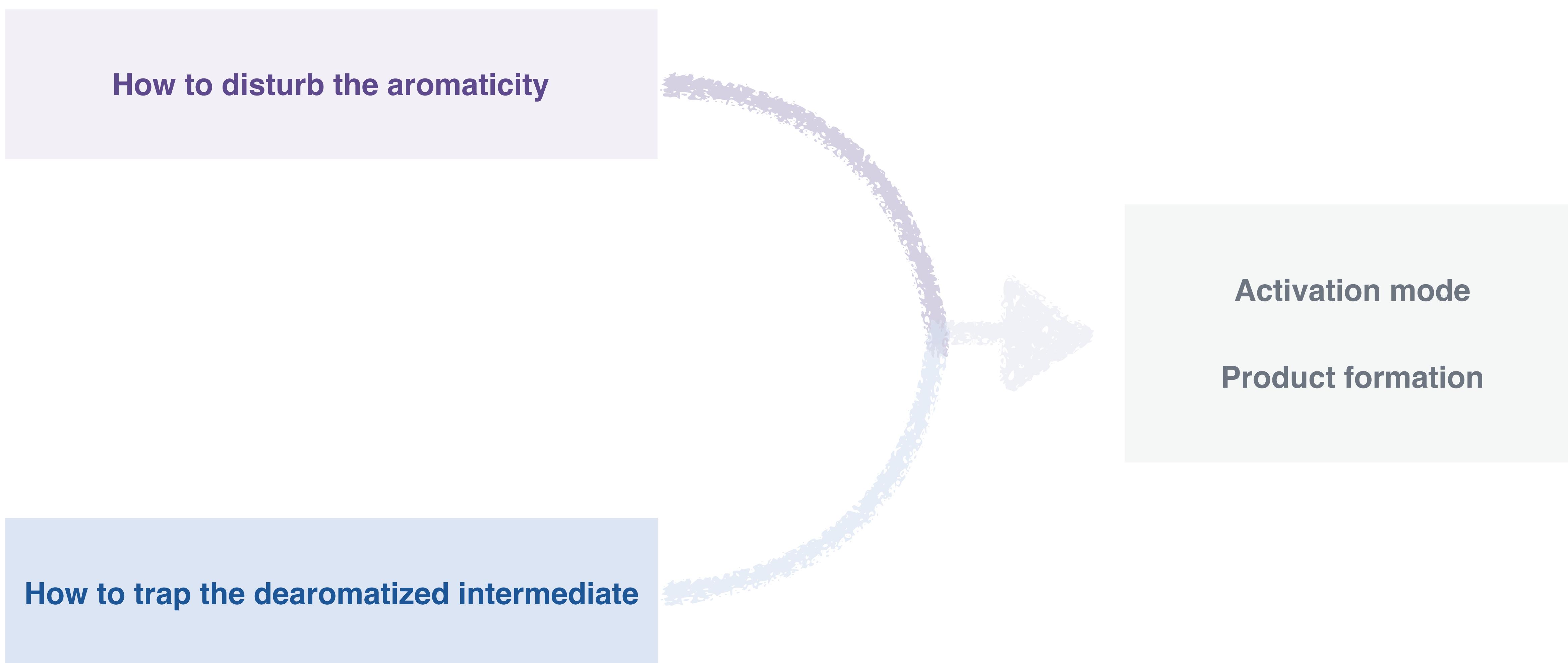
How to trap the dearomatized intermediate

Fundamental Logic of Dearomatization Strategies

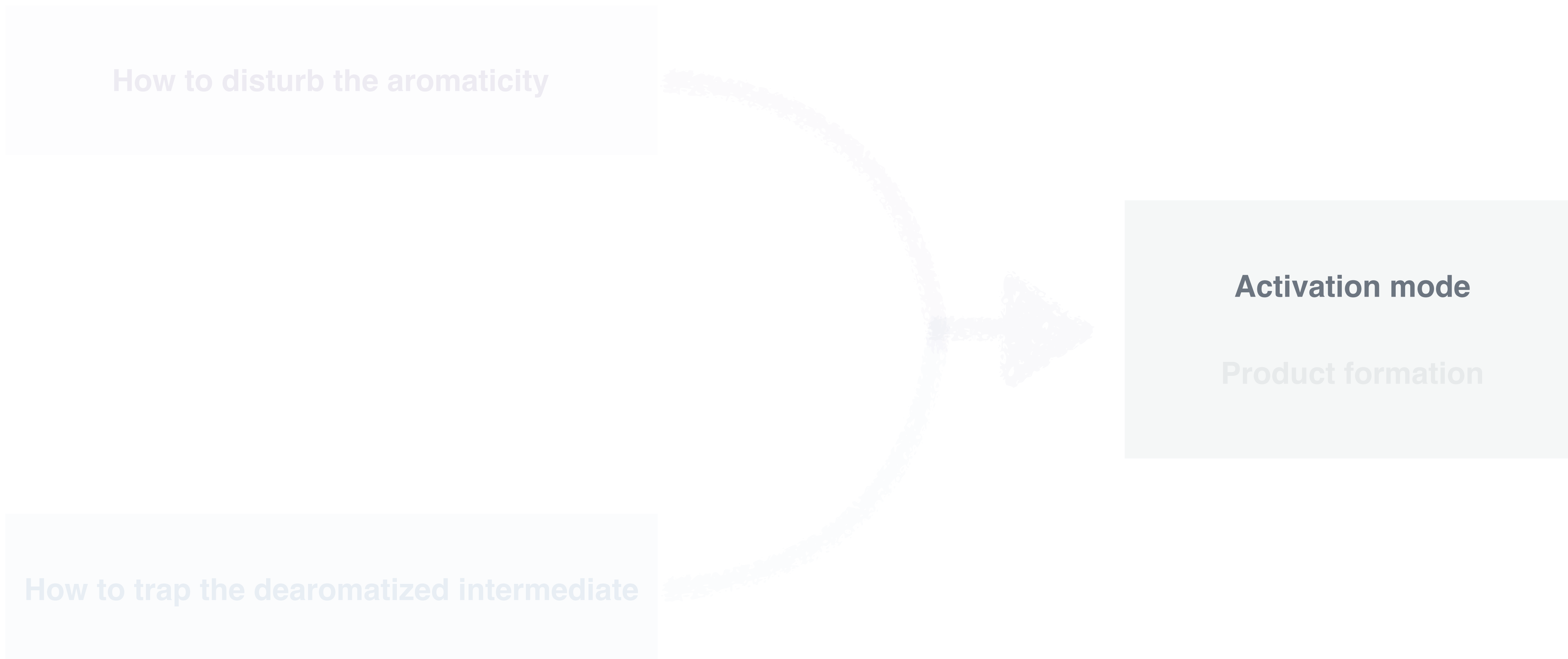
How to disturb the aromaticity

How to trap the dearomatized intermediate

Fundamental Logic of Dearomatization Strategies



Fundamental Logic of Dearomatization Strategies



Overview of Dearomatization Strategies

Wertjes, W. C.; Southgate, E. H.; Sarlah, D. *Chem Soc Rev* **2018**, *47* (21), 7996-8017.

Overview of Dearomatization Strategies

Nucleophilic attack

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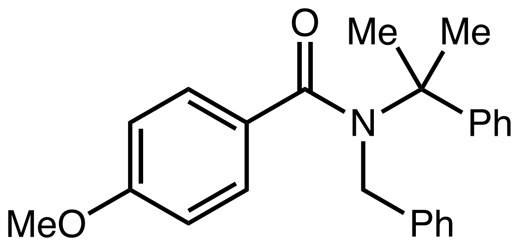

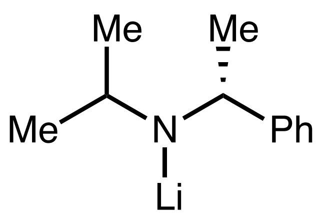

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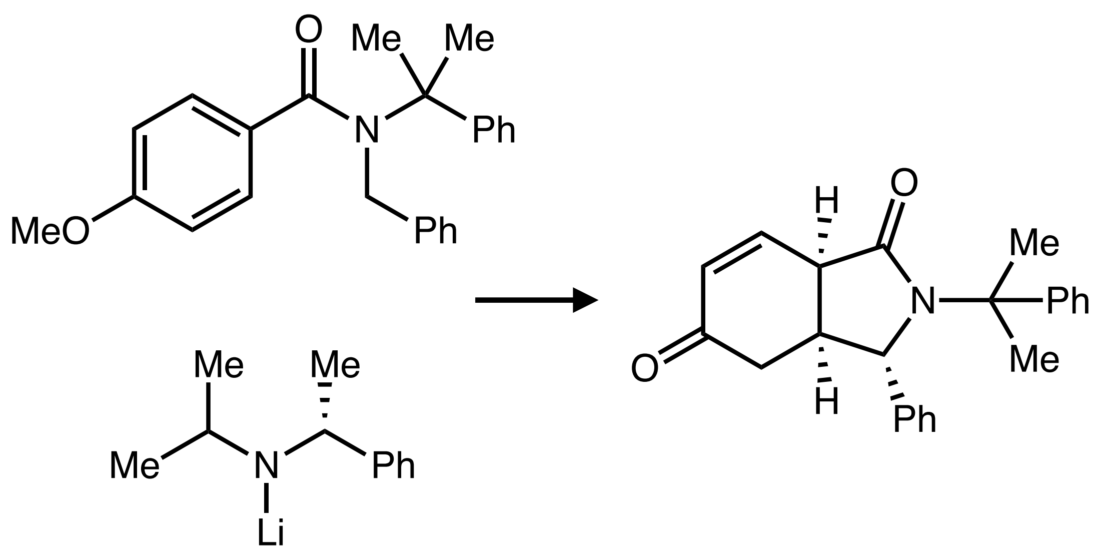

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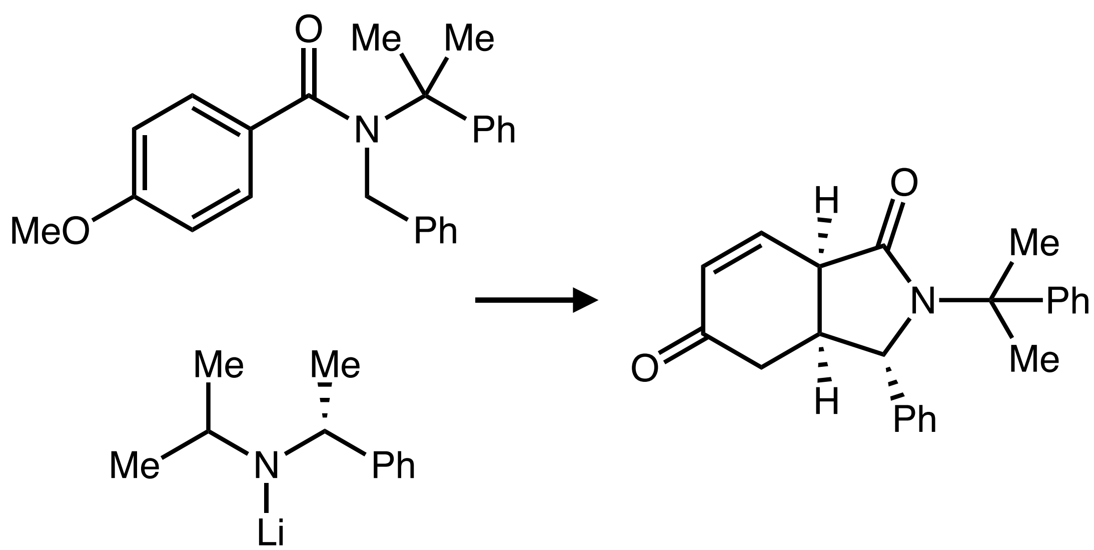

Radical approach

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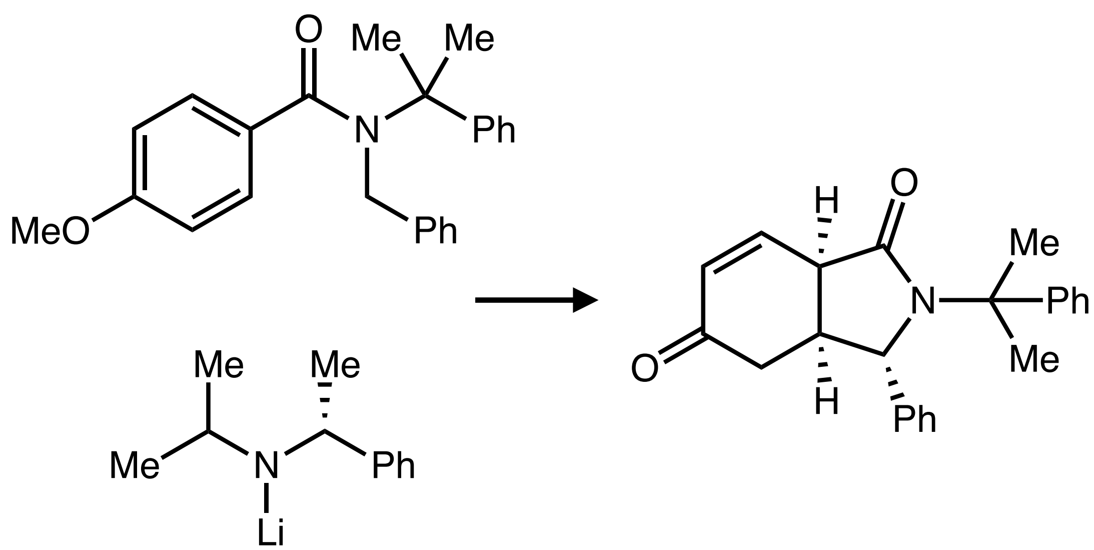
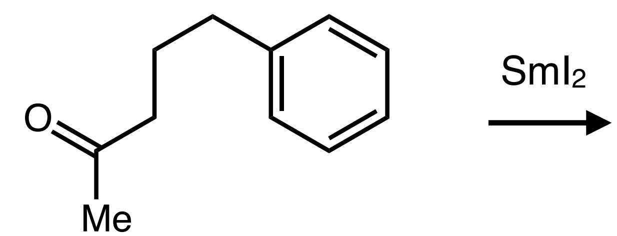


Radical approach



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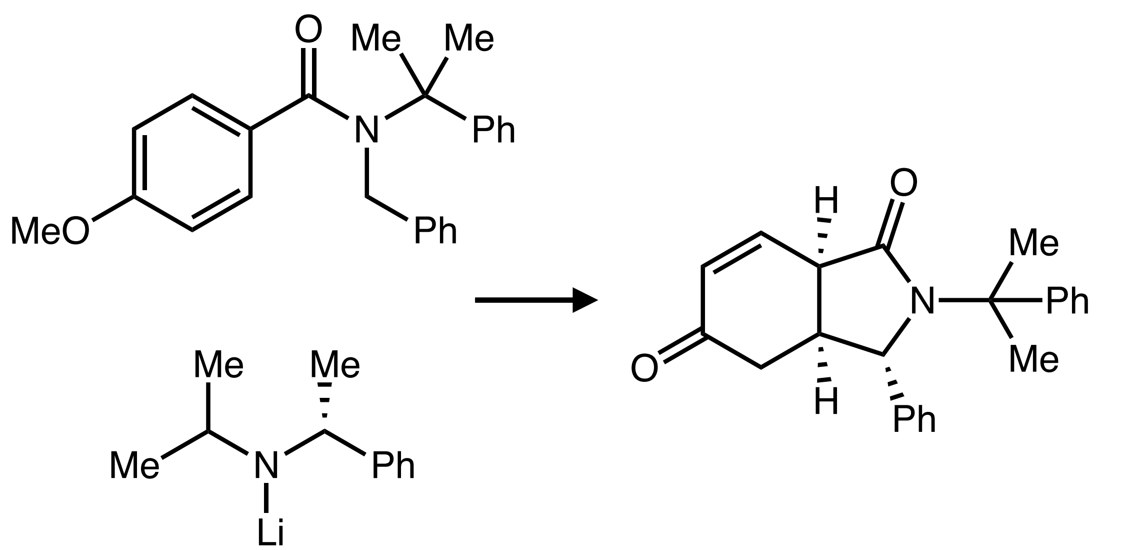
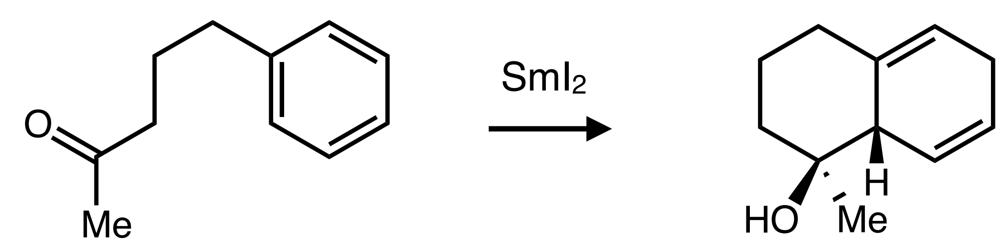


Radical approach



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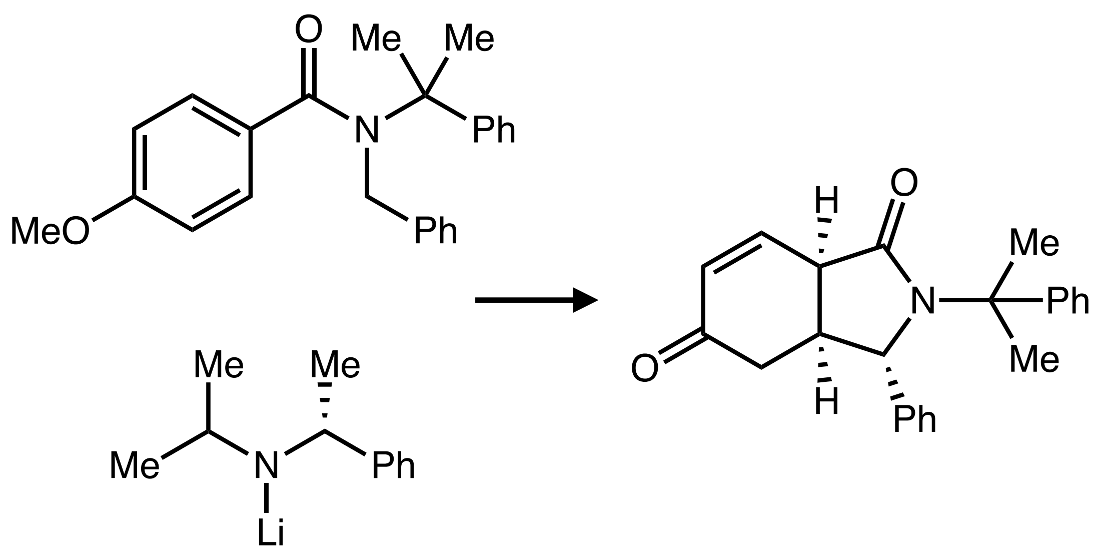

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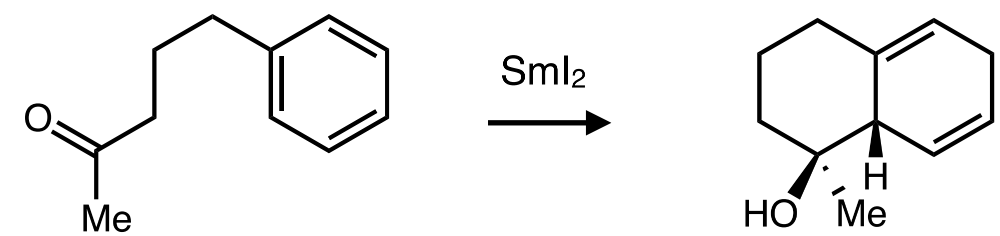

Transition-metal

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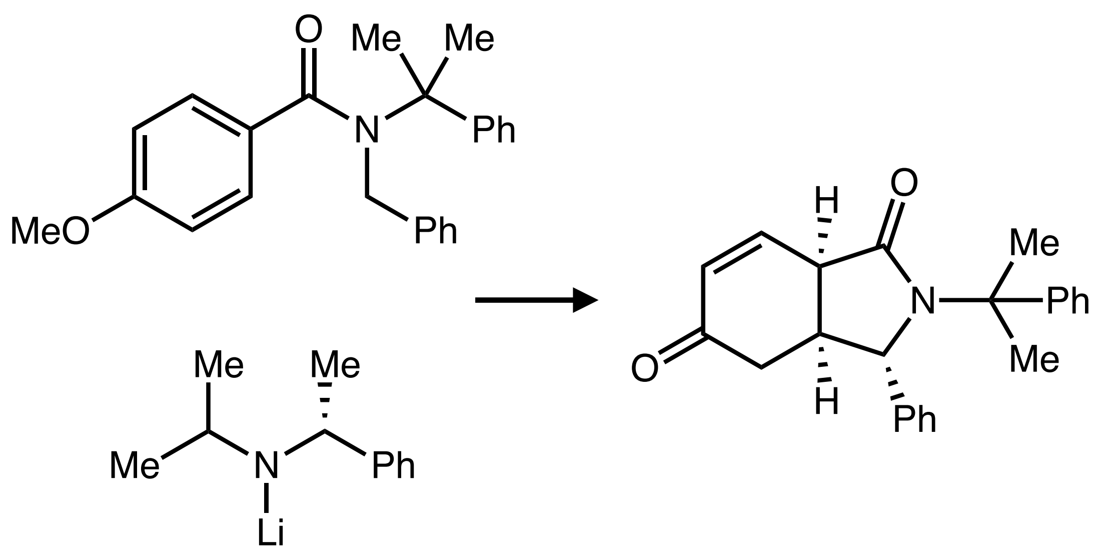

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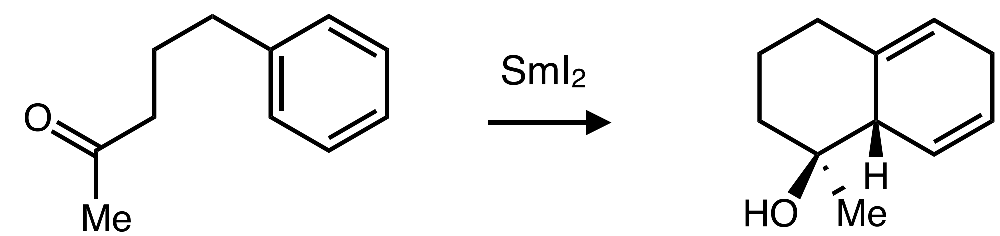
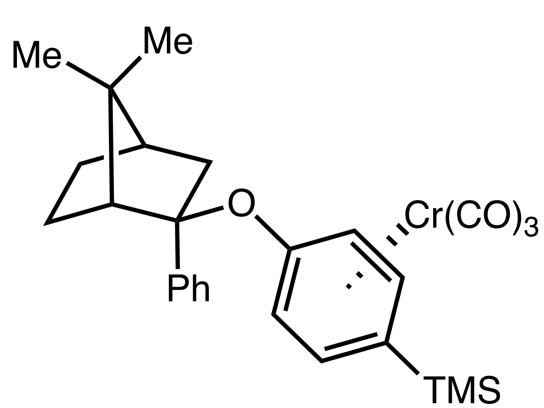


Transition-metal



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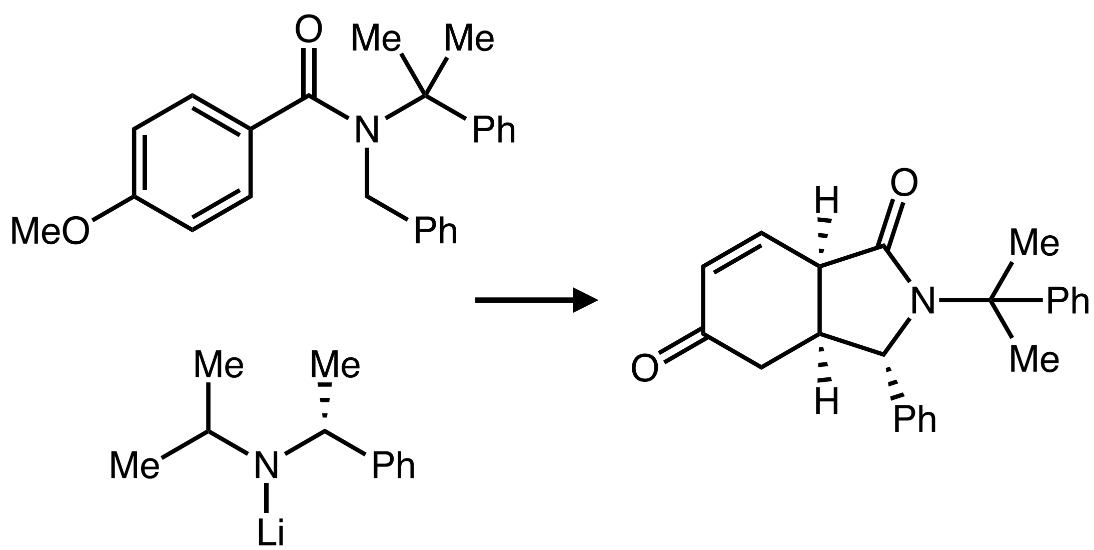

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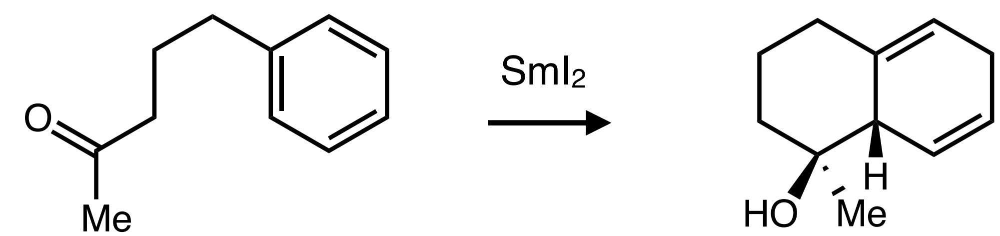

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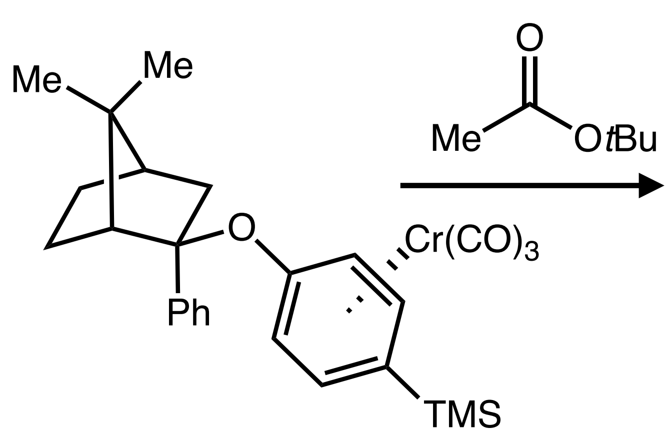

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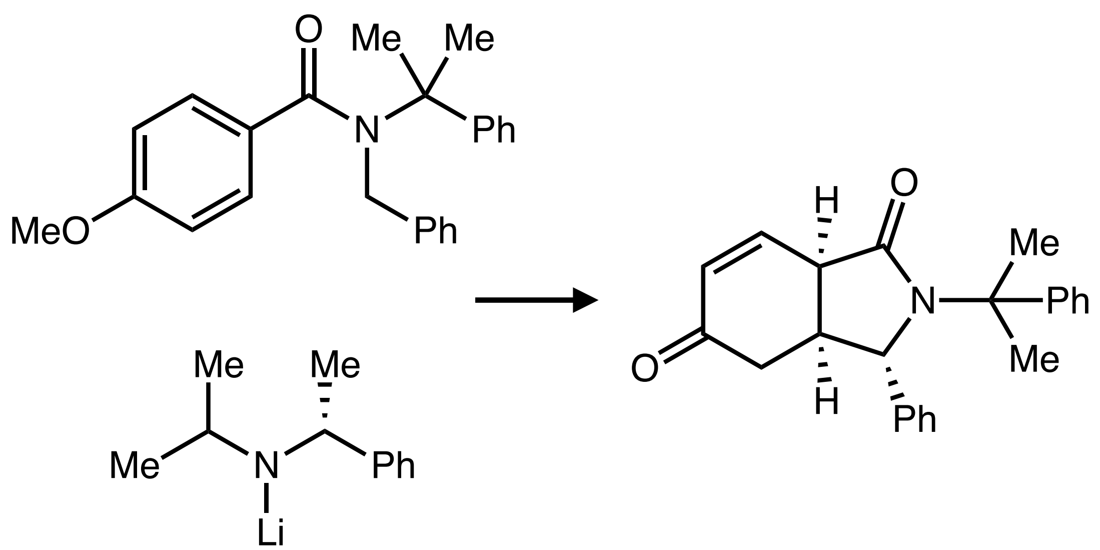
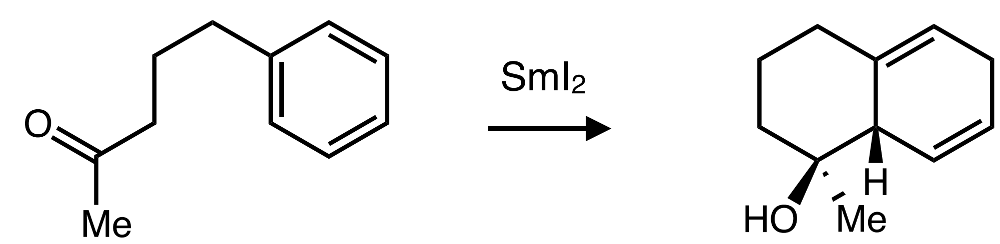
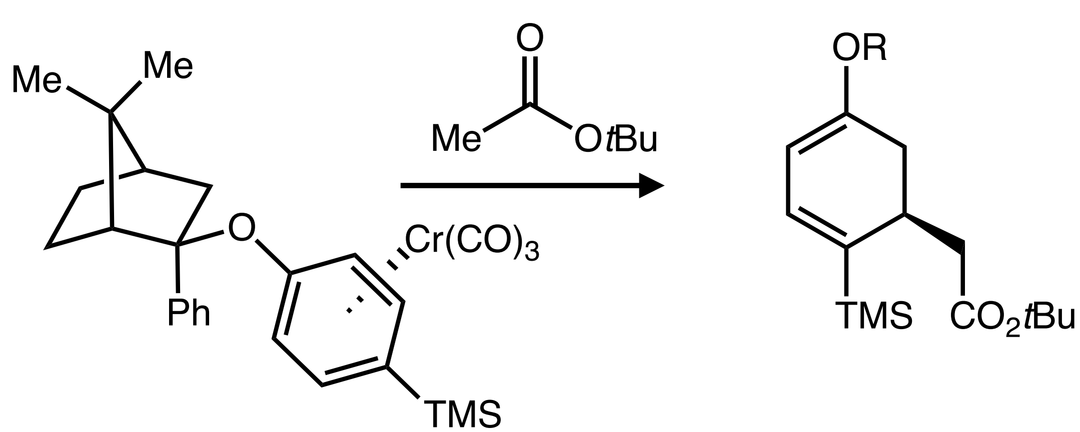


Radical approach



Transition-metal



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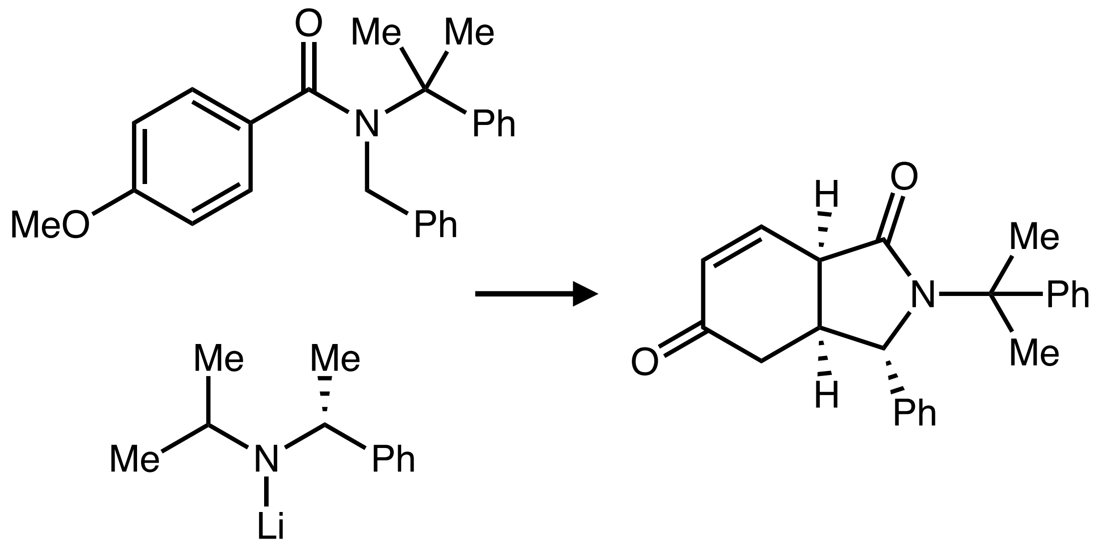

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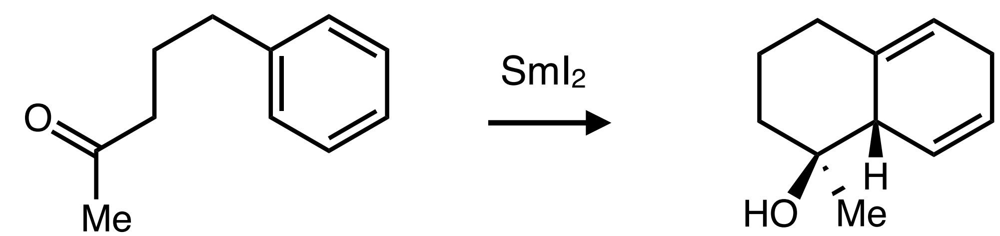

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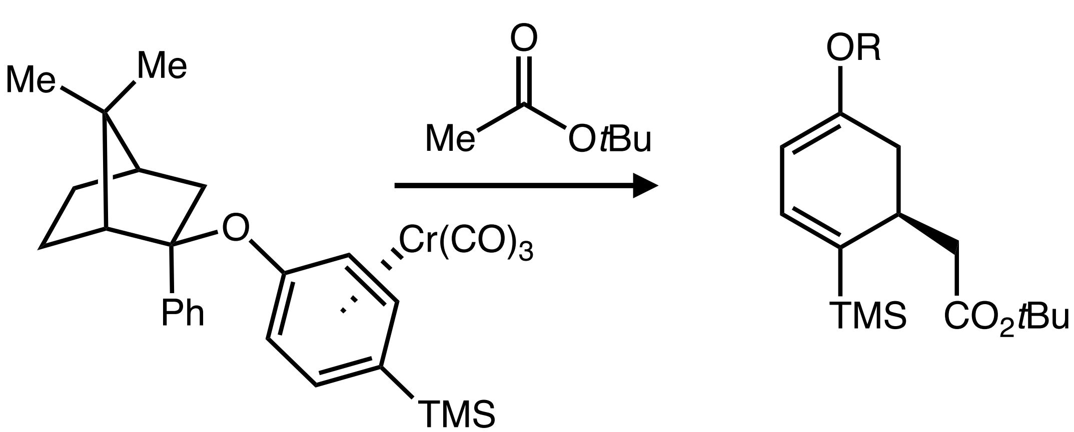

Thermal cycloaddition

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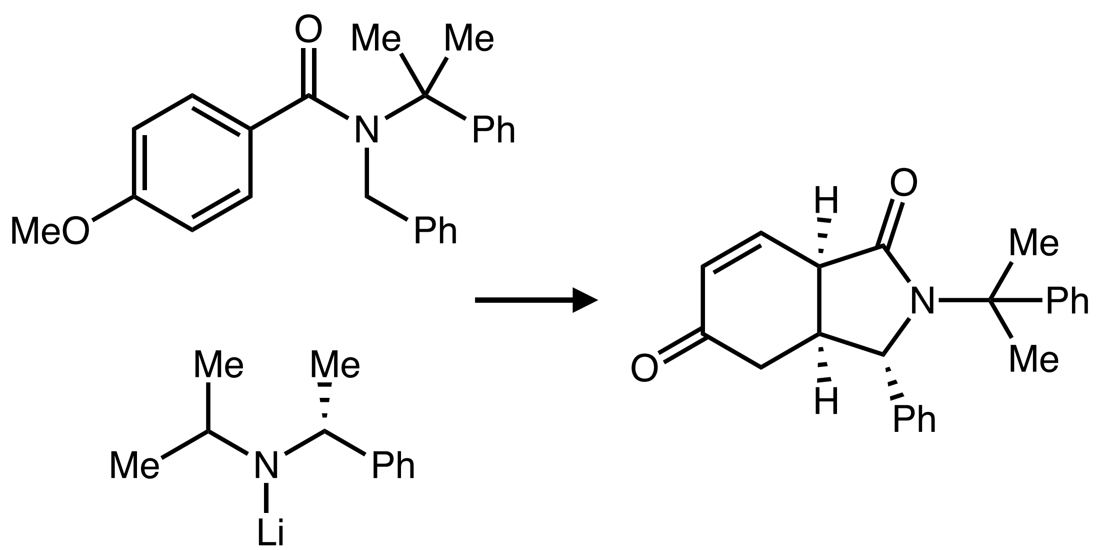

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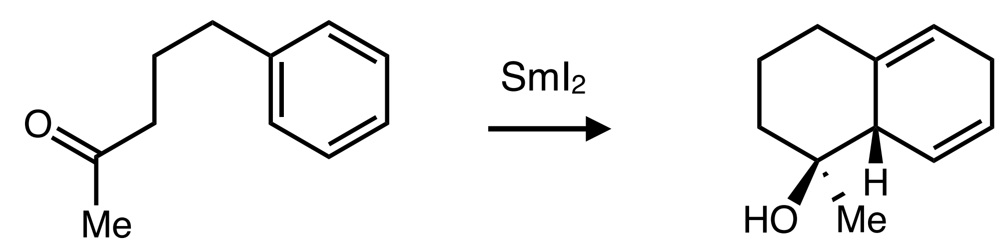

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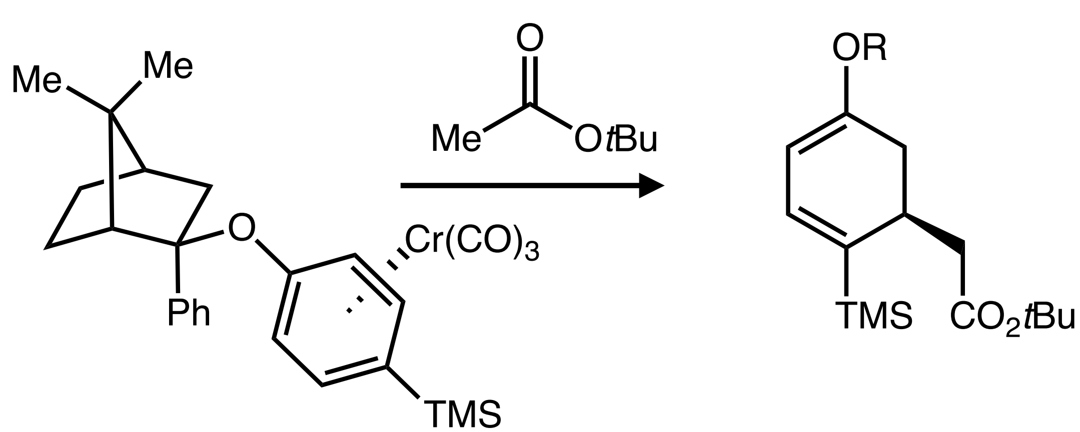

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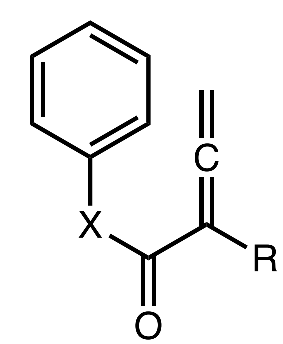

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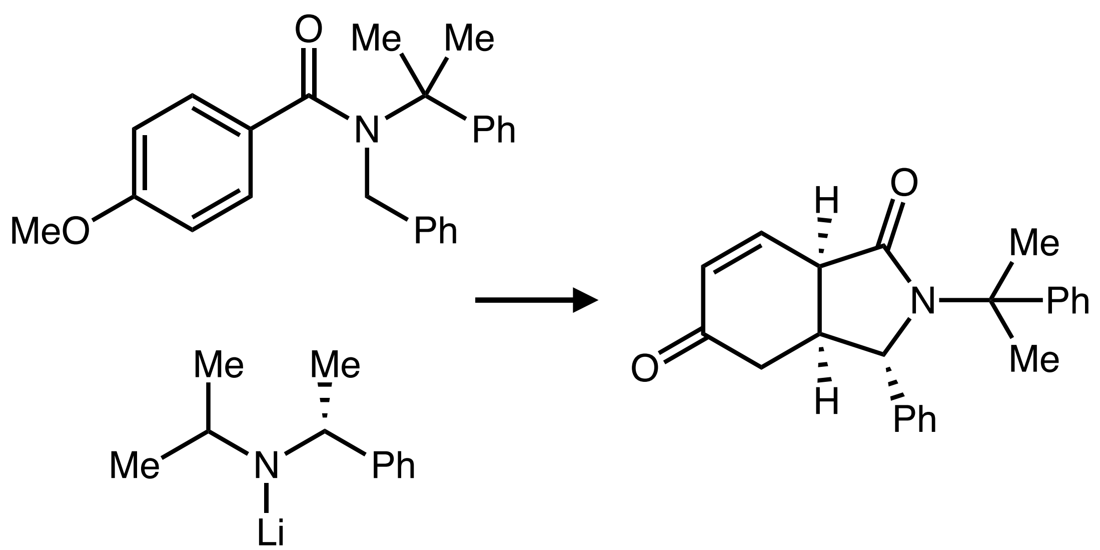

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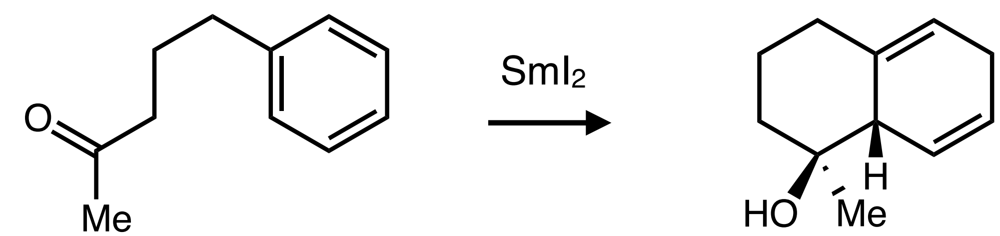

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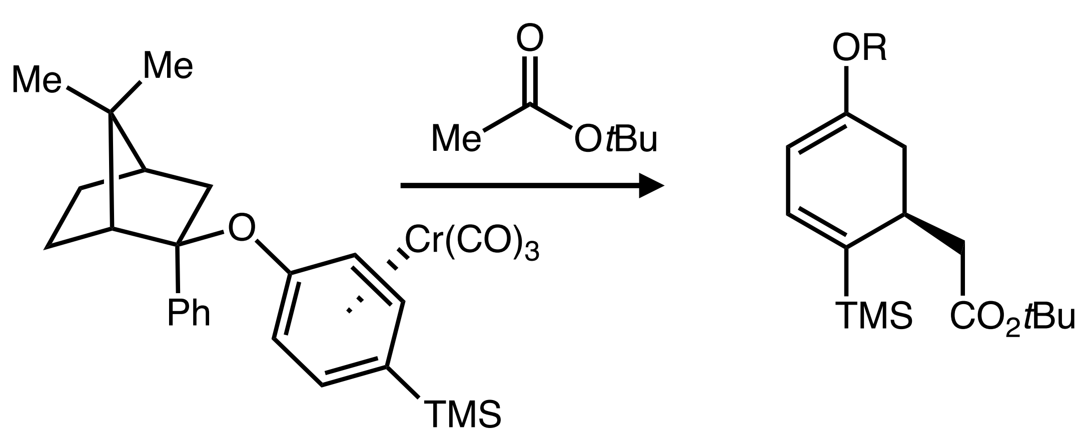

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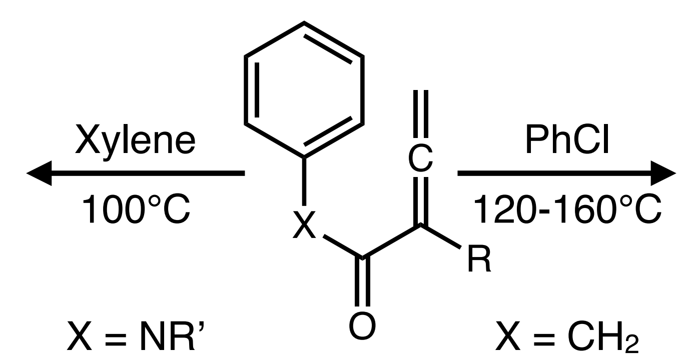

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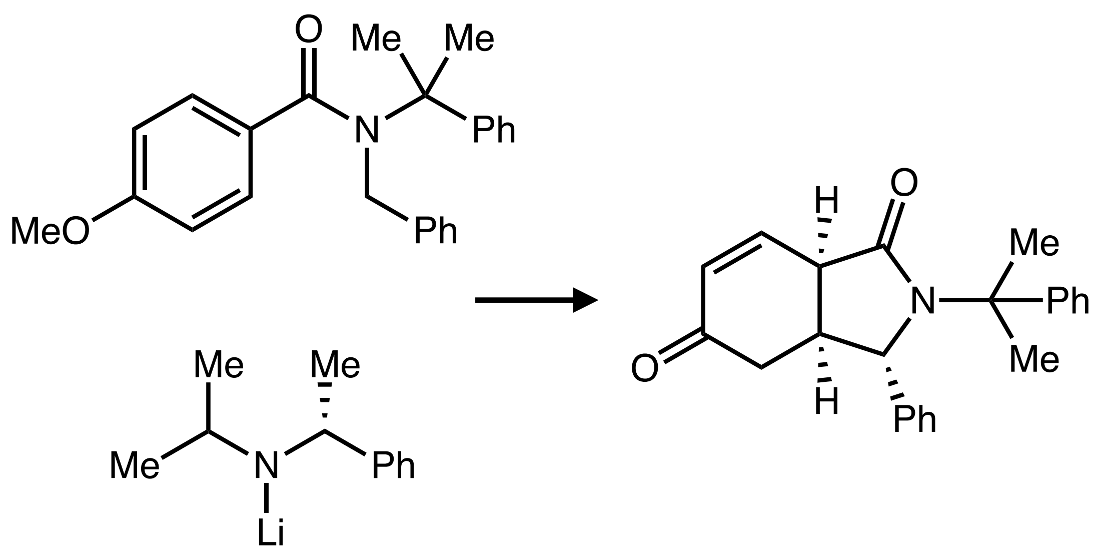

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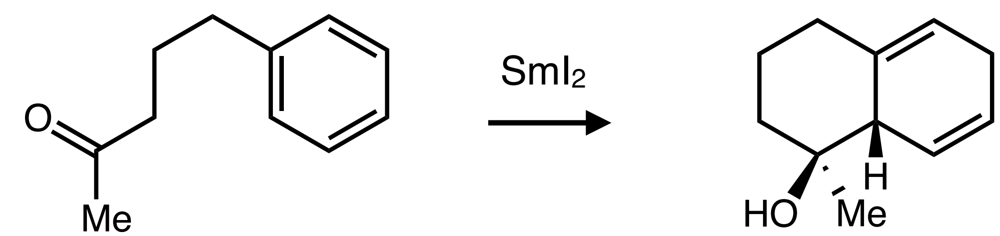

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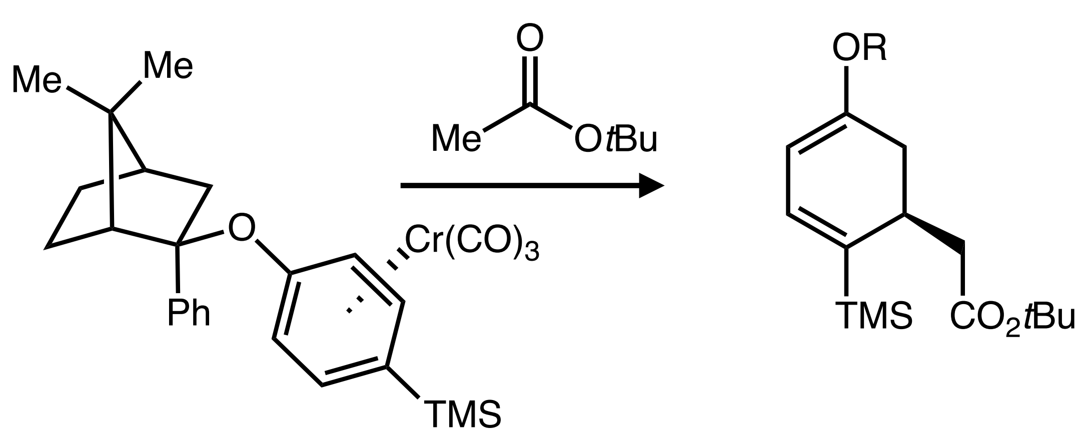

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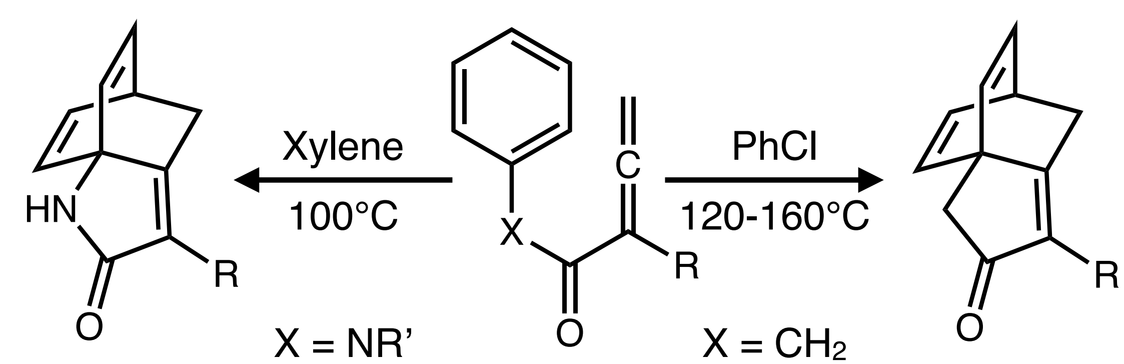

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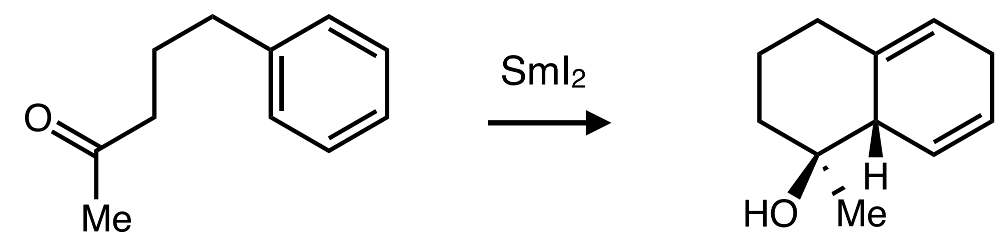
Overview of Dearomatization Strategies

Nucleophilic attack

Radical approach



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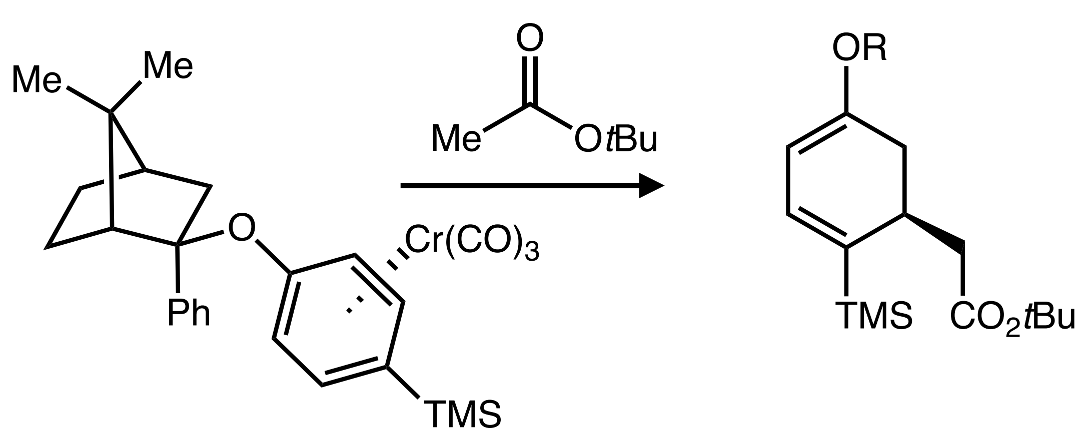

Thermal cycloaddition

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Outline

Radical approach

Transition-metal

Outline

Radical approach

Traditional radical generation

Transition-metal

Outline

Radical approach

Traditional radical generation Birch & SmI_2

Transition-metal

Outline

Radical approach

Traditional radical generation — Birch & SmI_2

Photochemical

Transition-metal

Outline

Radical approach

- **Traditional radical generation**
  - Birch & SmI_2
- **Photochemical**
  - **Single electron transfer**
    - Radical addition
    - Oxidation
    - Reduction
  - **Energy transfer**
    - Direct excitation
    - Sensitization

Transition-metal

Outline

Radical approach

- **Traditional radical generation**
  - Birch & SmI_2
- **Photochemical**
  - **Single electron transfer**
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Transition-metal

- **Mediated**
  - η^2
  - η^6

Outline

Radical approach

- **Traditional radical generation**
  - Birch & SmI_2
- **Photochemical**
  - **Single electron transfer**
    - Radical addition
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    - Reduction
  - **Energy transfer**
    - Direct excitation
    - Sensitization

Transition-metal

- **Mediated**
  - *η^2*
  - *η^6*
- **Catalyzed**
  - *Pd*

Outline

Radical approach

Traditional radical generation — Birch & SmI_2

Photochemical

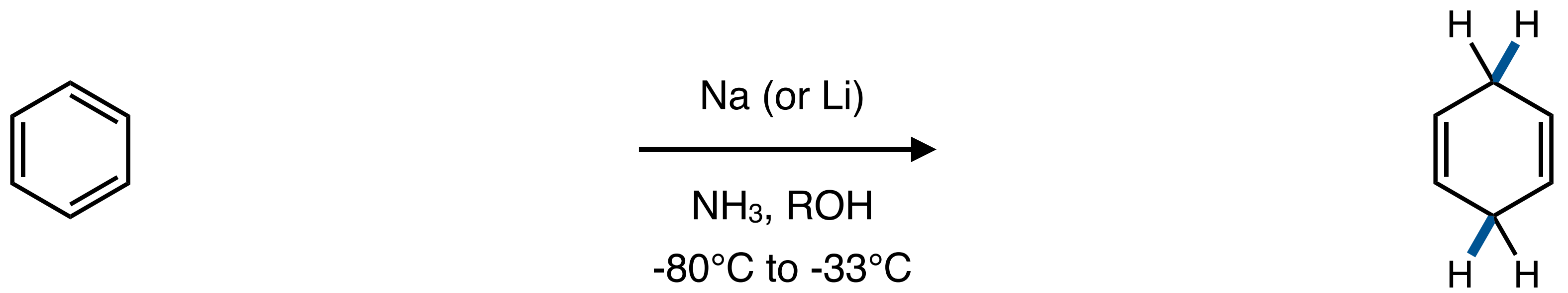
- **Single electron transfer**
  - Radical addition
  - Oxidation
  - Reduction
- **Energy transfer**
  - Direct excitation
  - Sensitization

Transition-metal

- **Mediated**
  - η^2
  - η^6
- **Catalyzed** — *Pd*

Radical Approach to Dearomatization

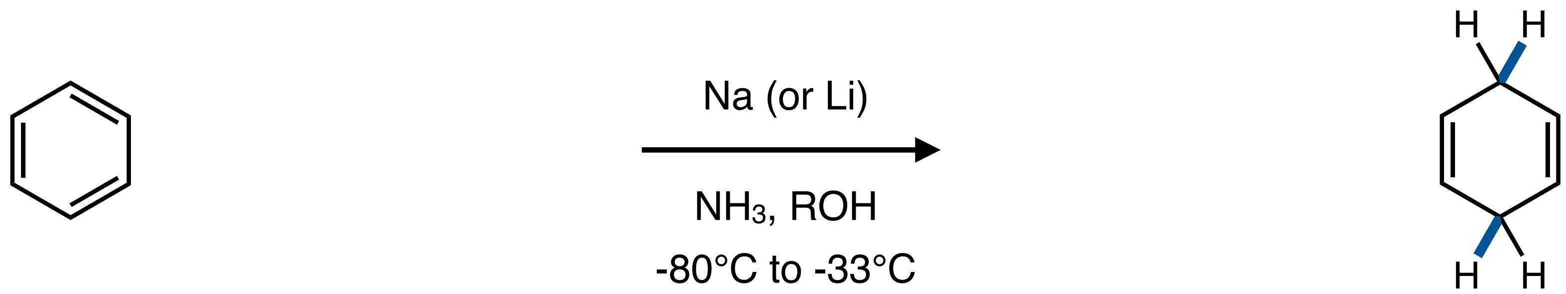
Traditional approach - Birch reduction



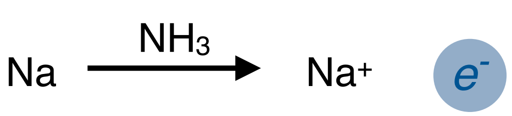
Birch, A. J. *J. Chem Soc*. **1944**, 430–436. Birch, A. J. *J. Chem. Soc*. **1945**, 809–813

Radical Approach to Dearomatization

Traditional approach - Birch reduction



Mechanism



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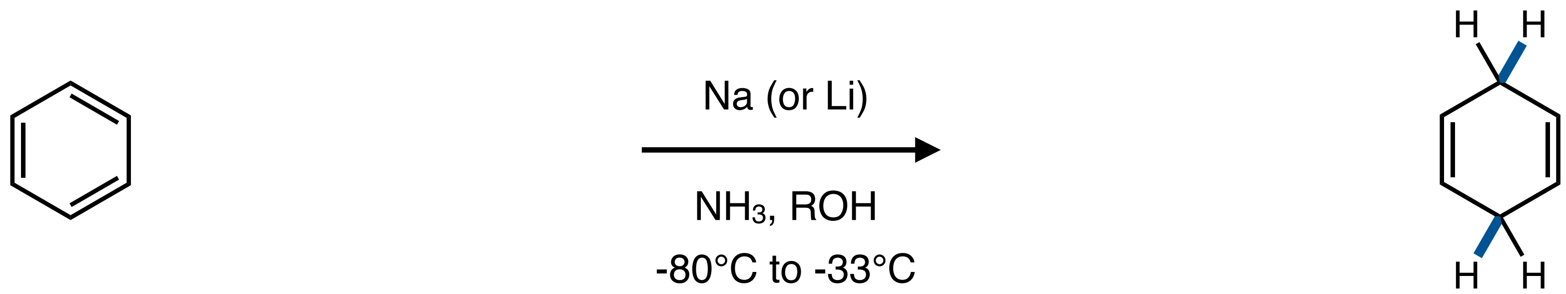

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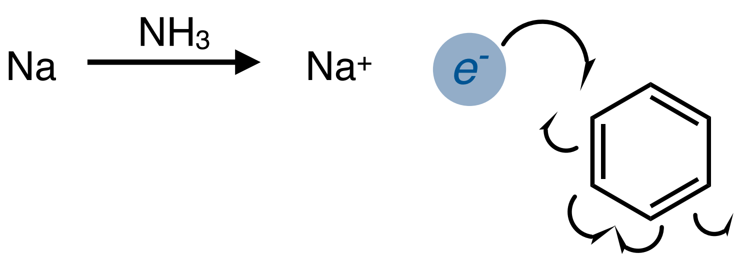

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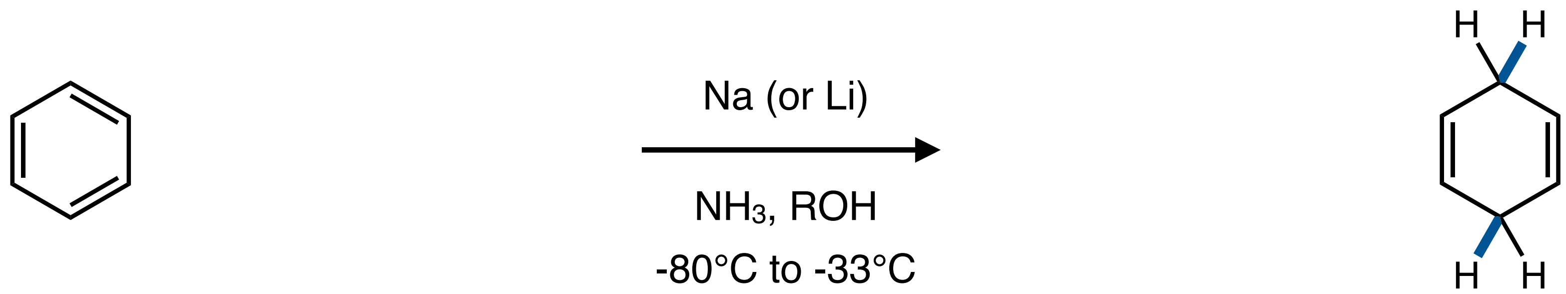

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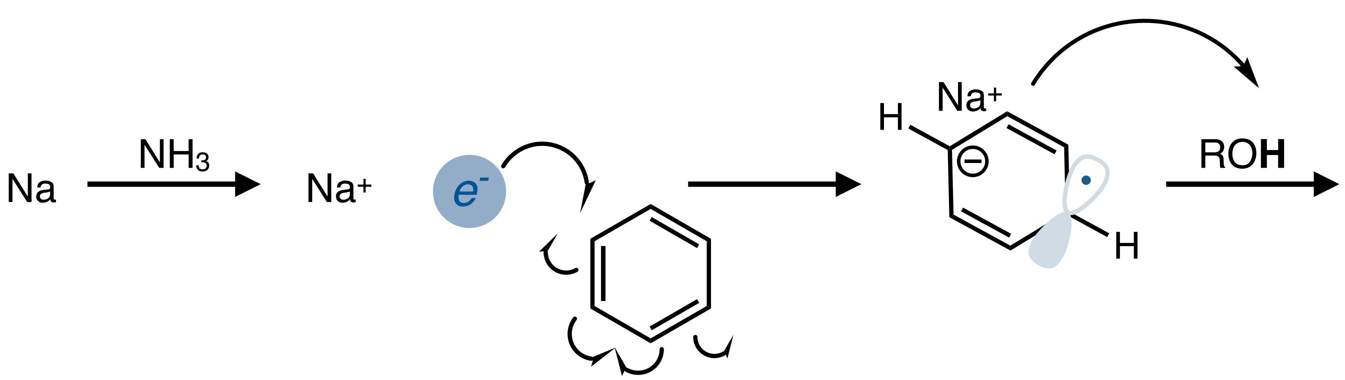

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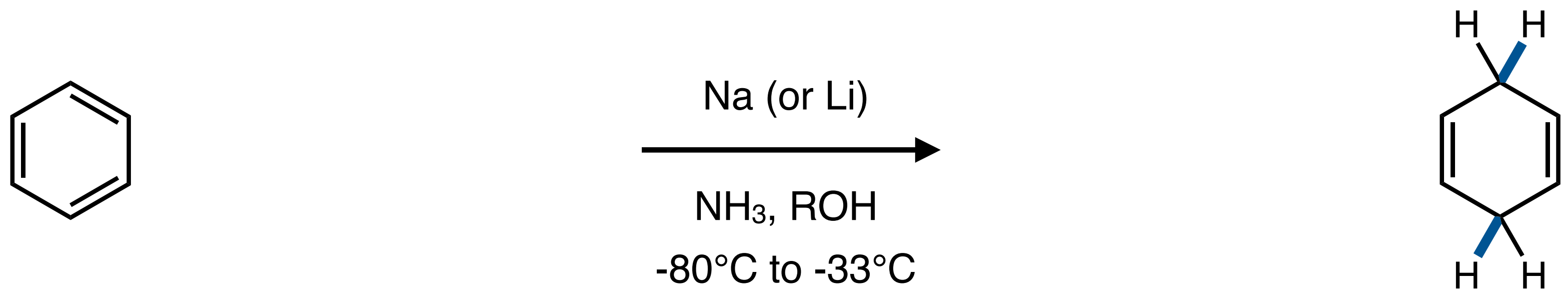

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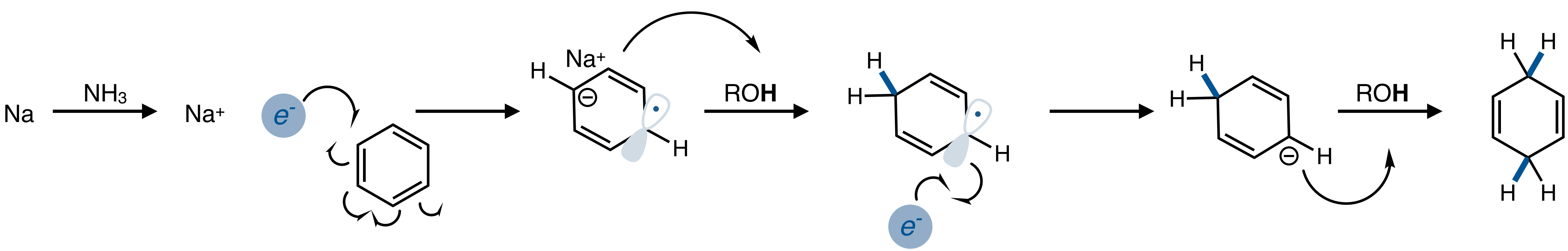

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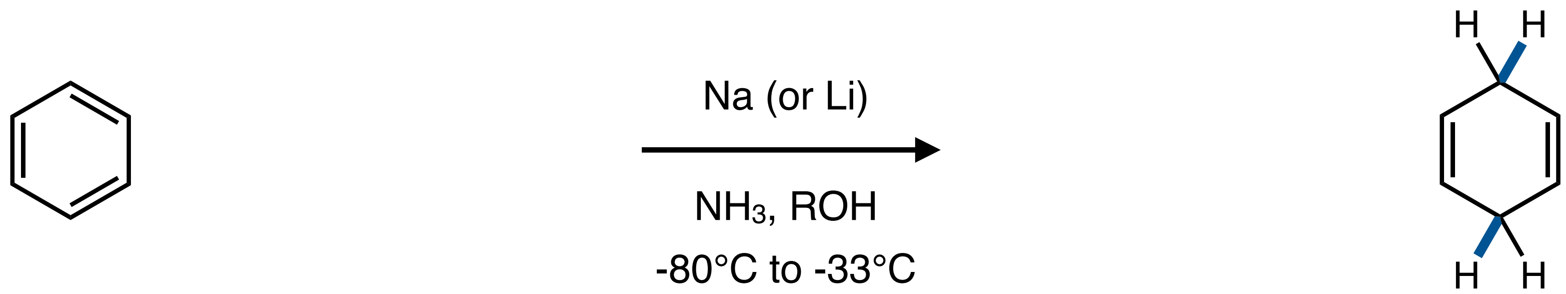

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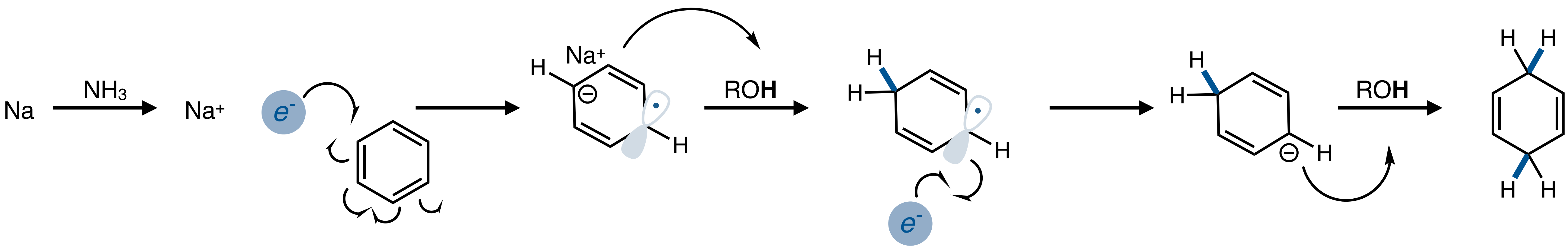
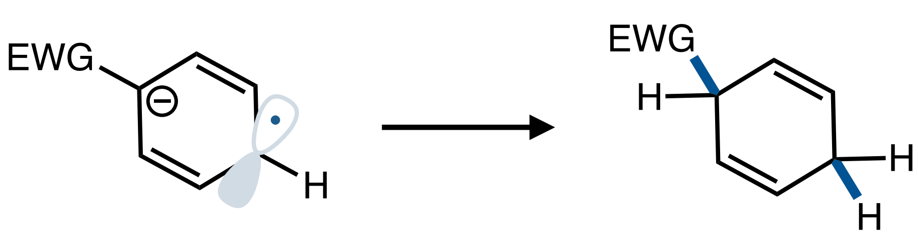


Selectivity



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Radical Approach to Dearomatization

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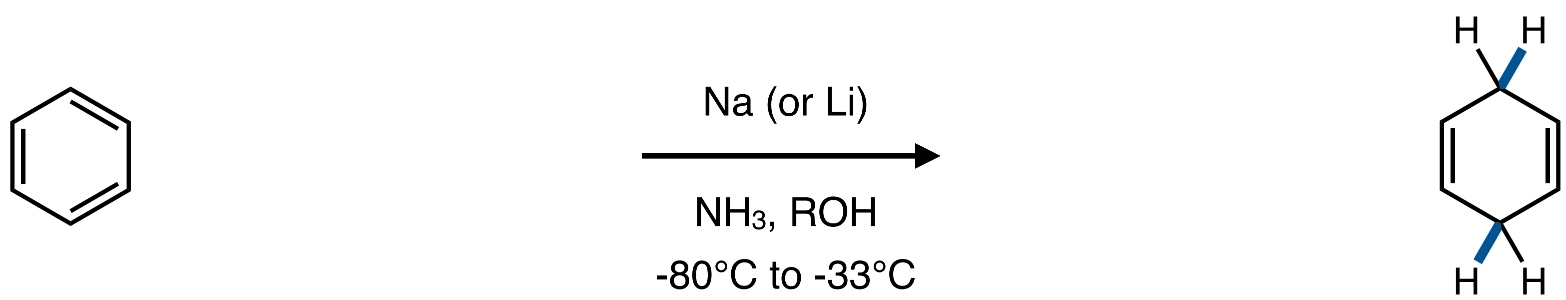

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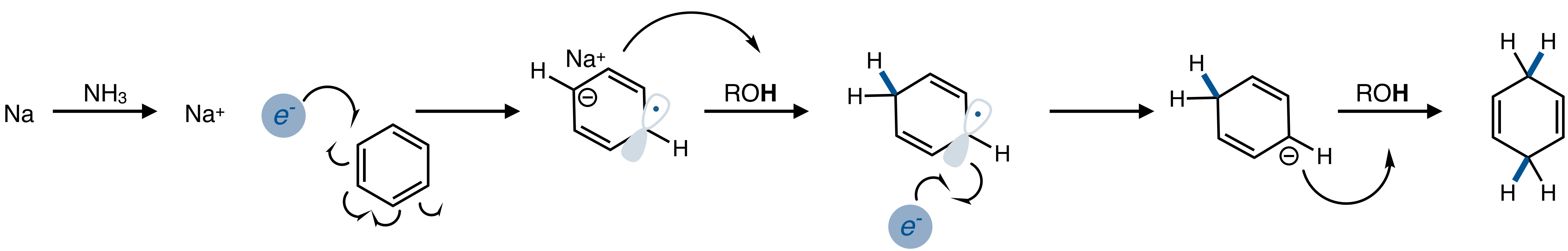

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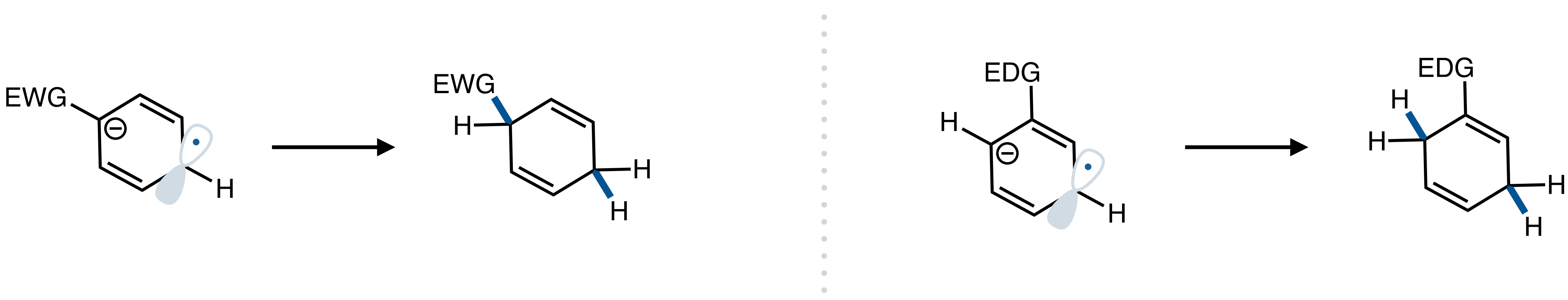

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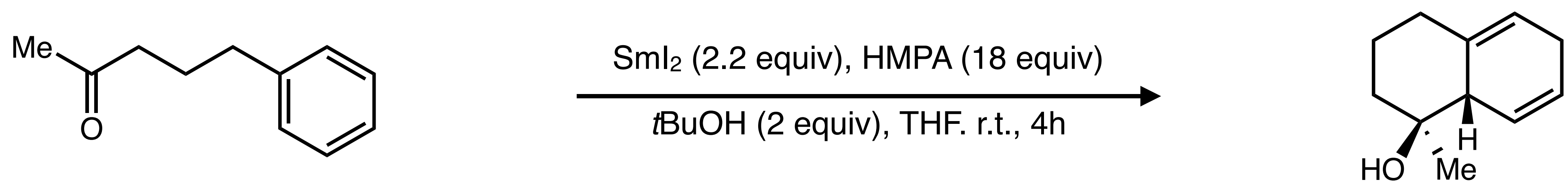
Radical Approach to Dearomatization

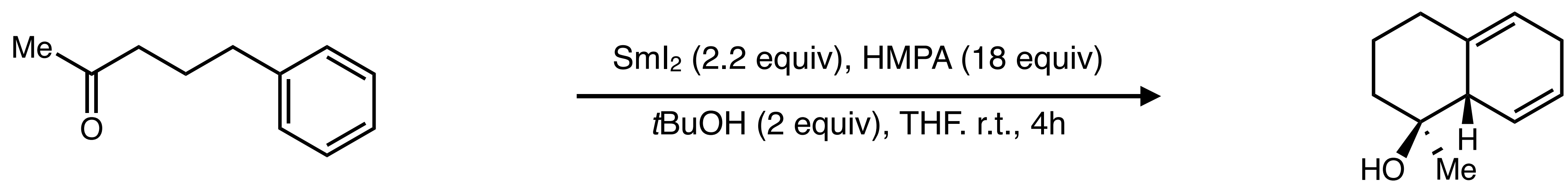
Traditional approach - SmI_2



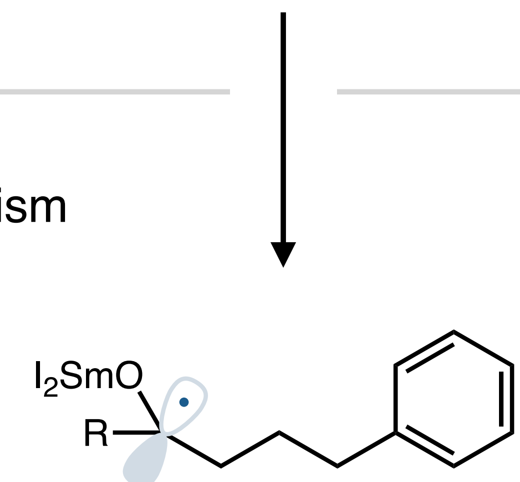
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



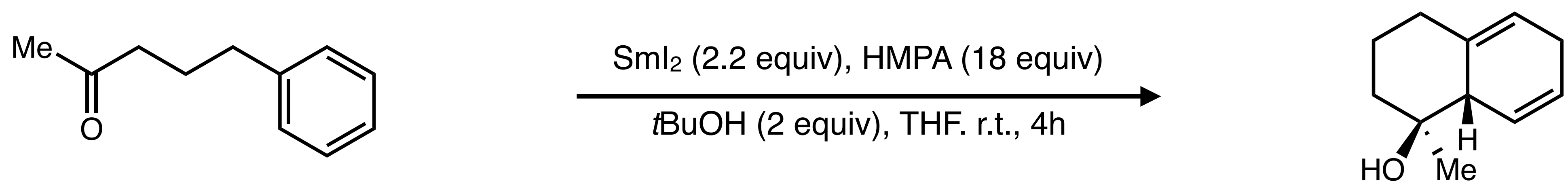
- Mechanism



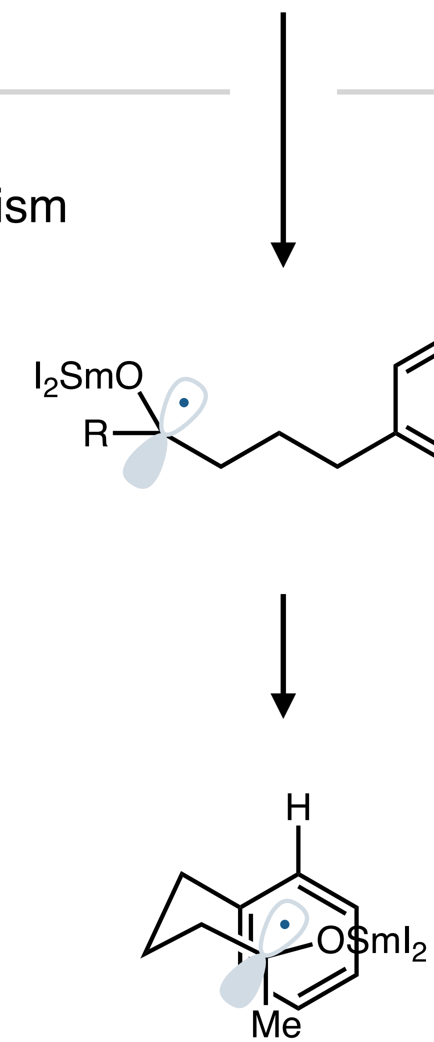
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



Mechanism



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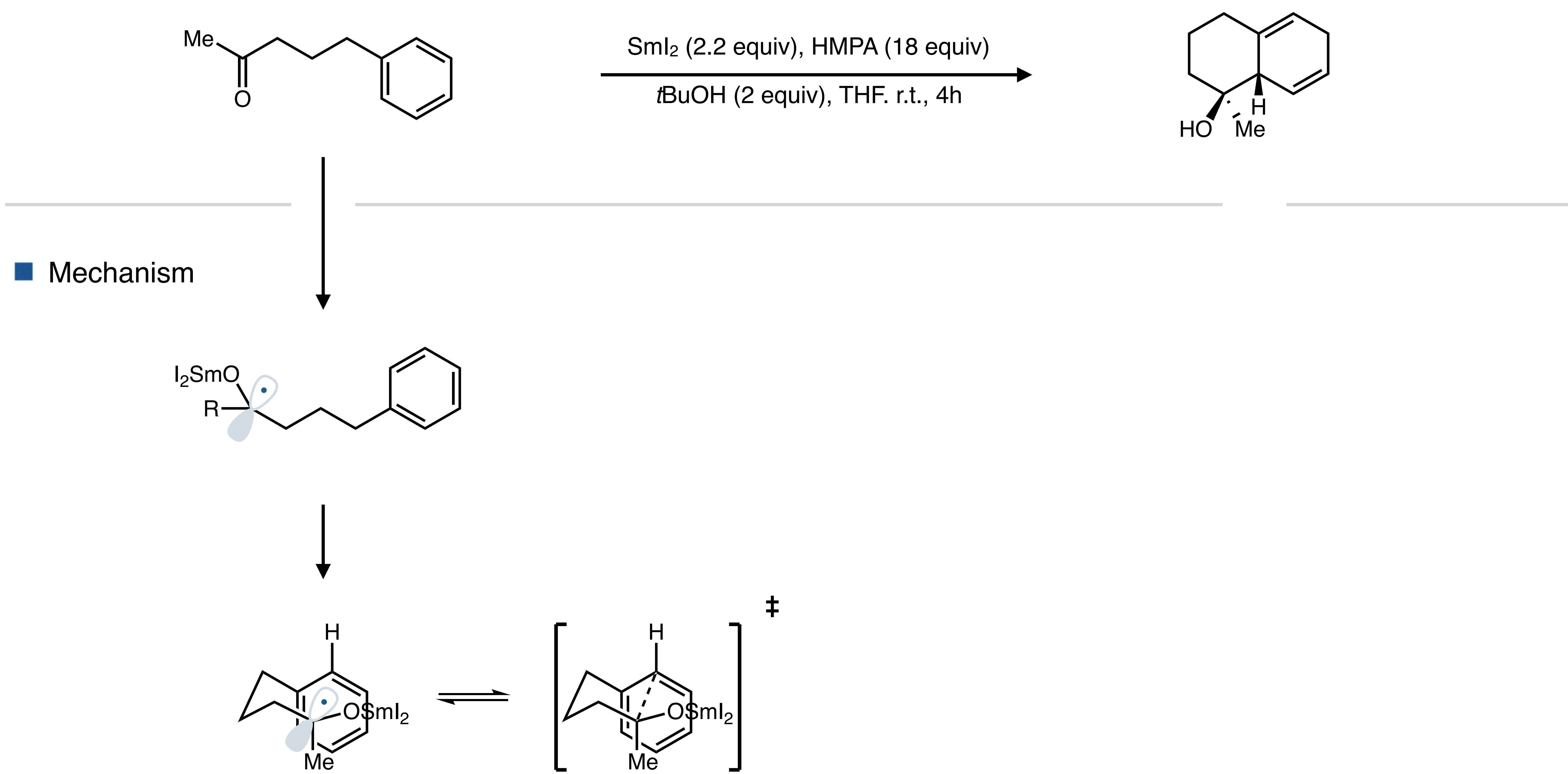

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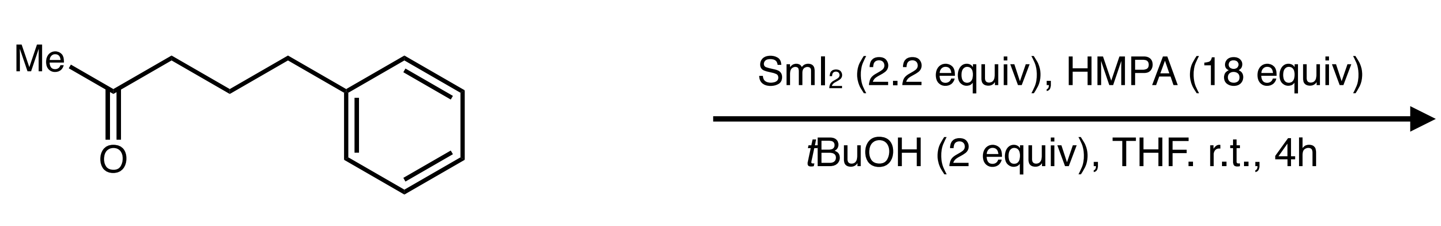
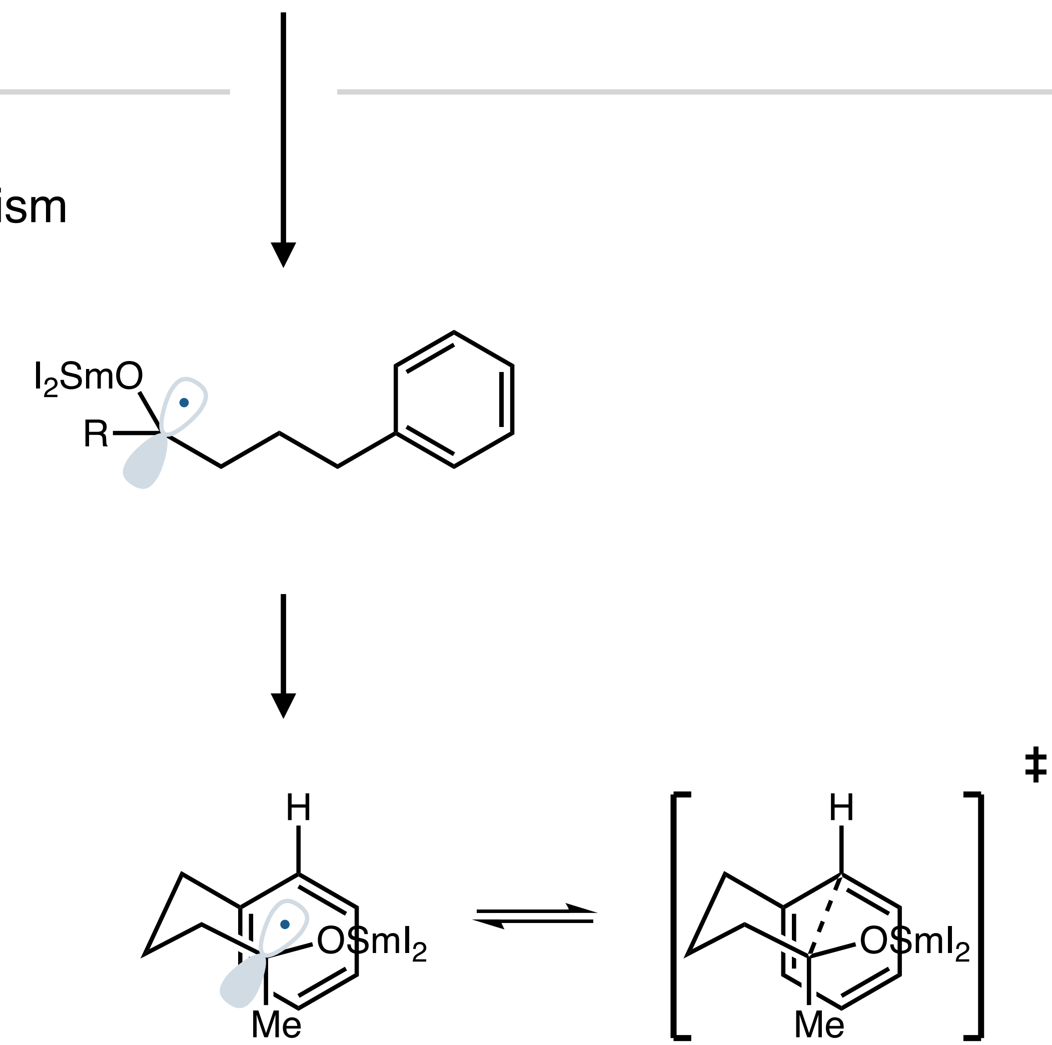
Radical Approach to Dearomatization

Traditional approach - SmI_2



■ Mechanism

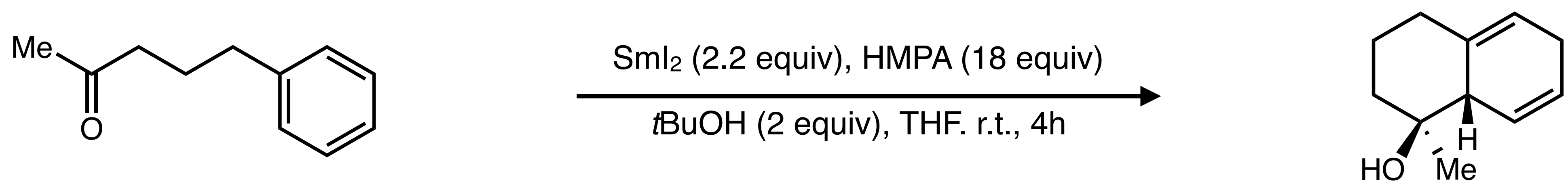


Chair transition state

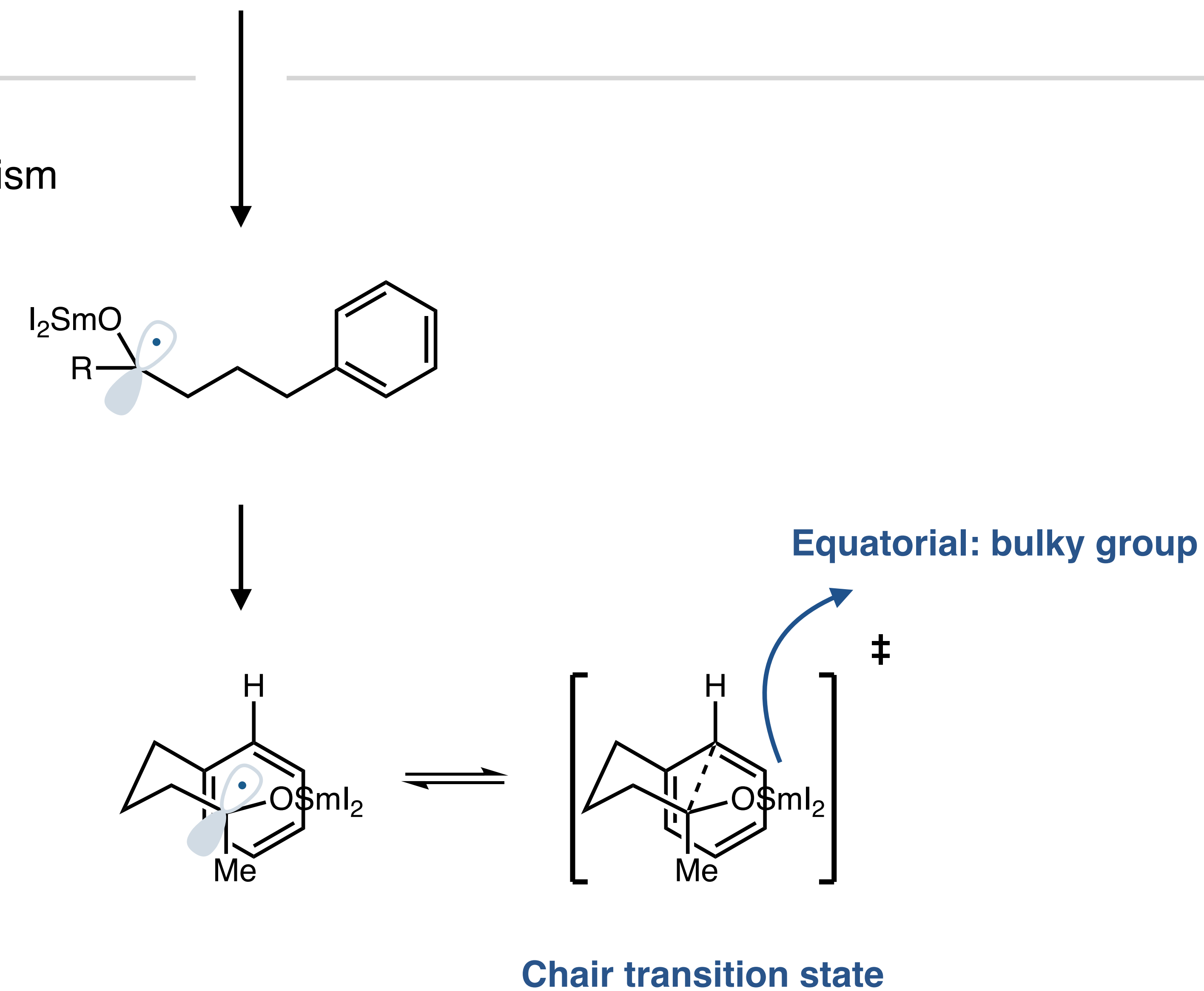
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



Mechanism



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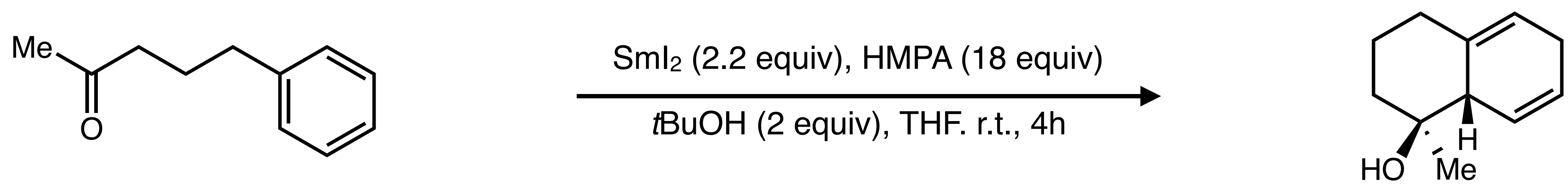
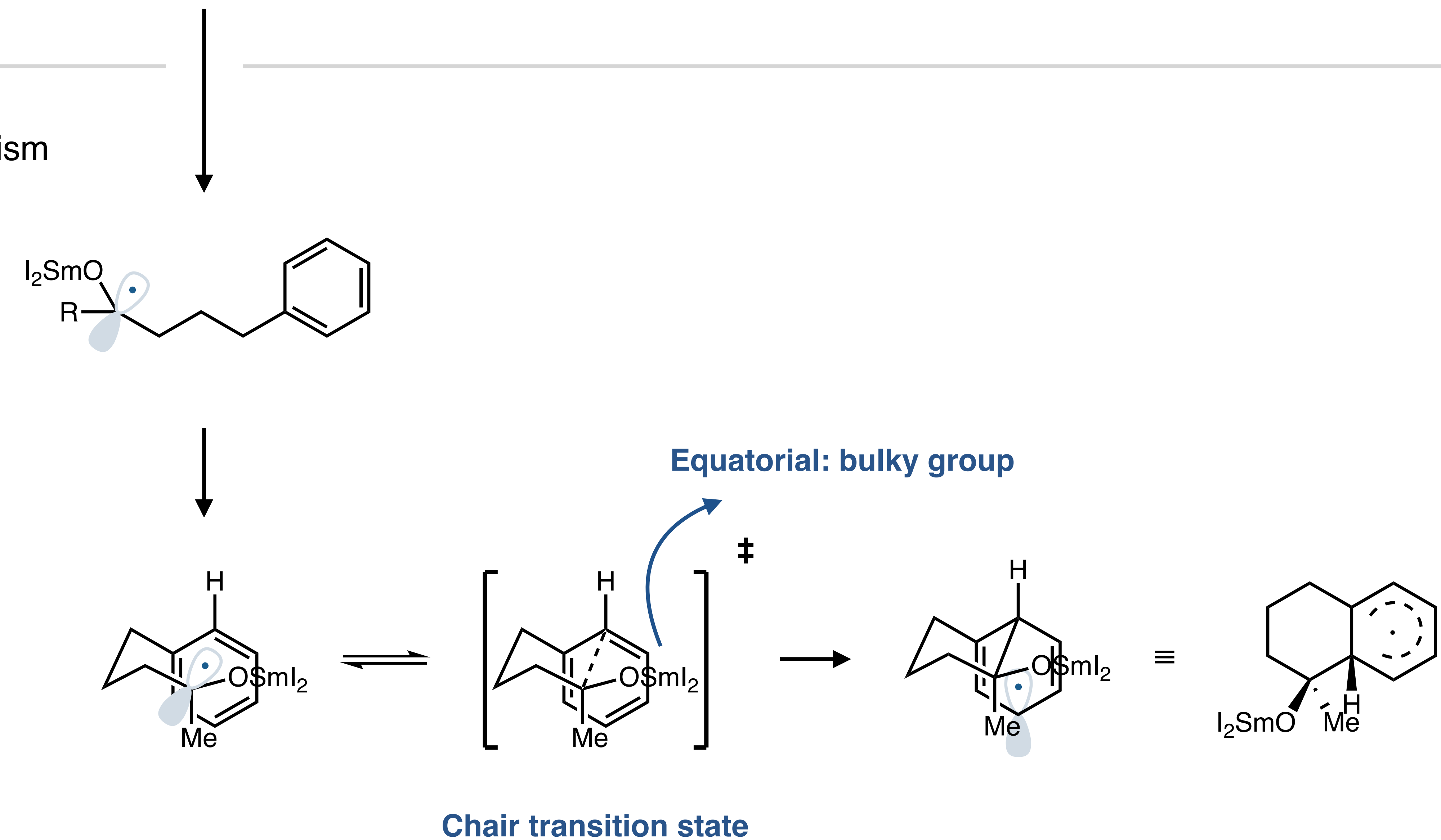
Traditional approach - SmI_2



■ Mechanism



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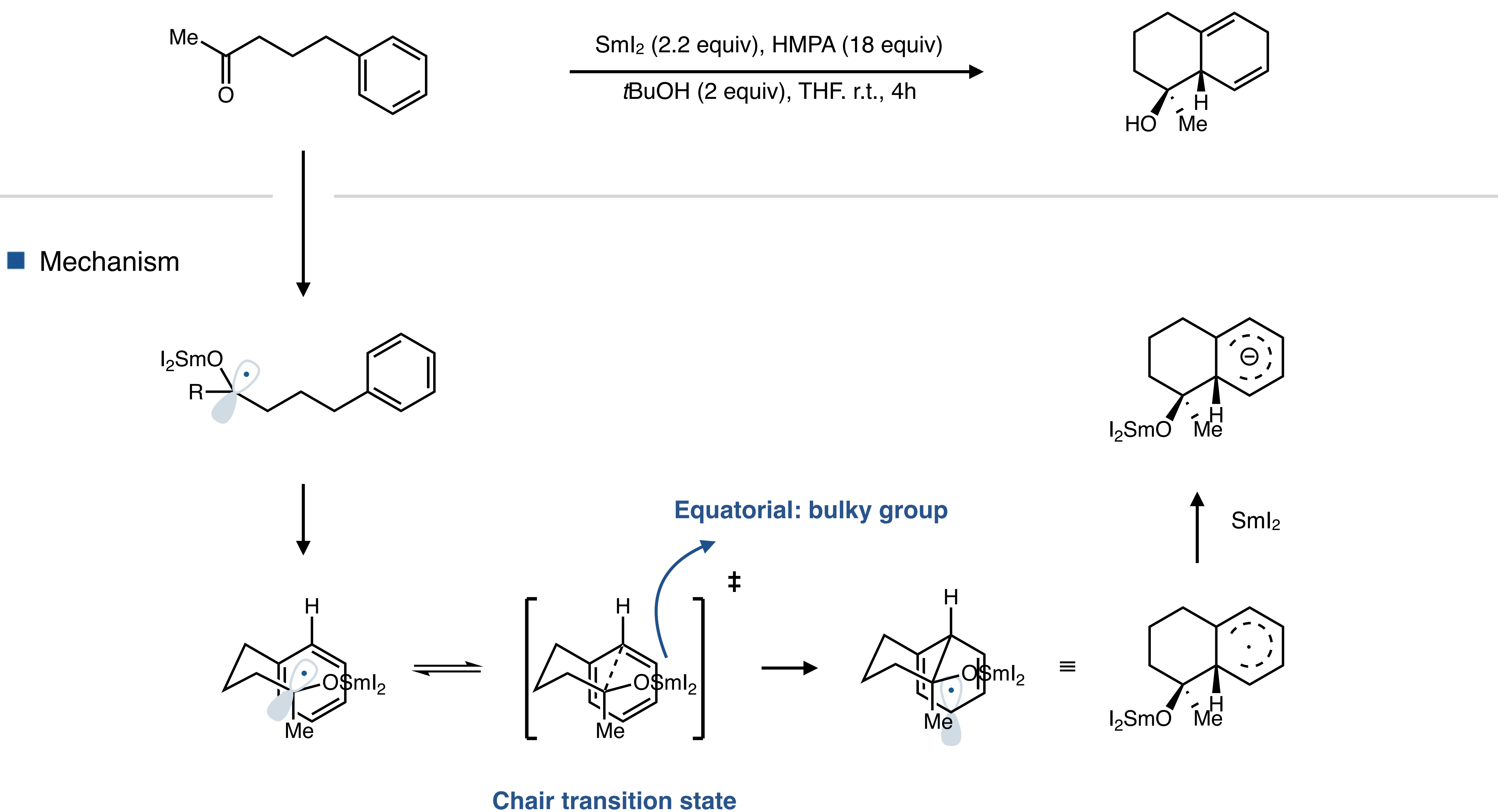

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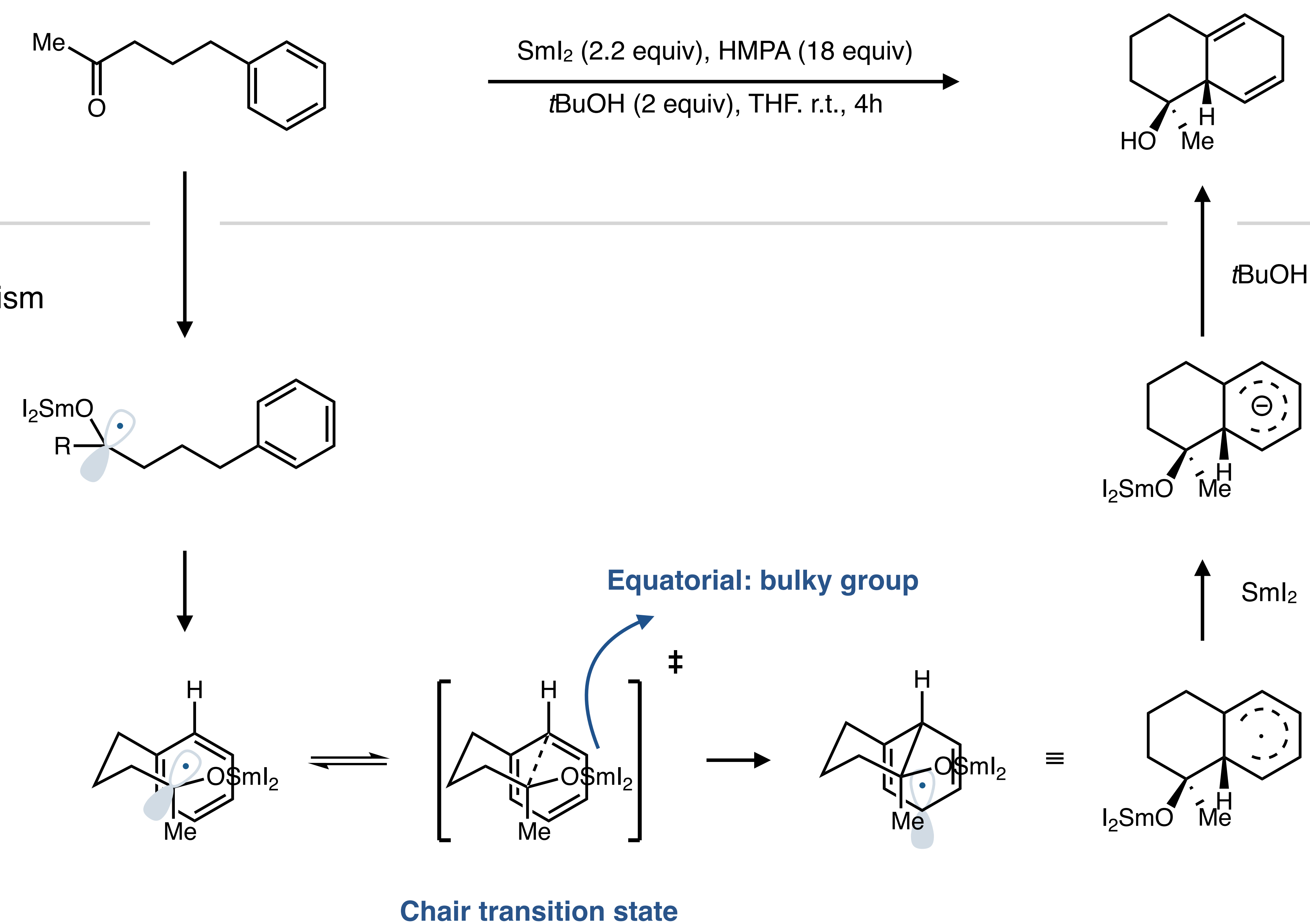

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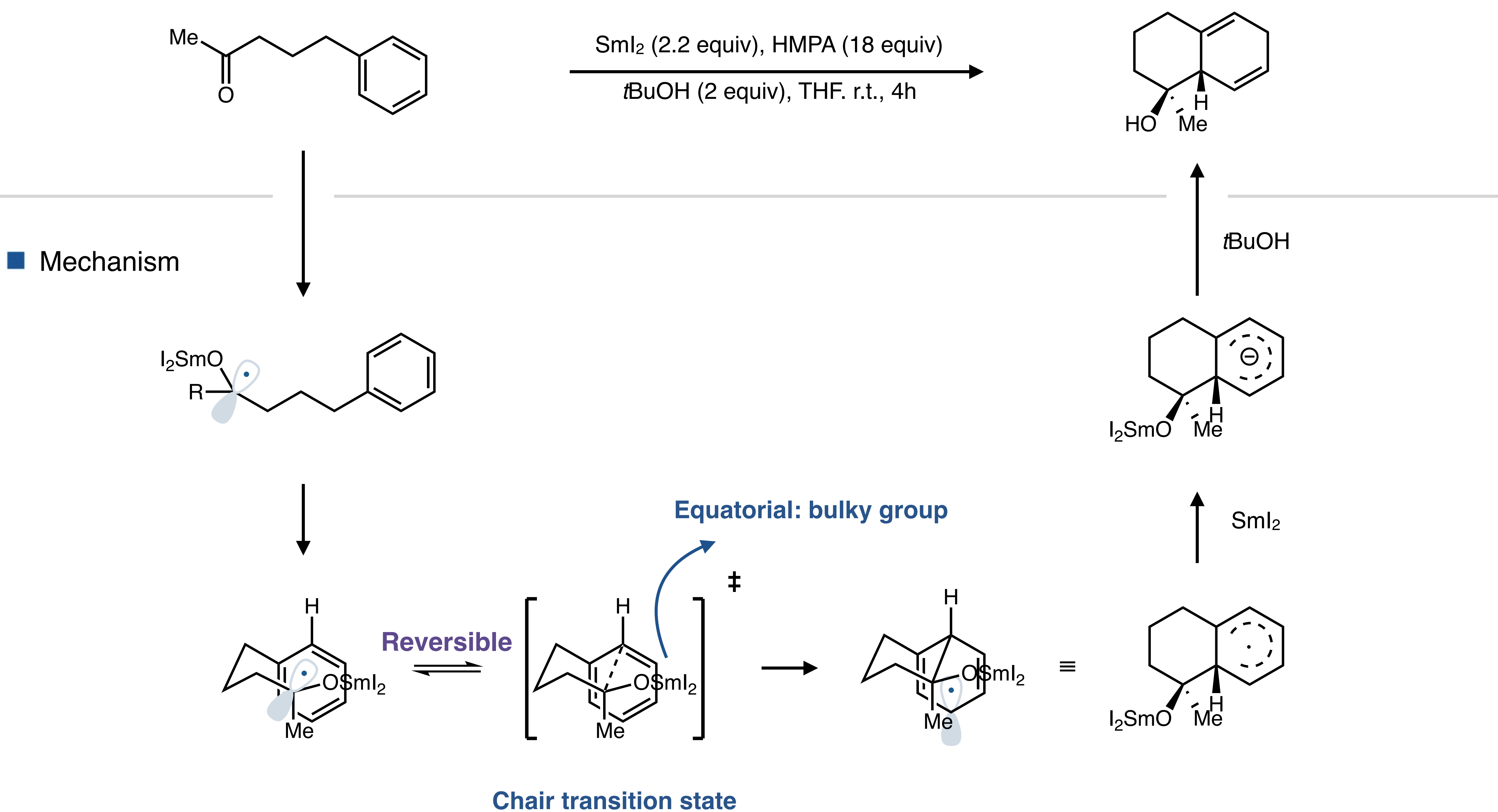

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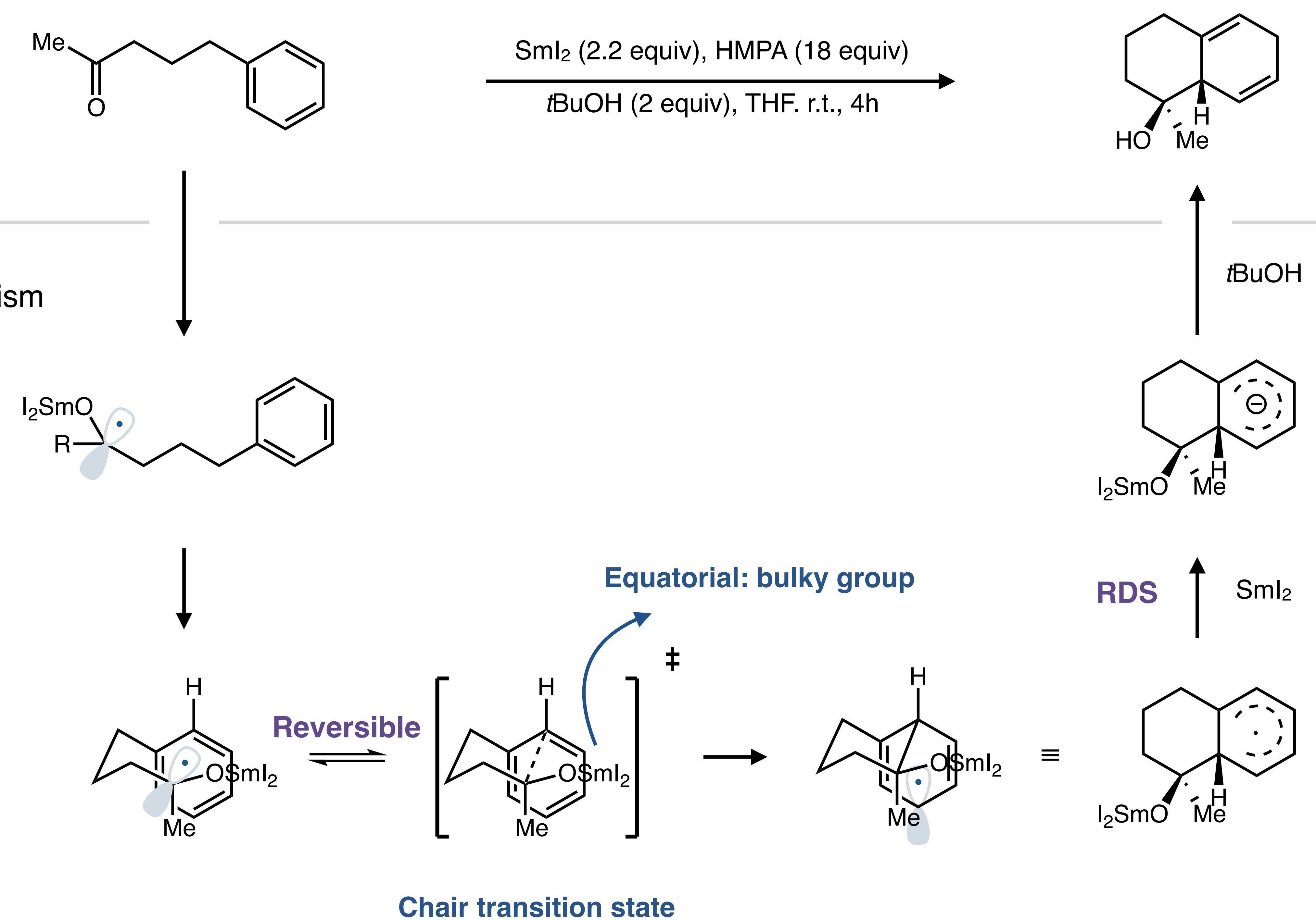

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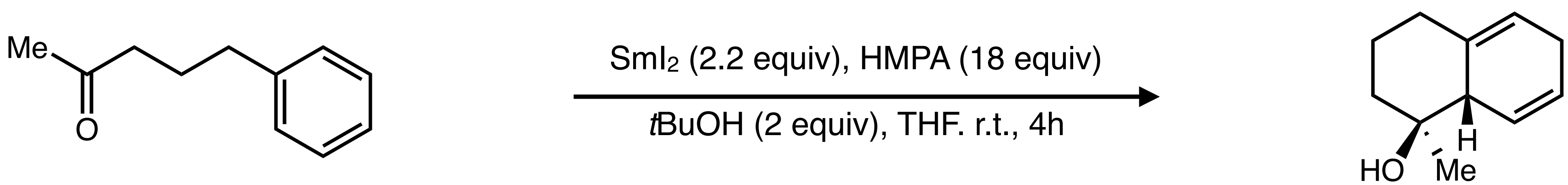
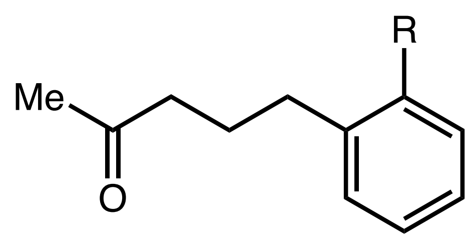
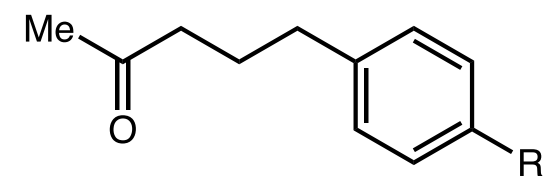


- Substituent effect

Ortho **Para**





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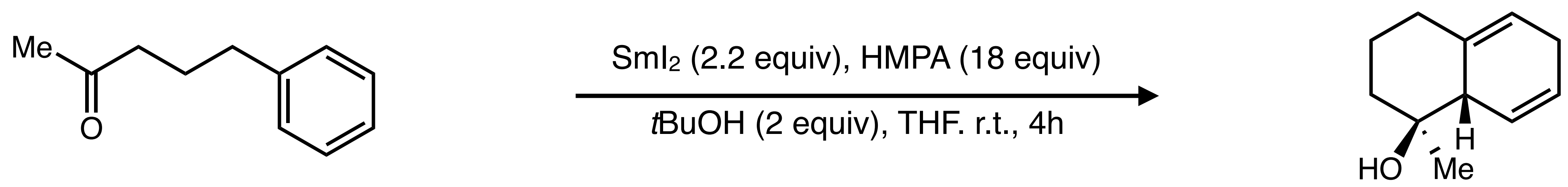
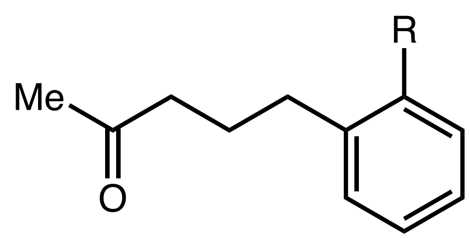
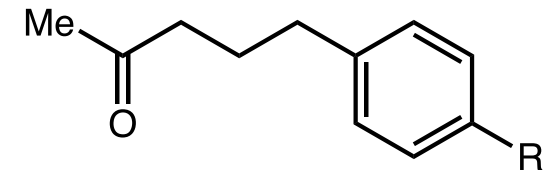


- Substituent effect

Ortho



Para



EWG

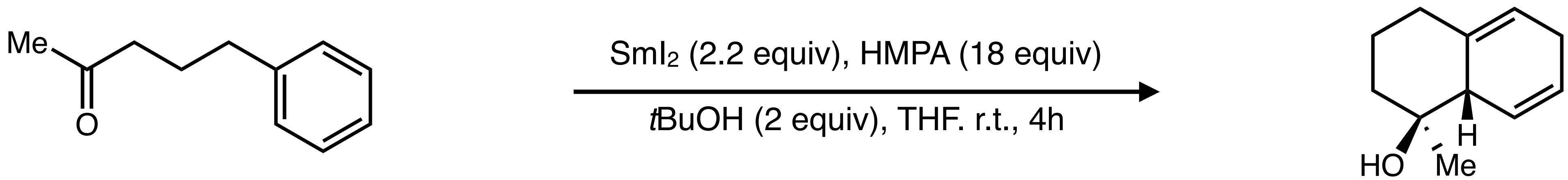
CN

CF_3

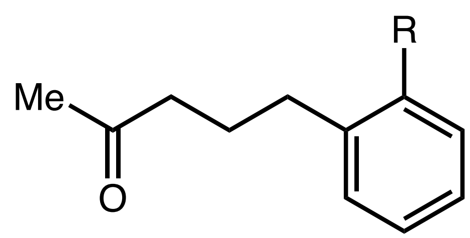
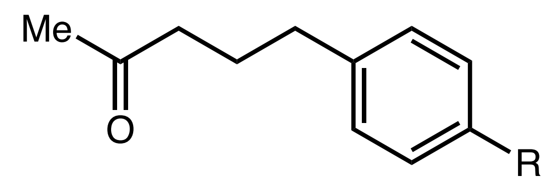
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



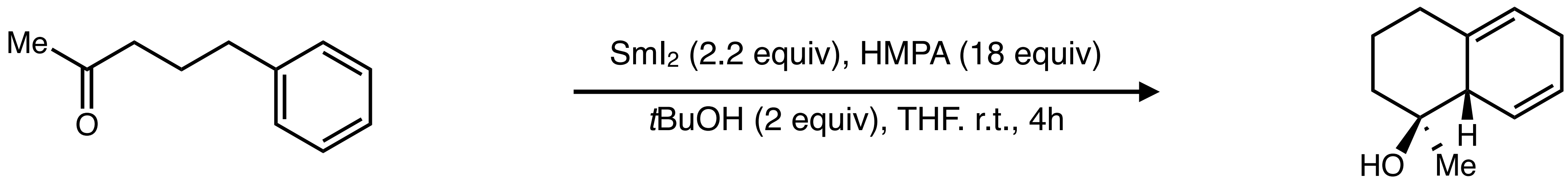
- Substituent effect

		Ortho	Para
			
EWG	CN	54%	55%
	CF_3	51%	56%

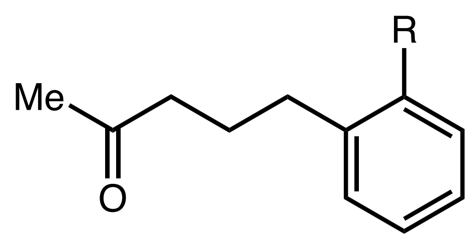
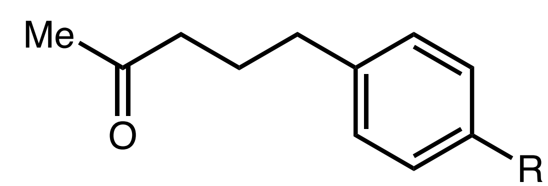
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



- Substituent effect

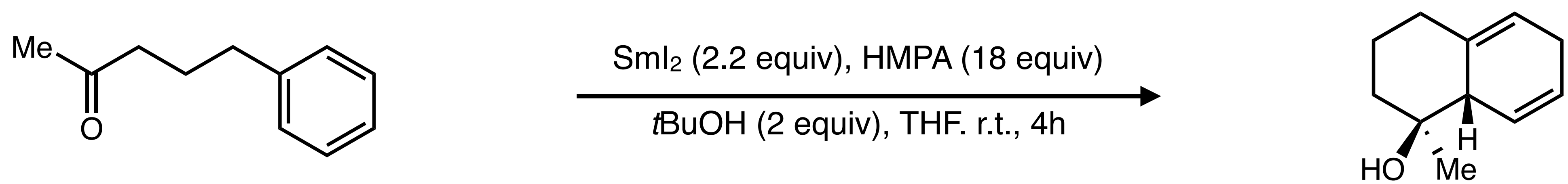
EWG	R	Ortho	Para
			
	CN	**54%**	**55%**
	CF_3	**51%**	**56%**

Facilitate second SET

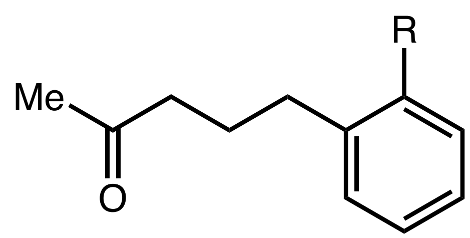
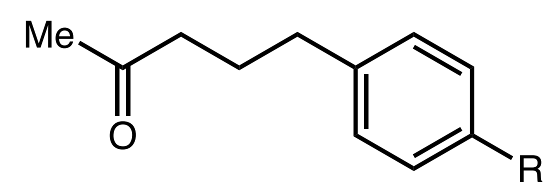
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



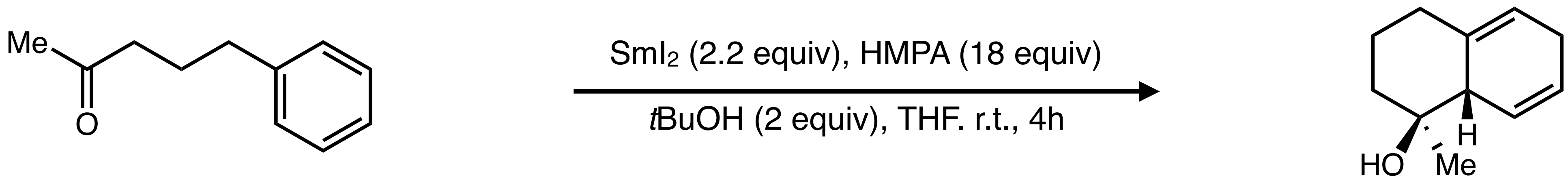
- Substituent effect

		Ortho	Para	
				
EWG	CN	54%	55%	Facilitate second SET
	CF_3	51%	56%	
EDG	Me/OMe			

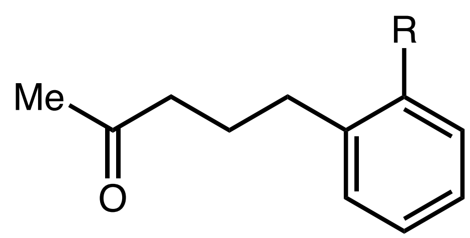
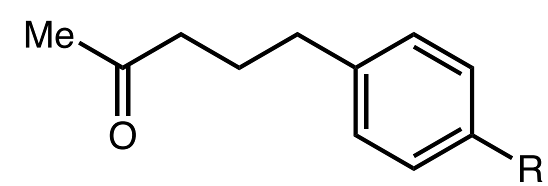
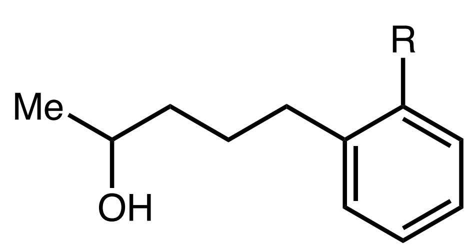
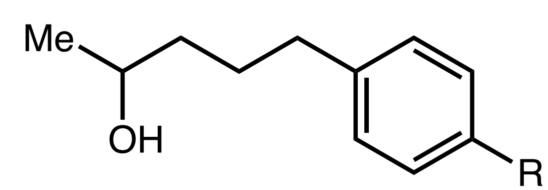
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



- Substituent effect

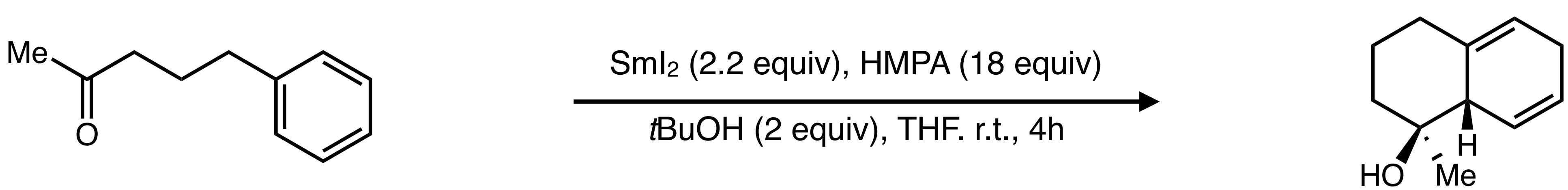
		Ortho	Para
			
EWG	CN	54%	55%
	CF_3	51%	56%
EDG	Me/OMe		

Facilitate second SET

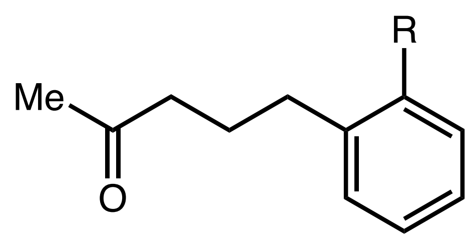
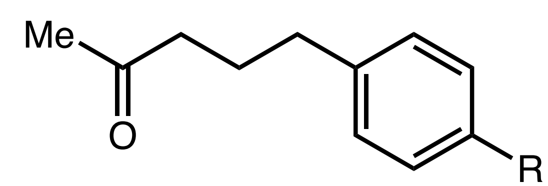
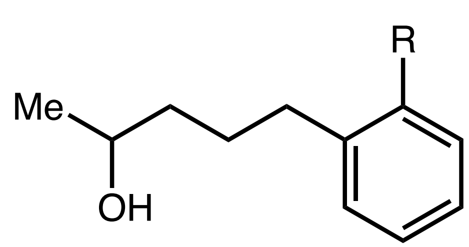
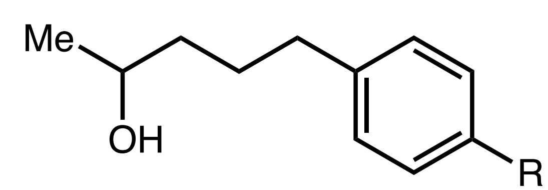
Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



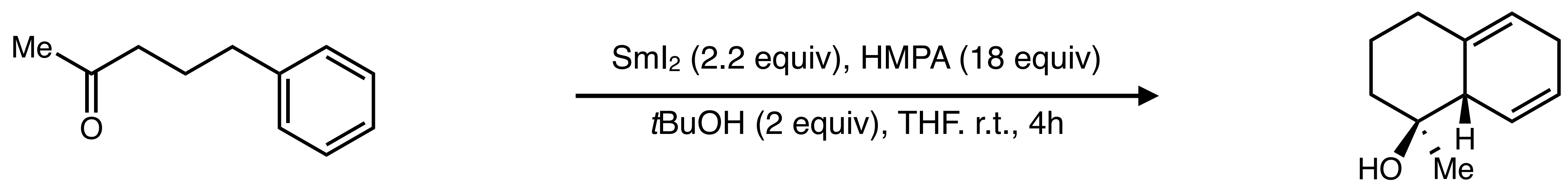
■ Substituent effect

		Ortho	Para	
				
EWG	CN	**54%**	**55%**	Facilitate second SET
	CF_3	**51%**	**56%**	
EDG	Me/OMe			Disfavor second SET

Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Radical Approach to Dearomatization

Traditional approach - SmI_2



- *Ipso* cyclization

Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

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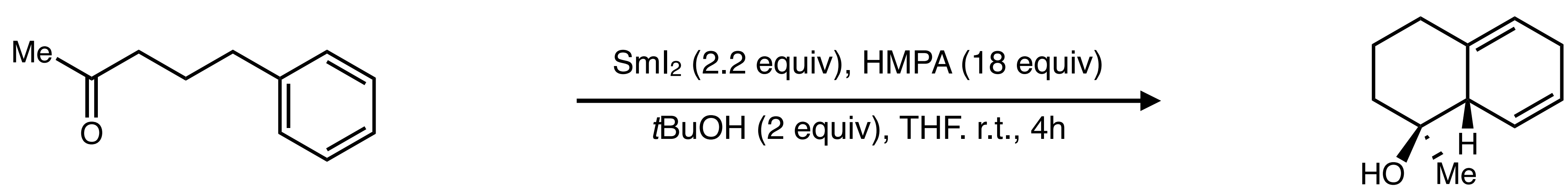

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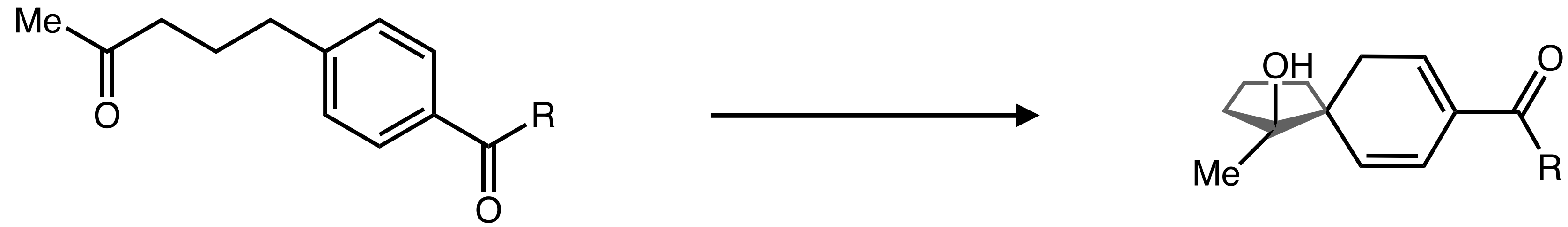

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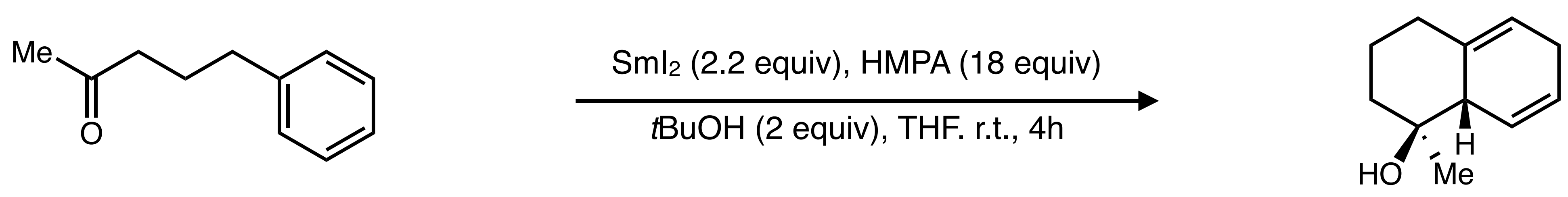
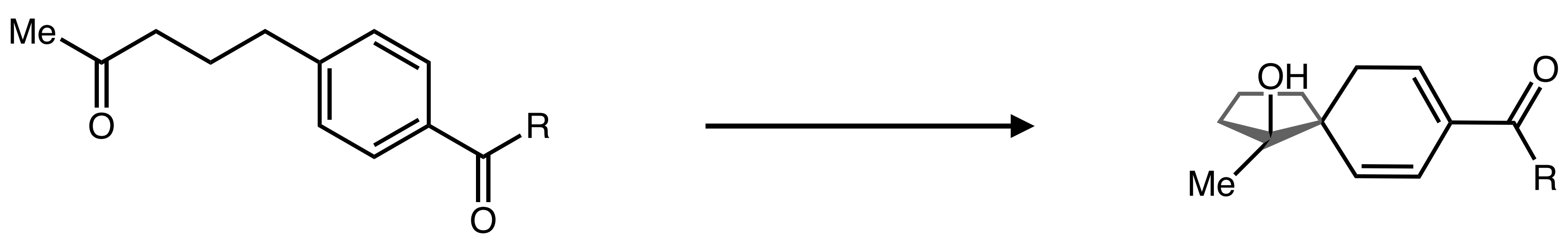


- *Ipso* cyclization



OMe

R group

Me

Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

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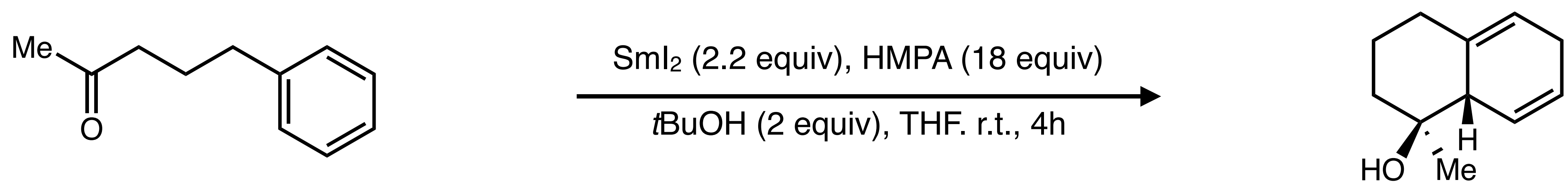
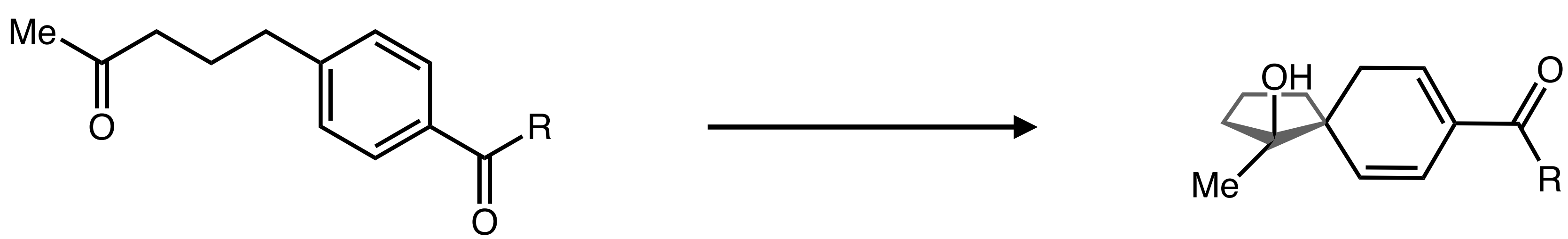


- *Ipso* cyclization



R group		
	OMe	58%
	Me	44%

Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

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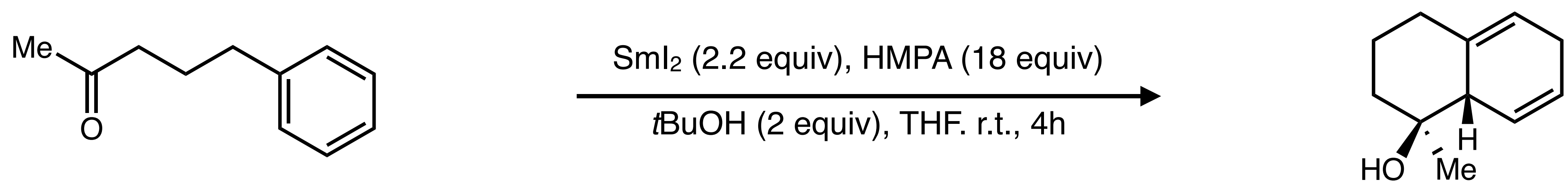
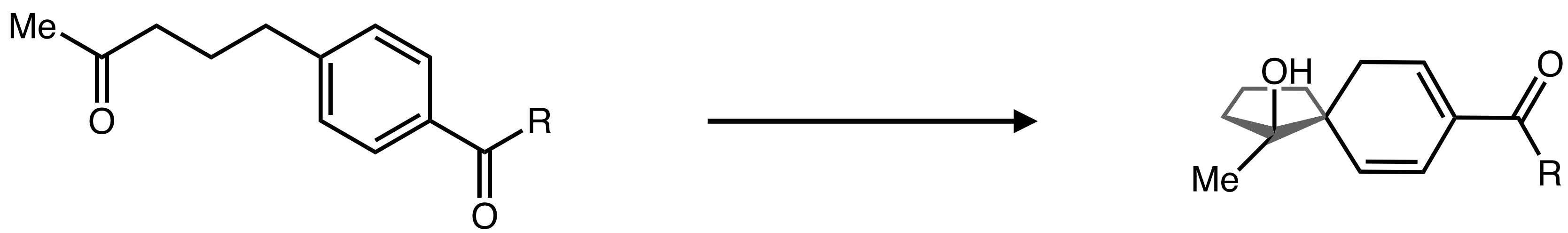
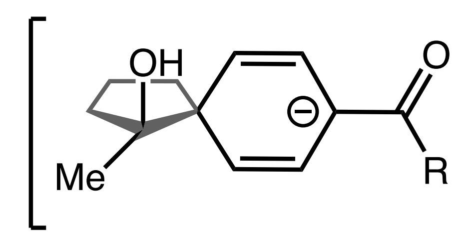


- *Ipso* cyclization



R group		
	OMe	58%
	Me	44%



Direct resonance stabilization from EWG para to alkyl chain gives ispo cyclization

Wefelscheid, U. K.; Berndt, M.; Reißig, H. U. *European Journal of Organic Chemistry* **2008**, *2008* (21), 3635-3646.

Outline

Radical approach

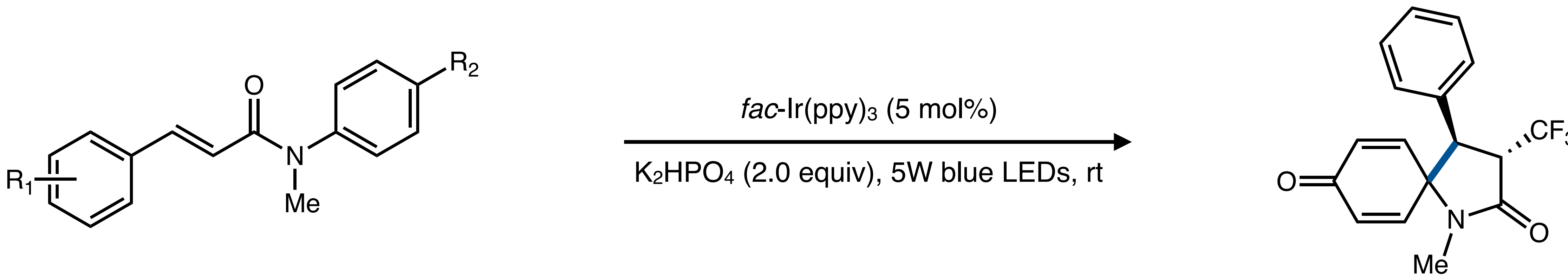
- Traditional radical generation
  - Birch & SmI_2
- Photochemical
  - Single electron transfer
    - Radical addition
    - Oxidation
    - Reduction
  - Energy transfer
    - Direct excitation
    - Sensitization

Transition-metal

- Mediated
  - η^2
  - η^6
- Catalyzed
  - *Pd*

Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - radical addition



Gao, F.; Yang, C.; Gao, G. L.; Zheng, L.; Xia, W. *Org Lett* **2015**, *17* (14), 3478-3481.

Radical Approach to Dearomatization

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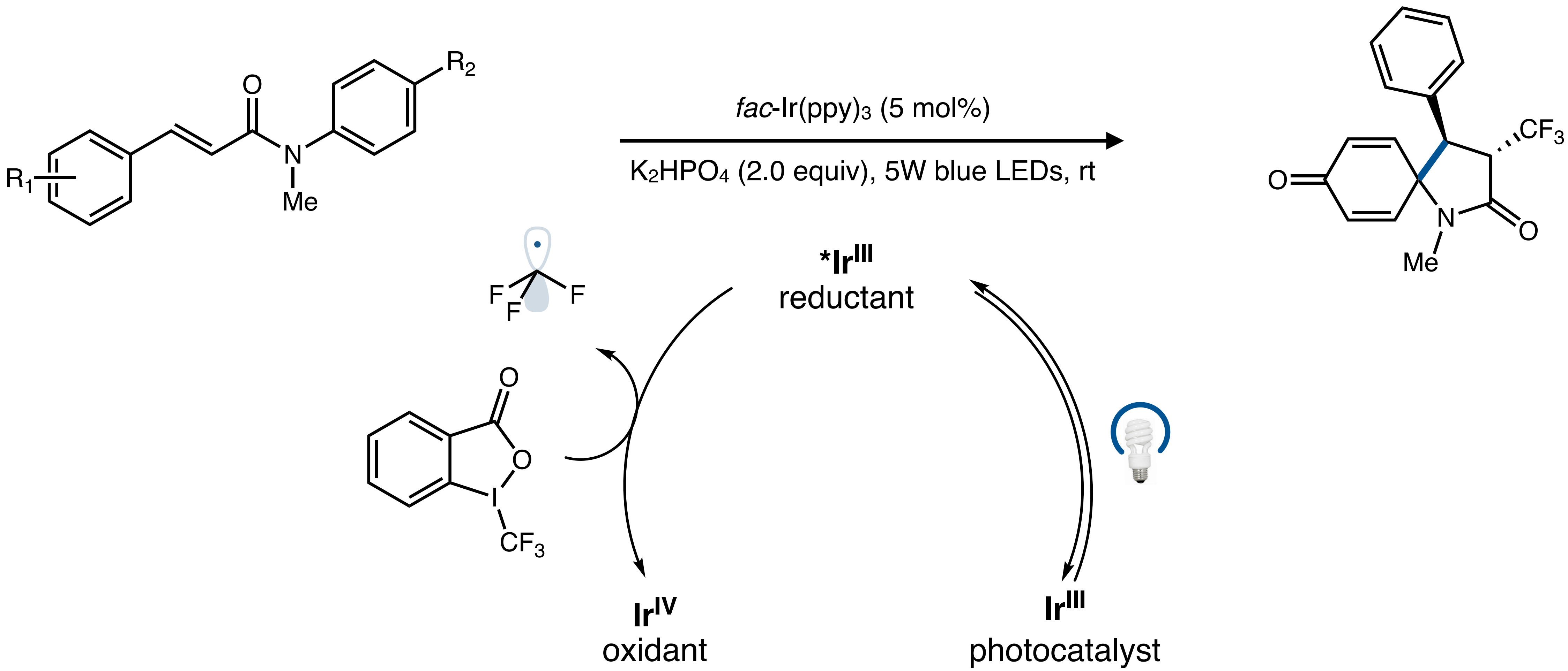

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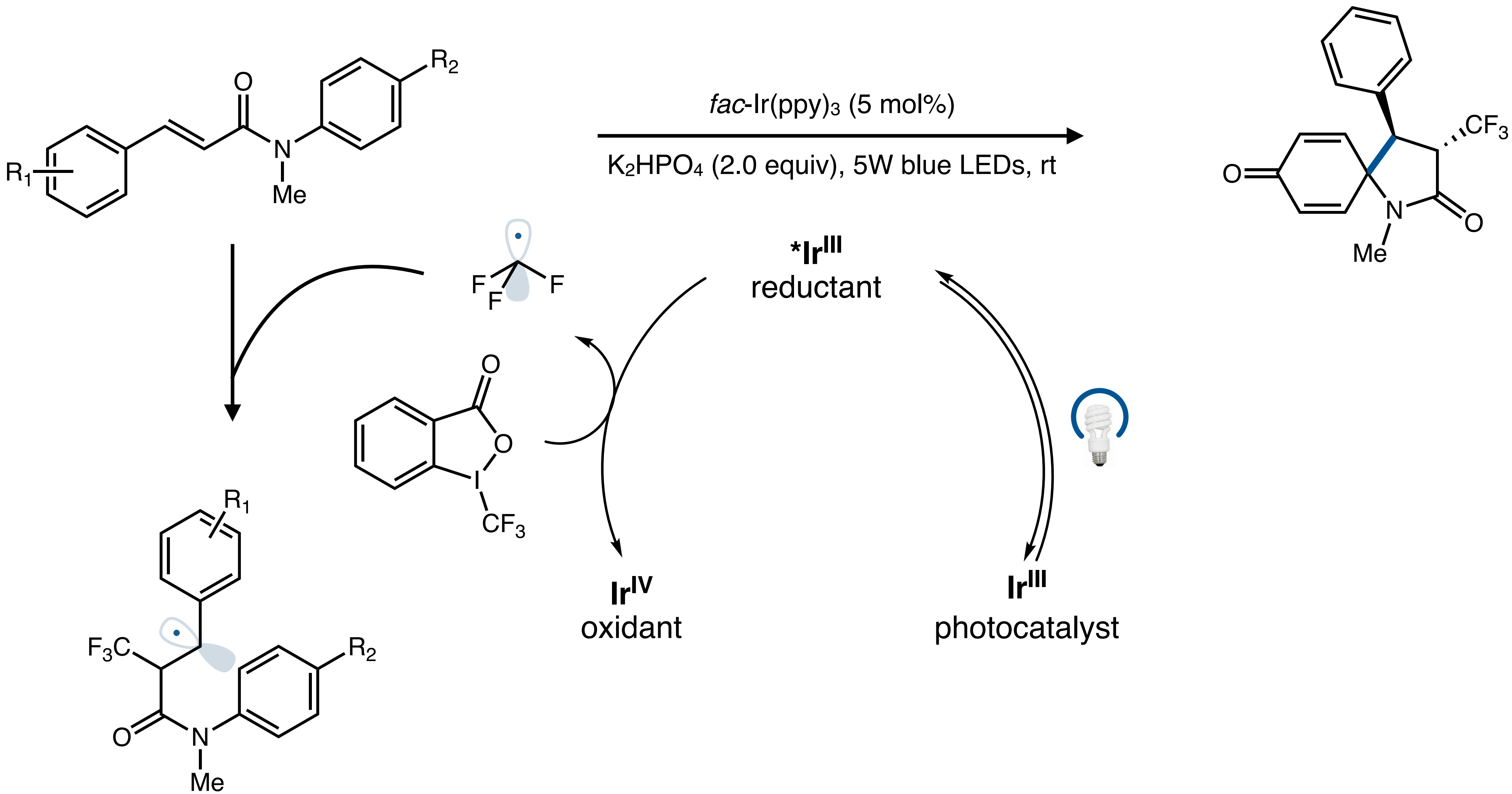

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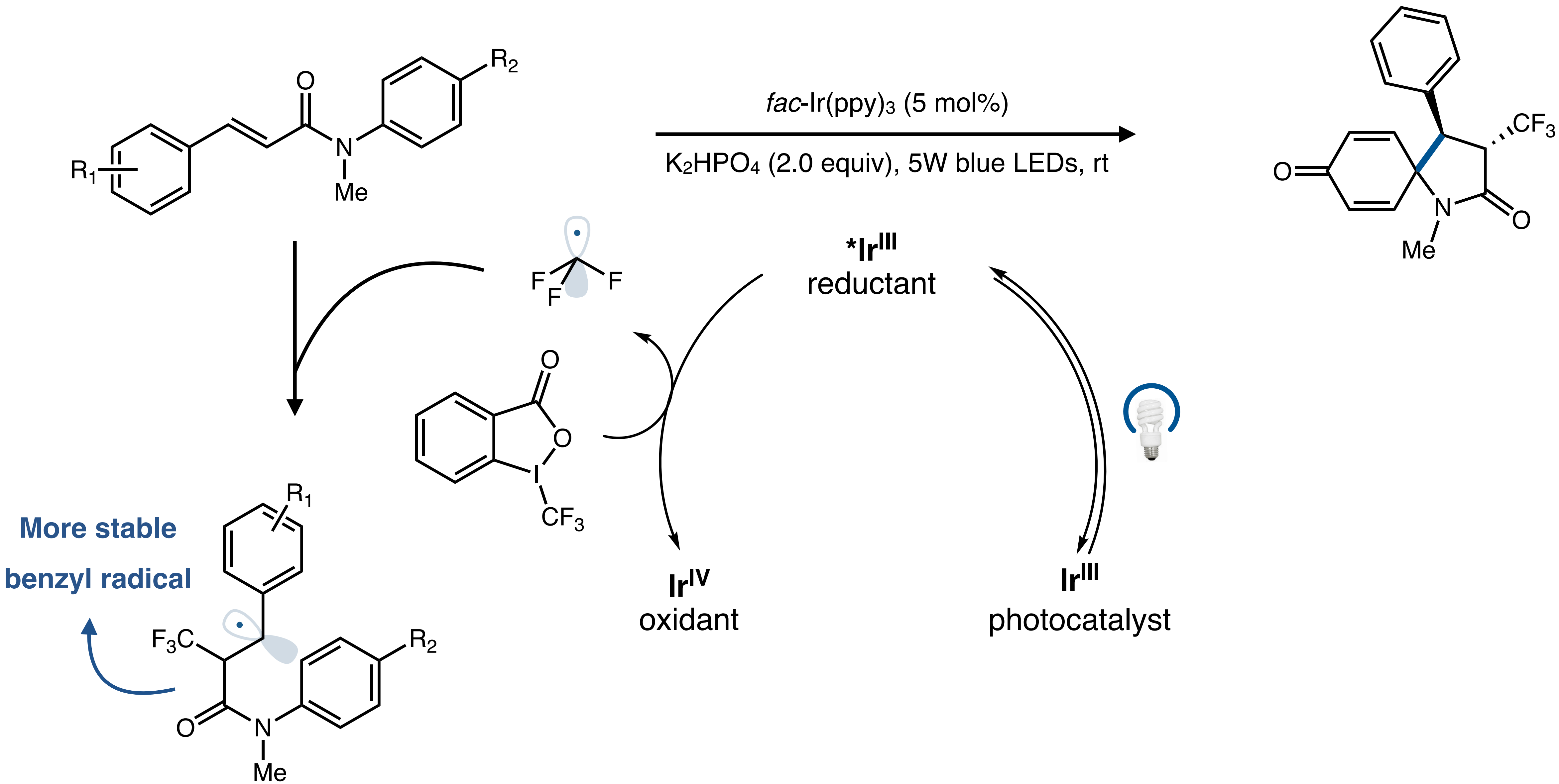

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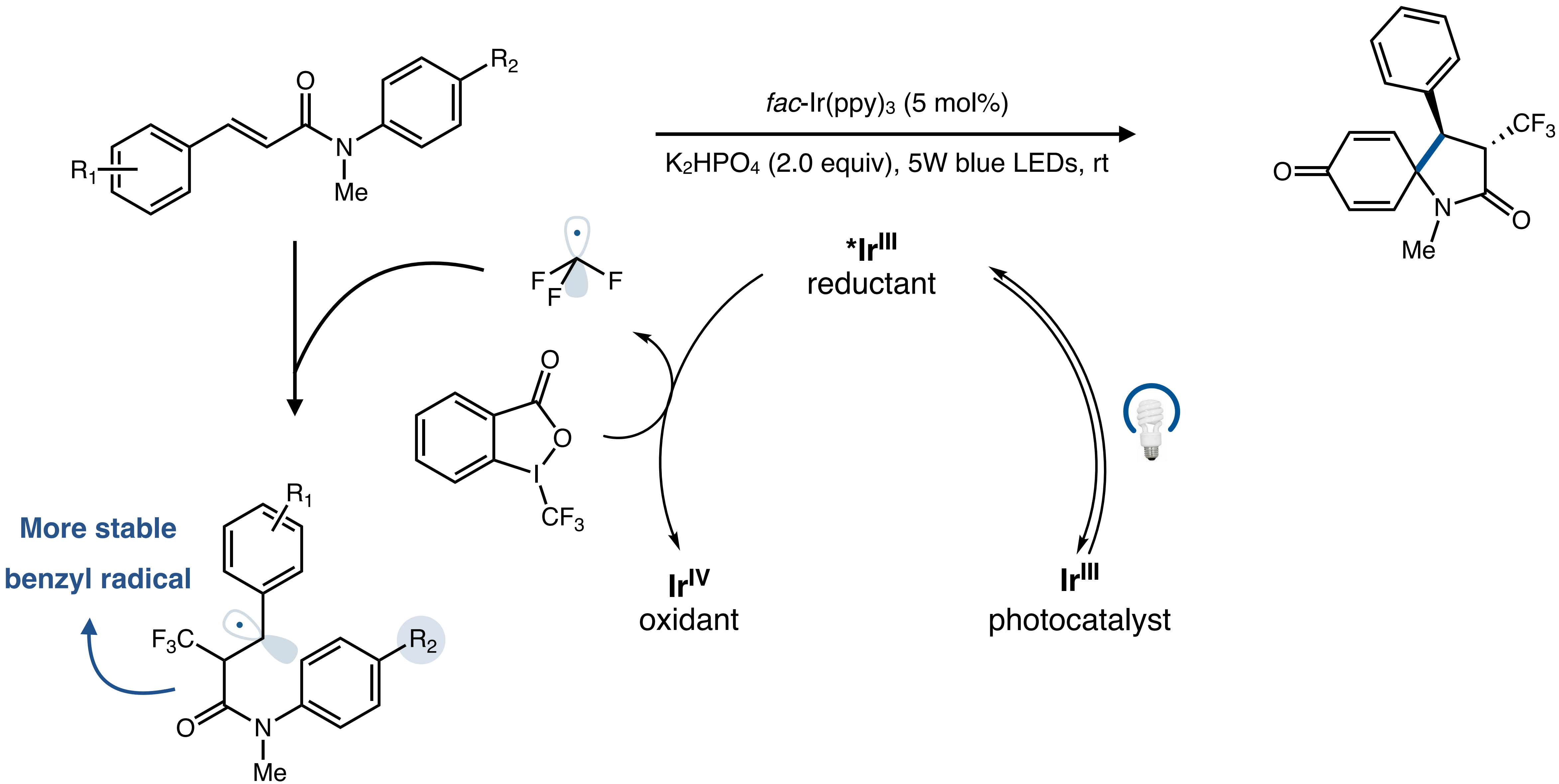

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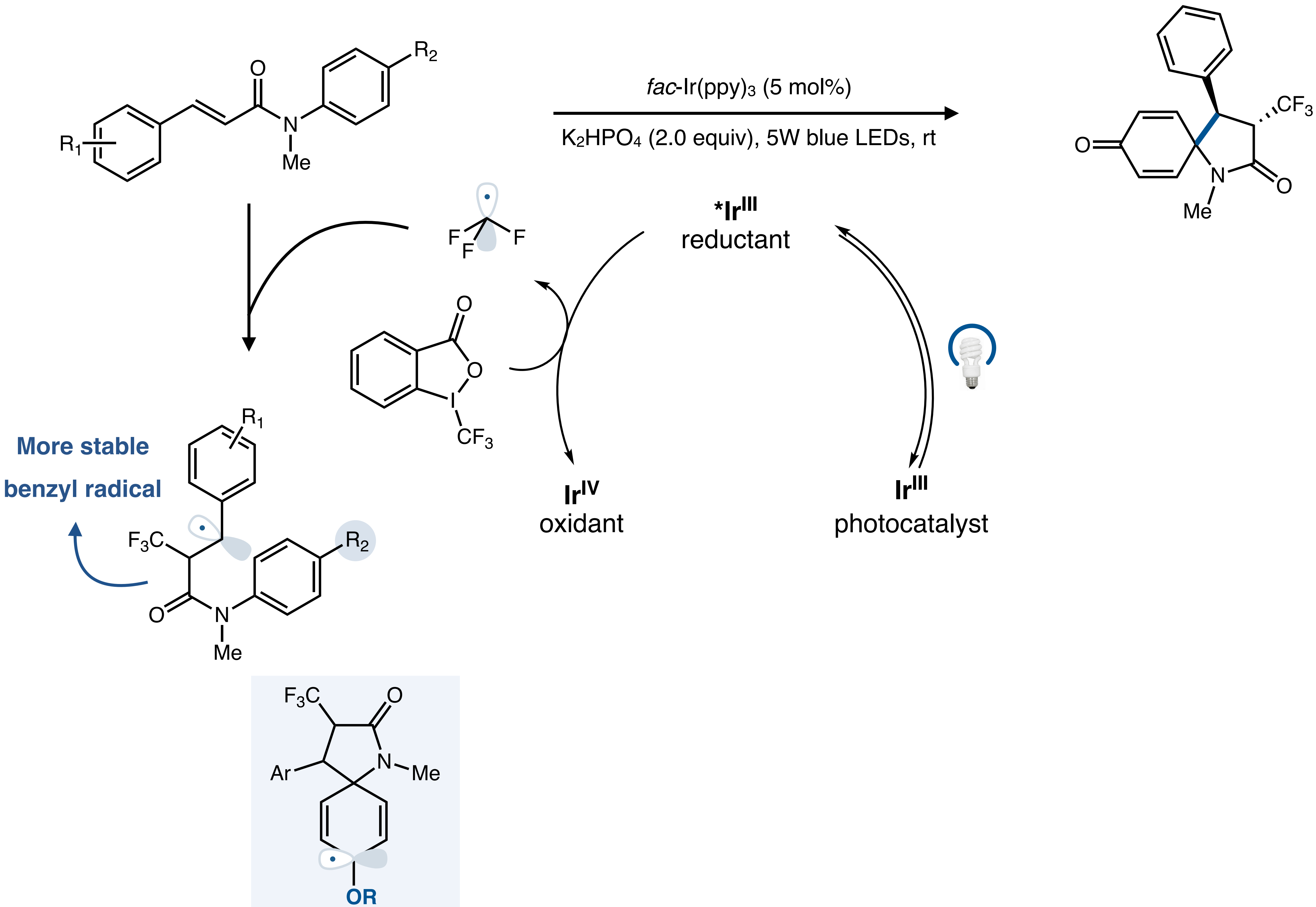
Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - radical addition



Gao, F.; Yang, C.; Gao, G. L.; Zheng, L.; Xia, W. *Org Lett* **2015**, *17* (14), 3478-3481.

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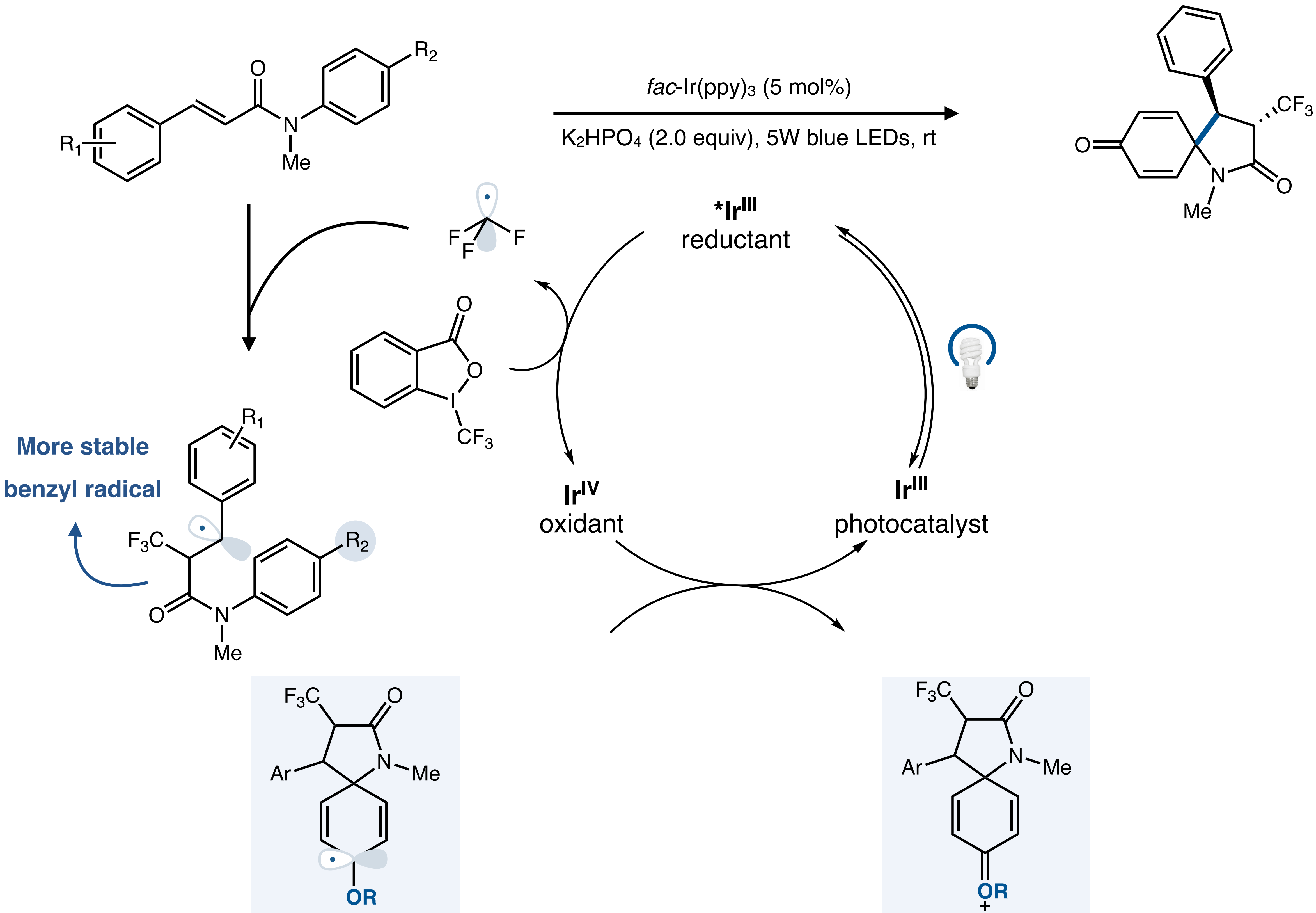

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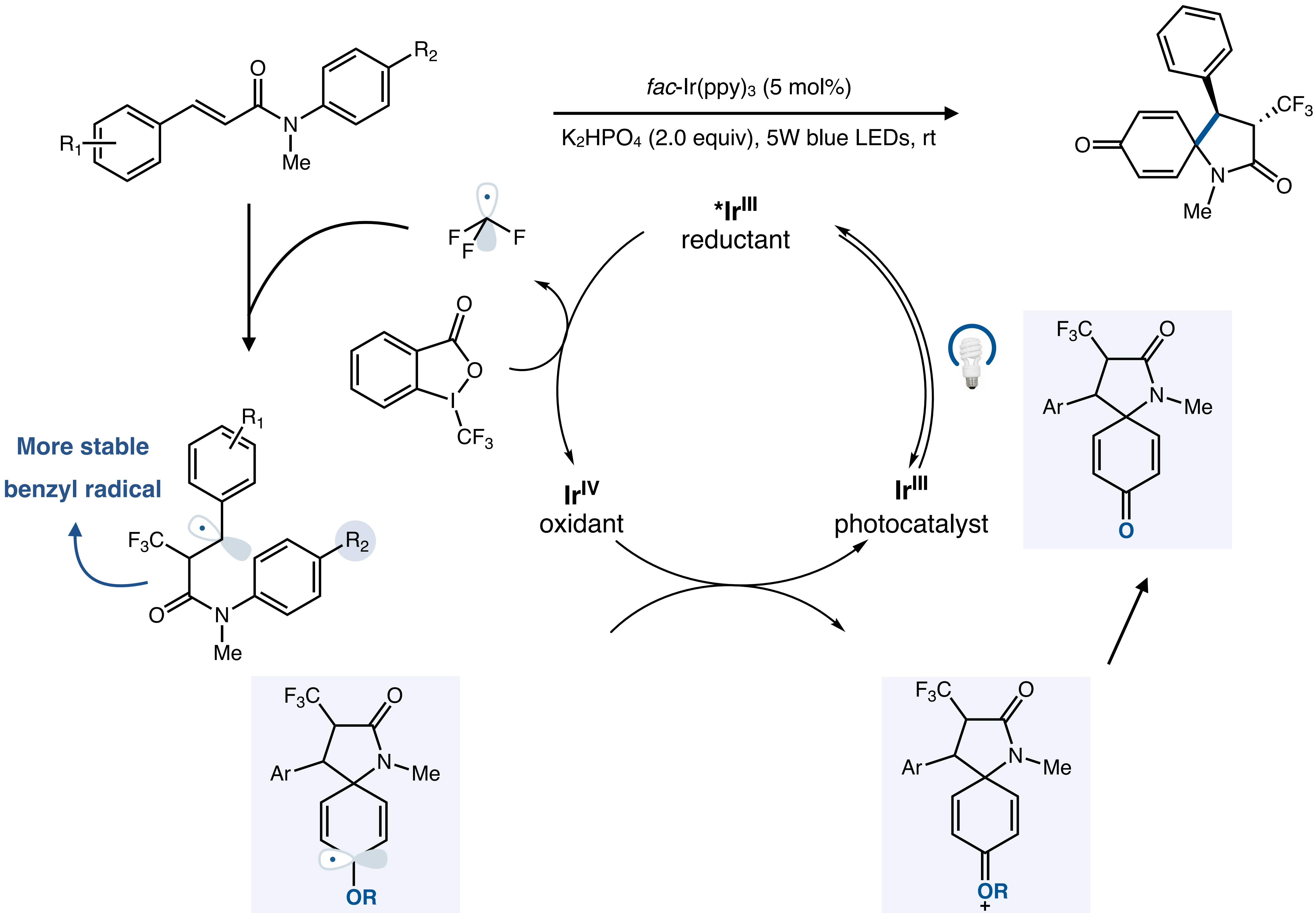

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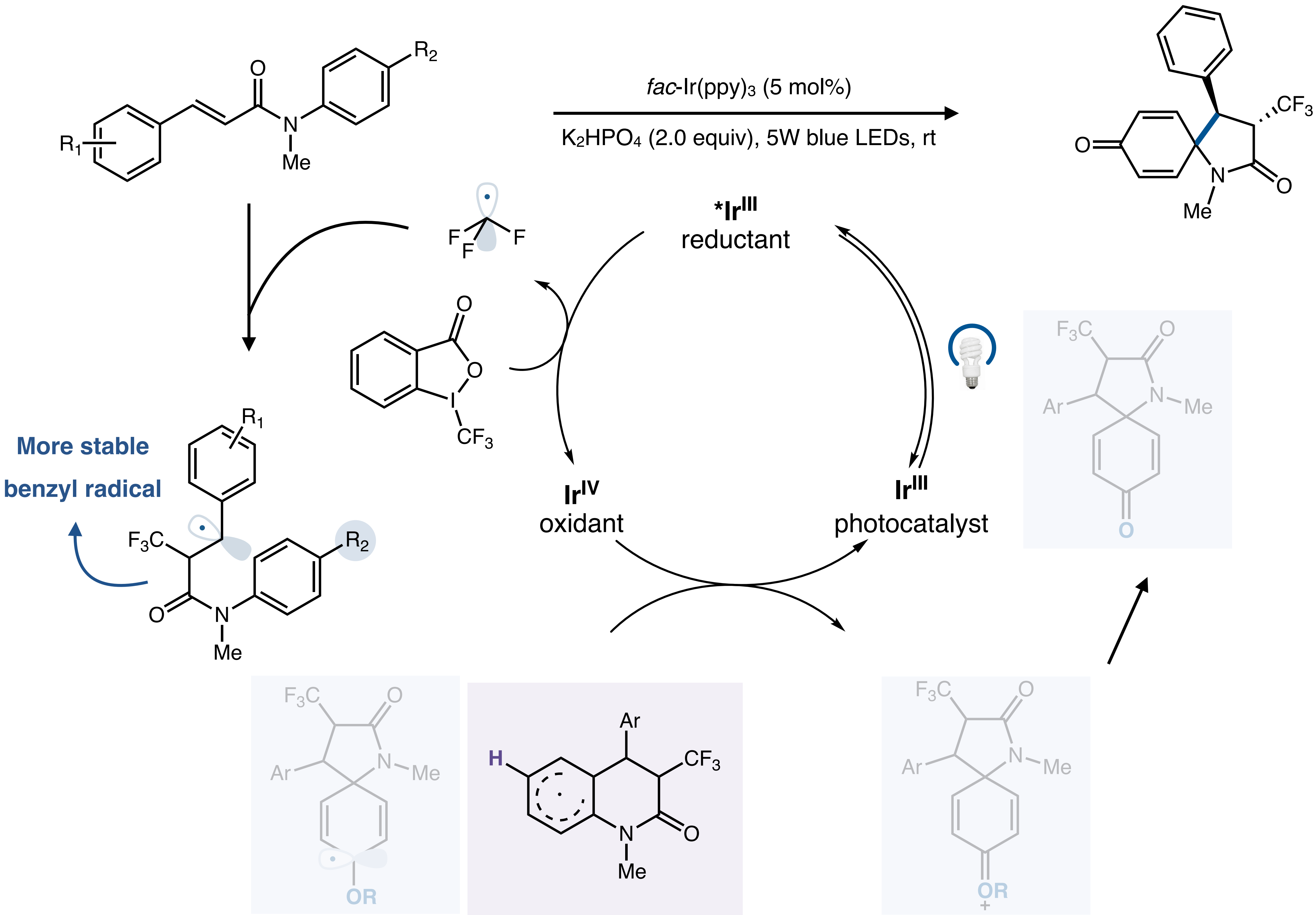

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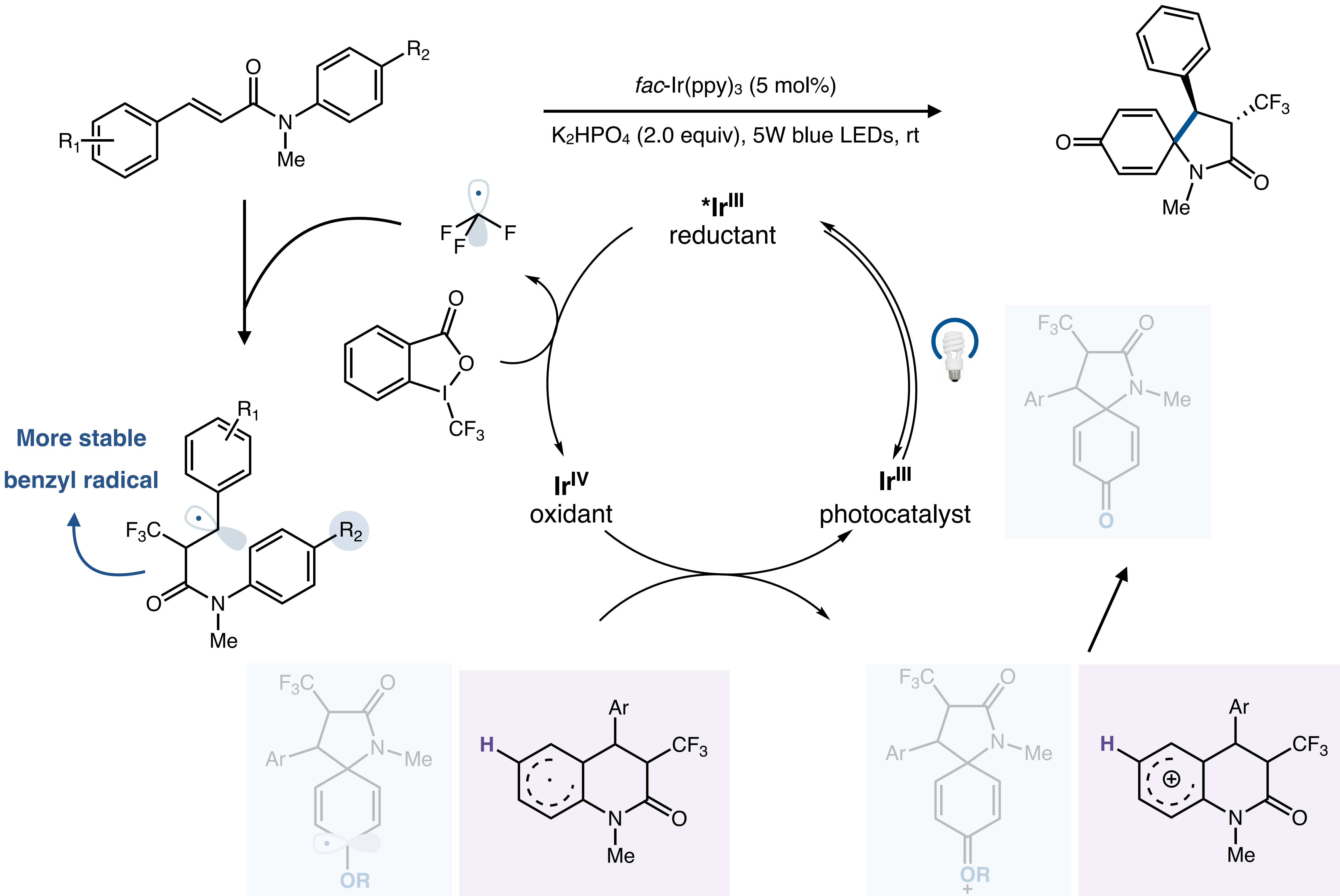

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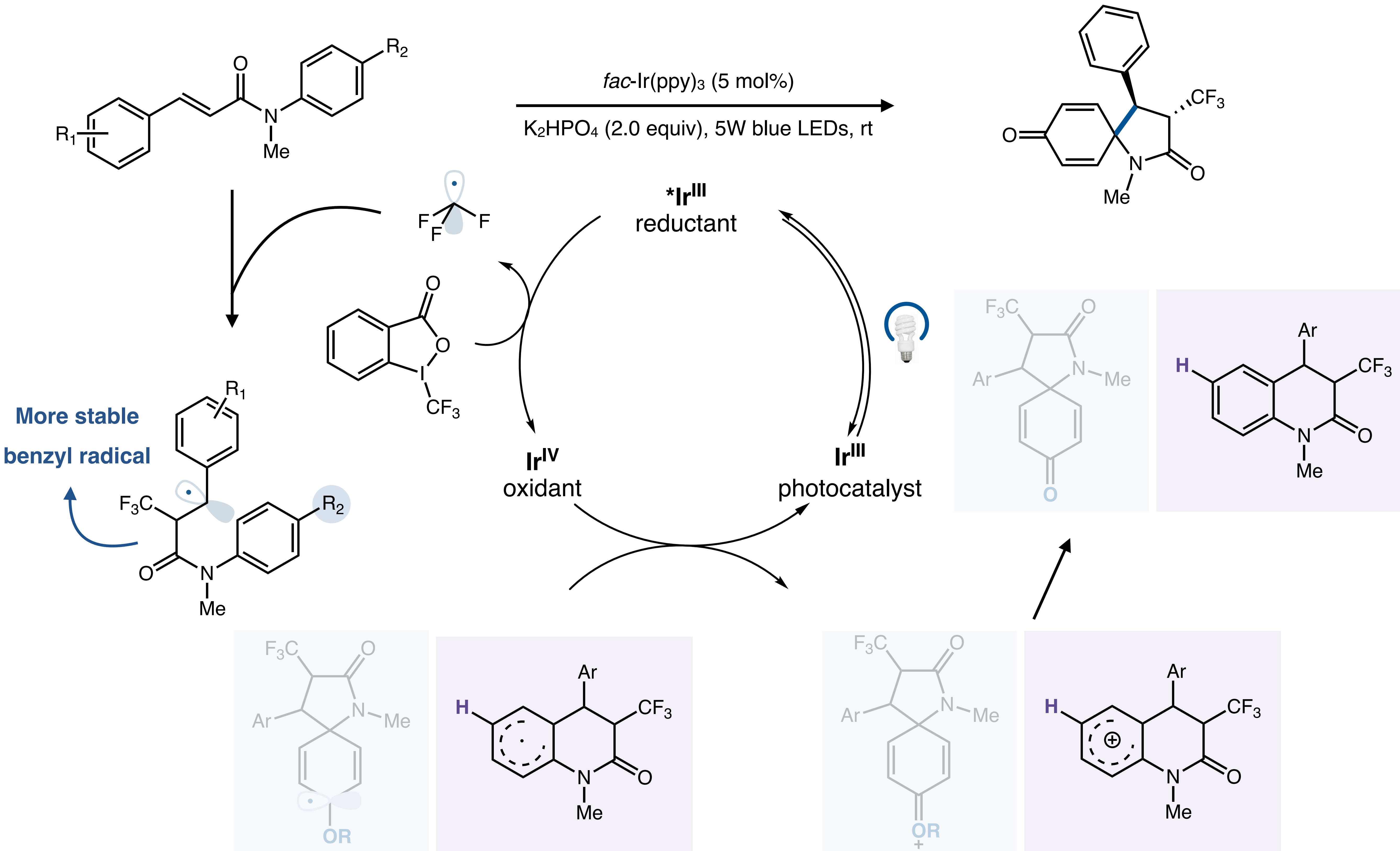

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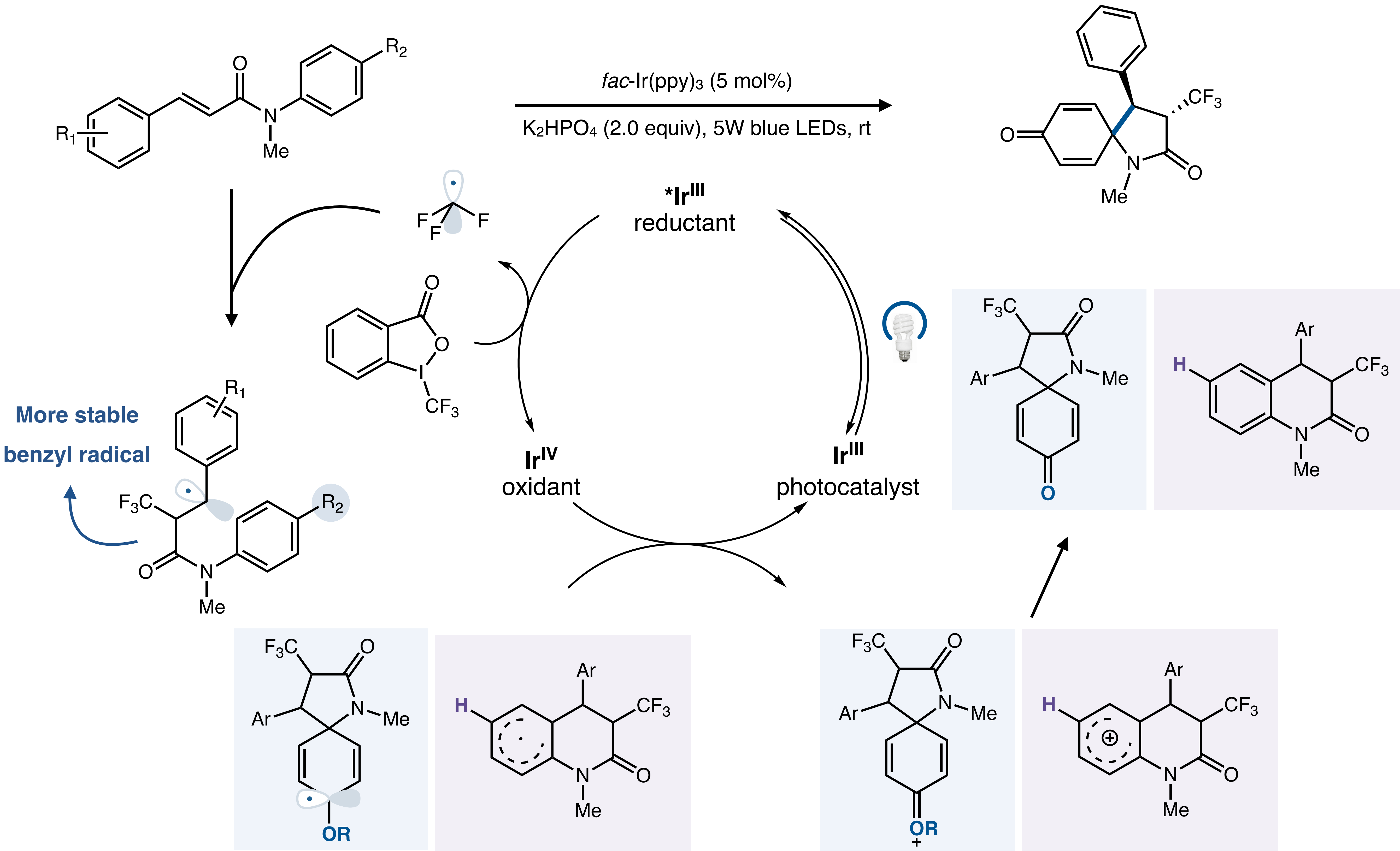

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Outline

Radical approach

Traditional radical generation — Birch & SmI_2

Photochemical

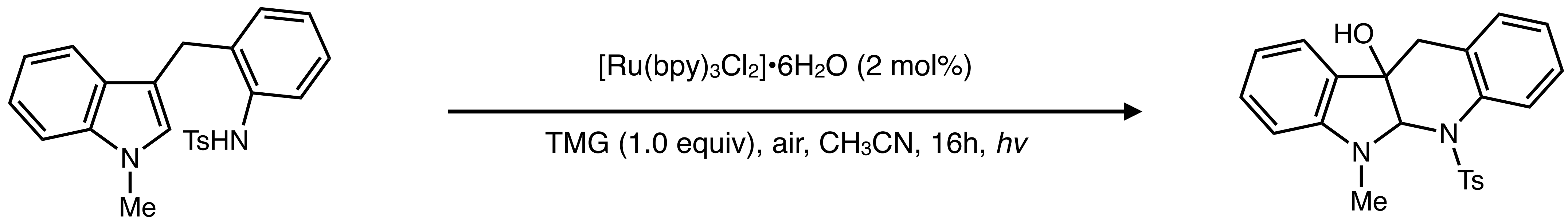
- **Single electron transfer**
  - Radical addition
  - Oxidation
  - Reduction
- **Energy transfer**
  - Direct excitation
  - Sensitization

Transition-metal

- **Mediated**
  - *η^2*
  - *η^6*
- **Catalyzed** — *Pd*

Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - oxidation



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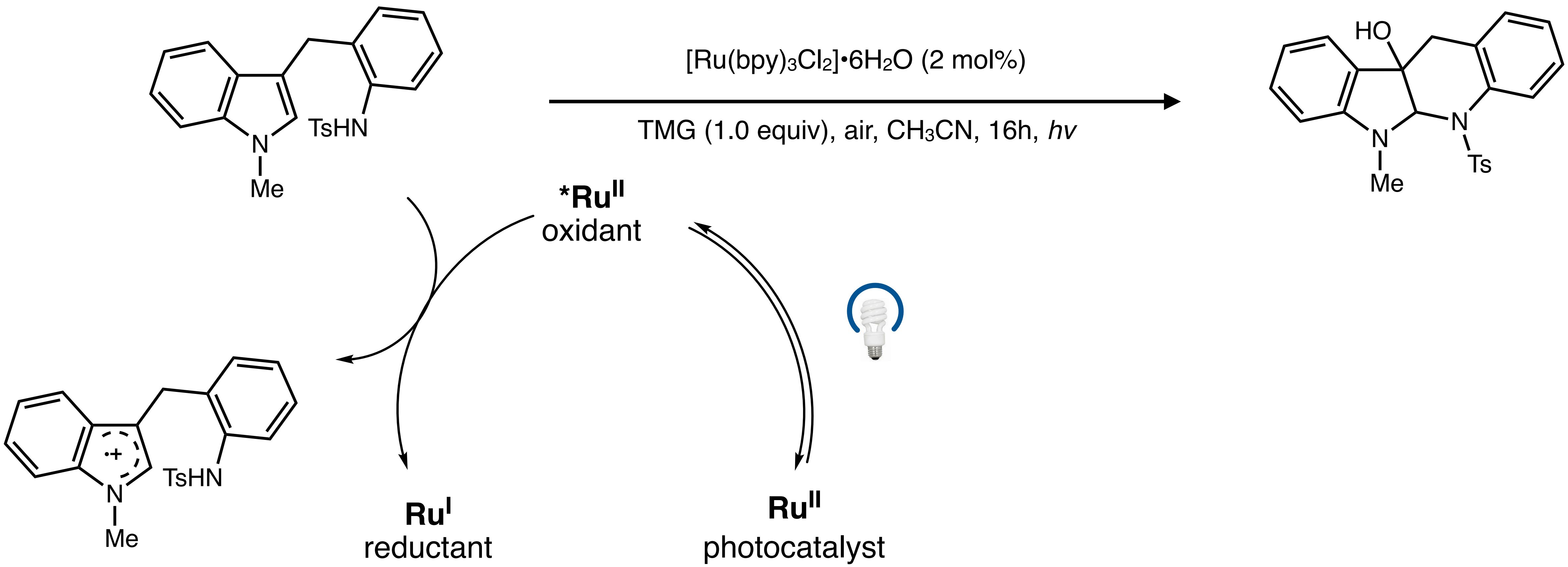

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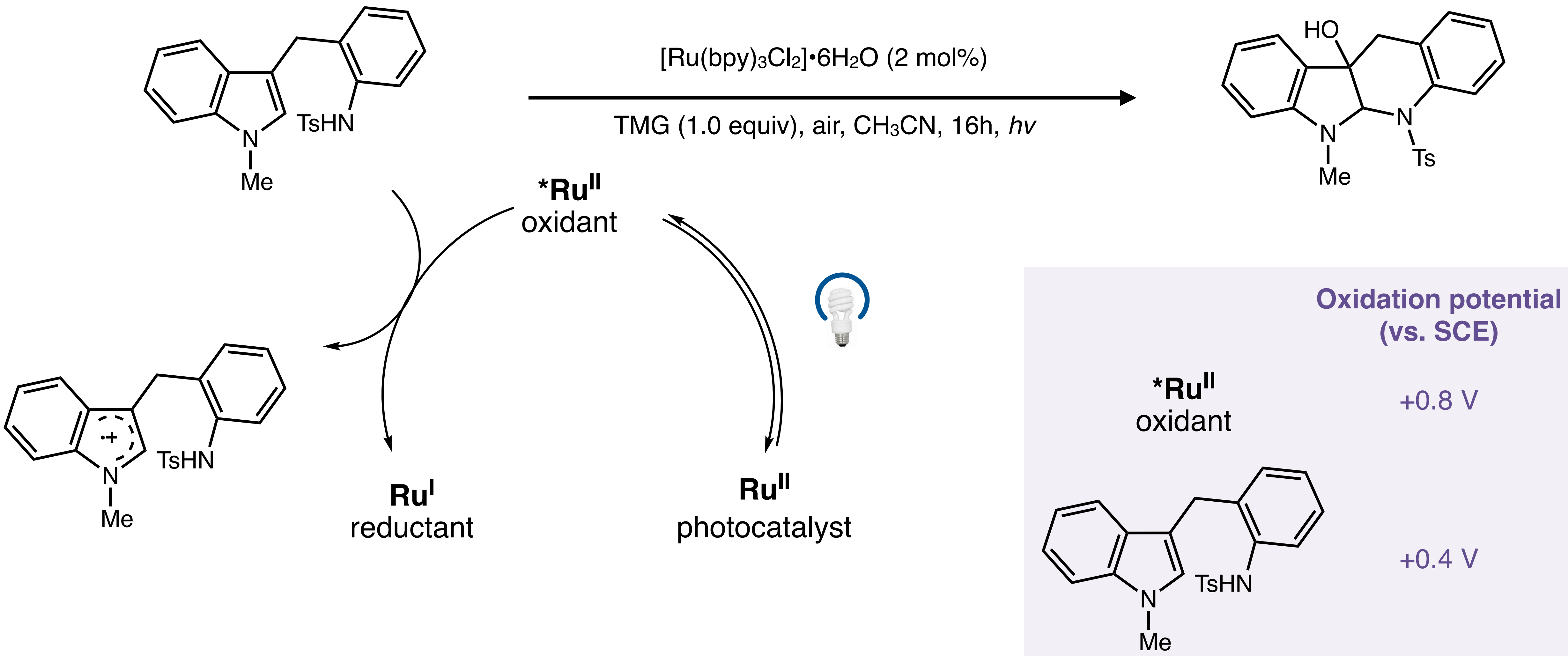

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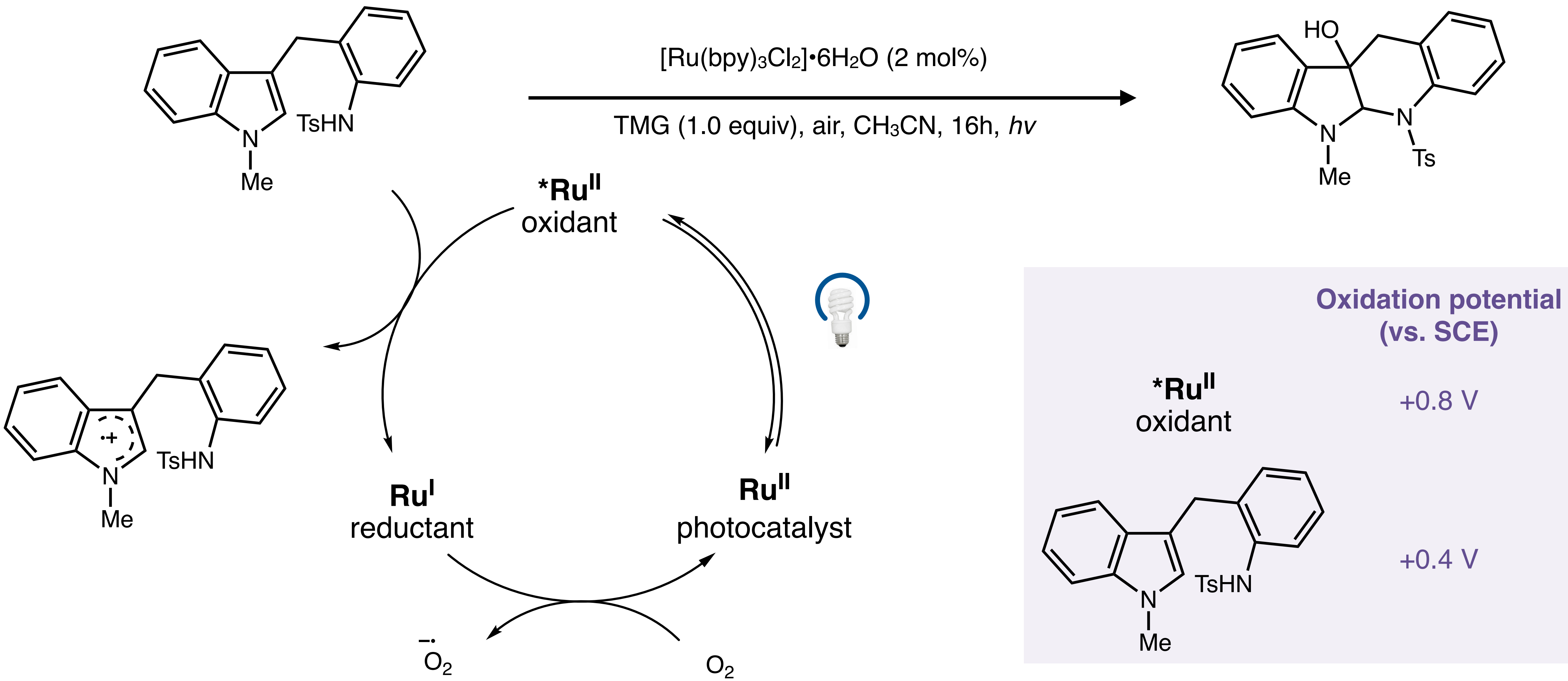

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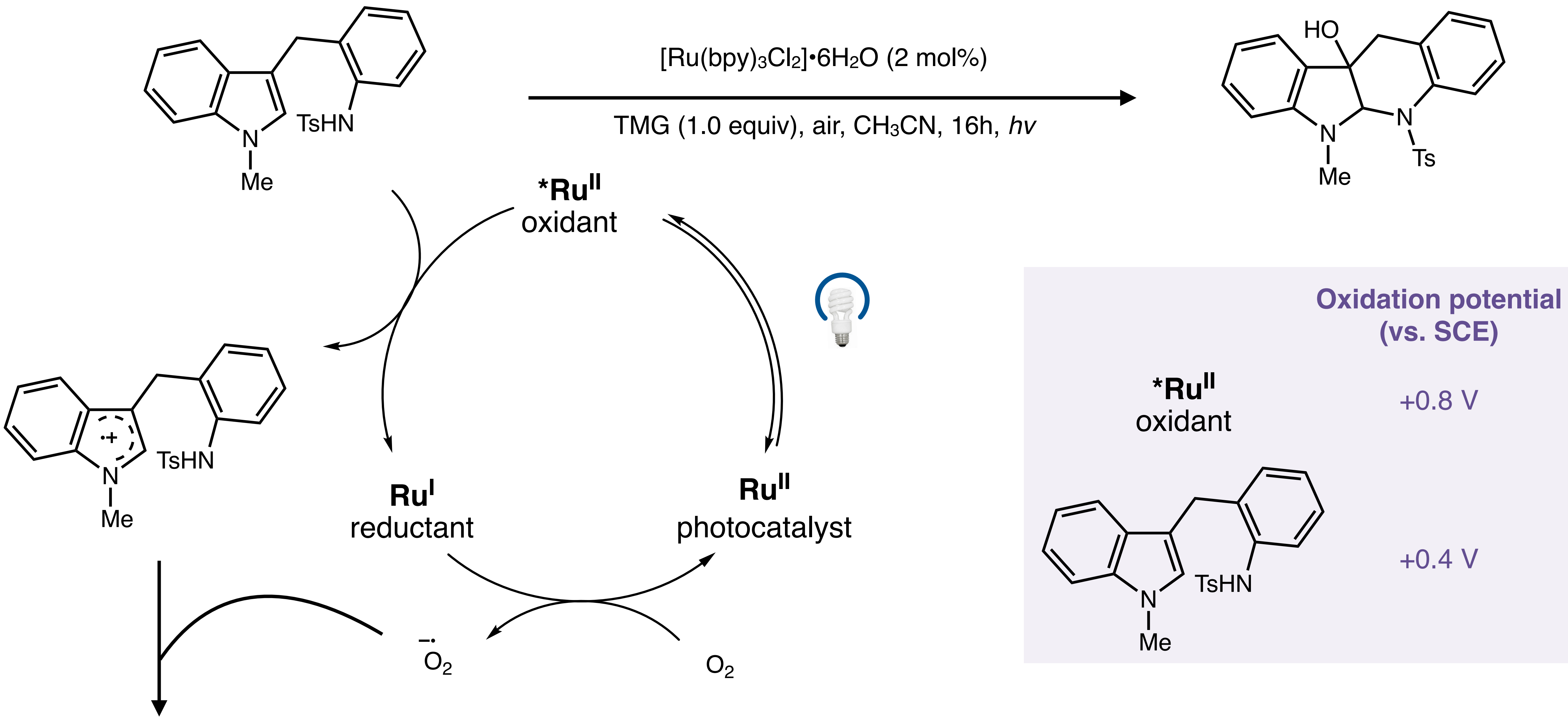

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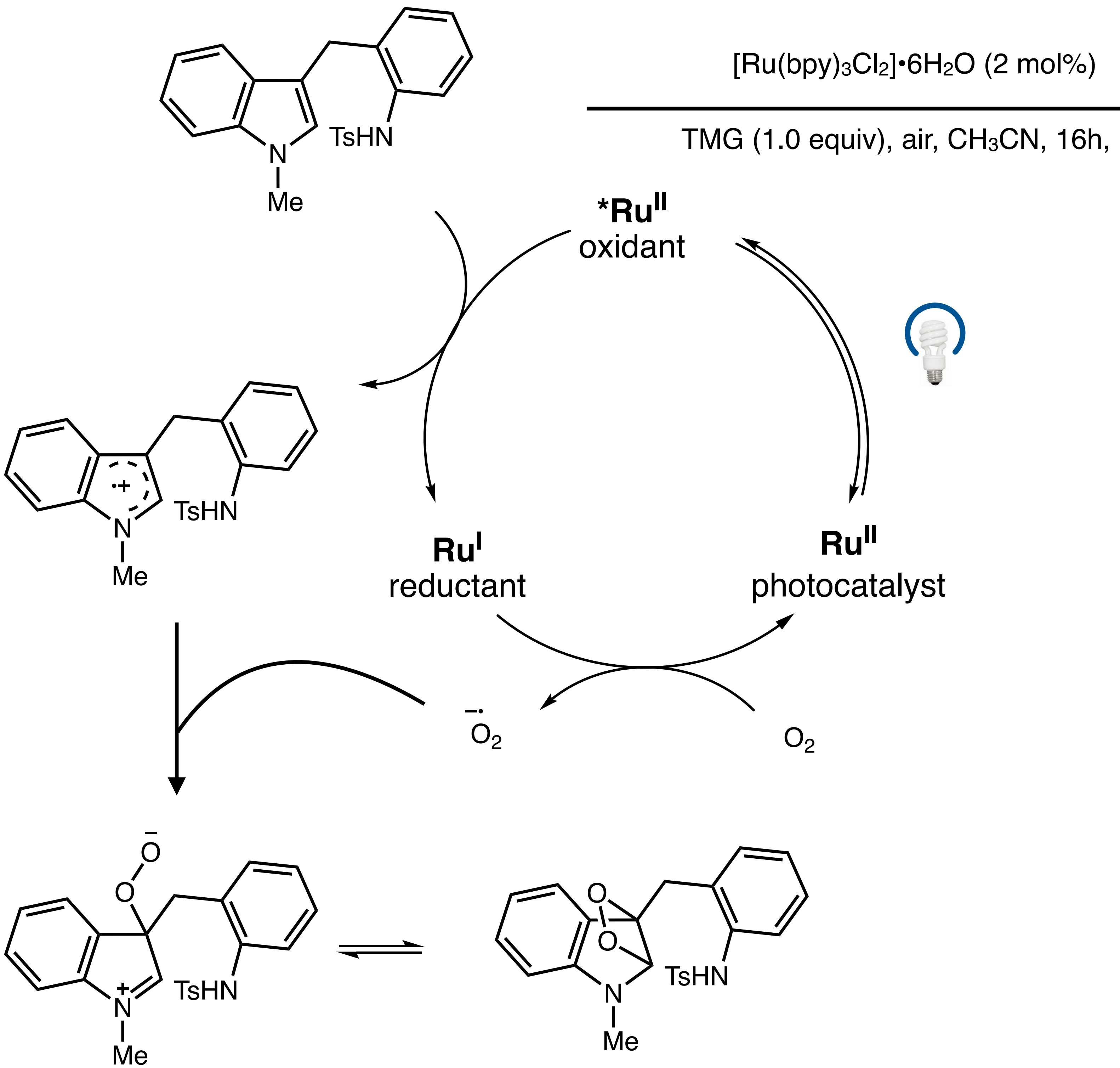
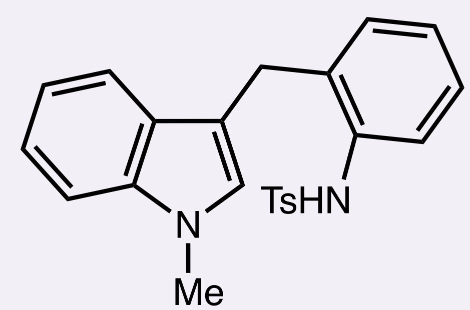


Oxidation potential (vs. SCE)

***Ru^{II}** oxidant: +0.8 V



+0.4 V

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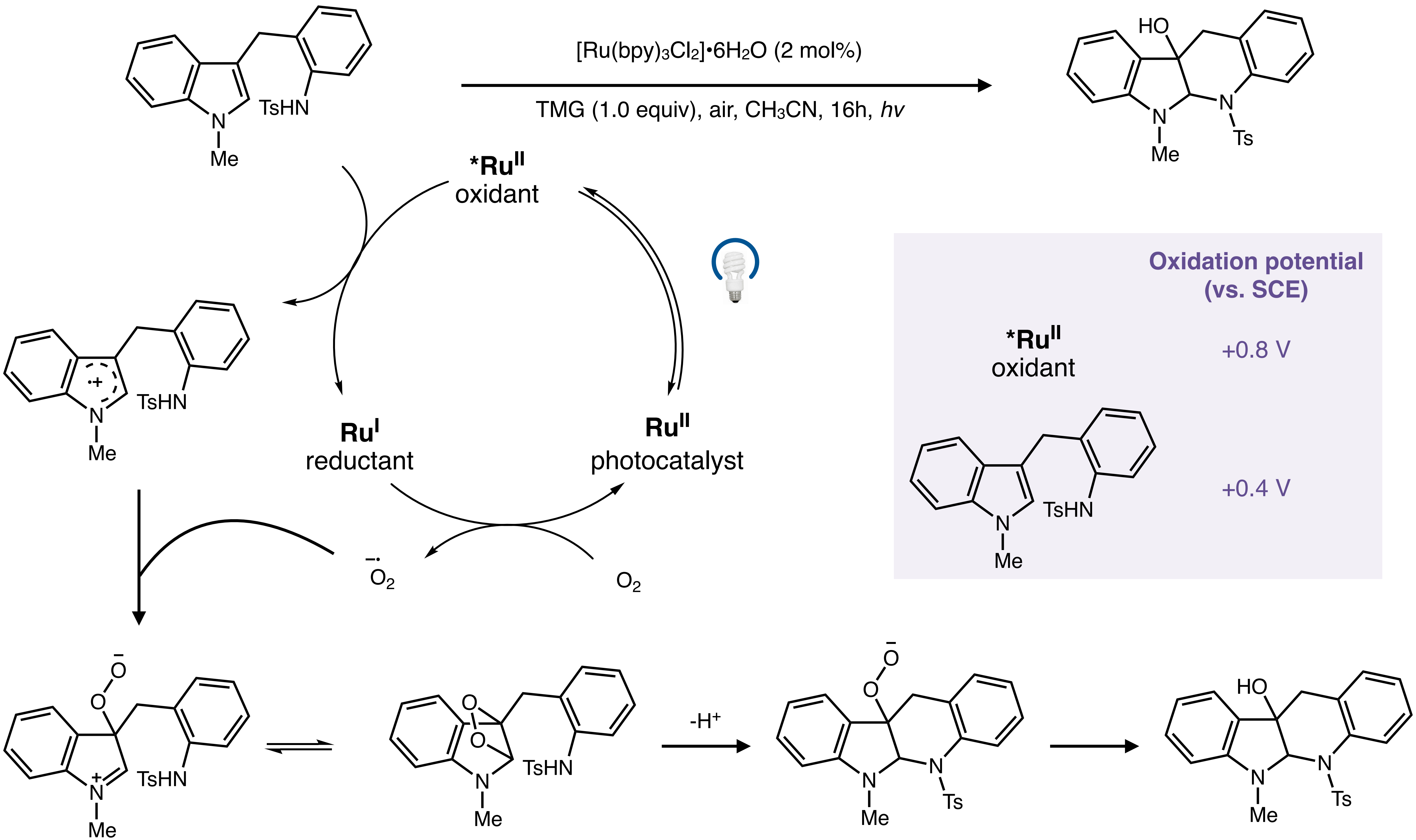

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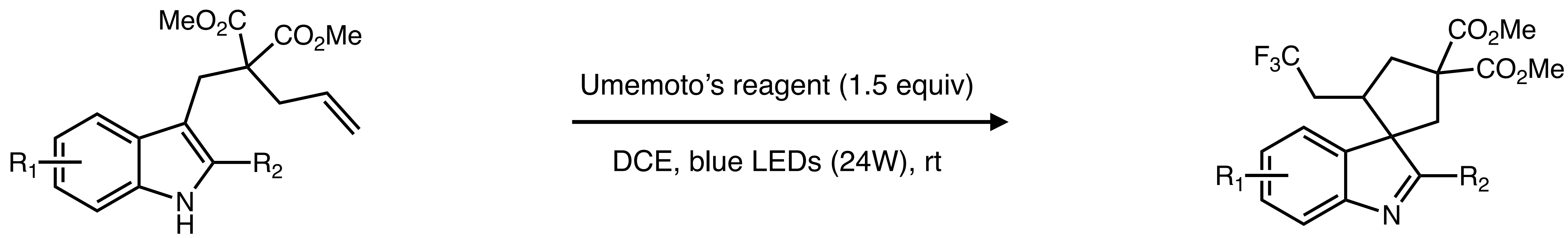

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Radical Approach to Dearomatization

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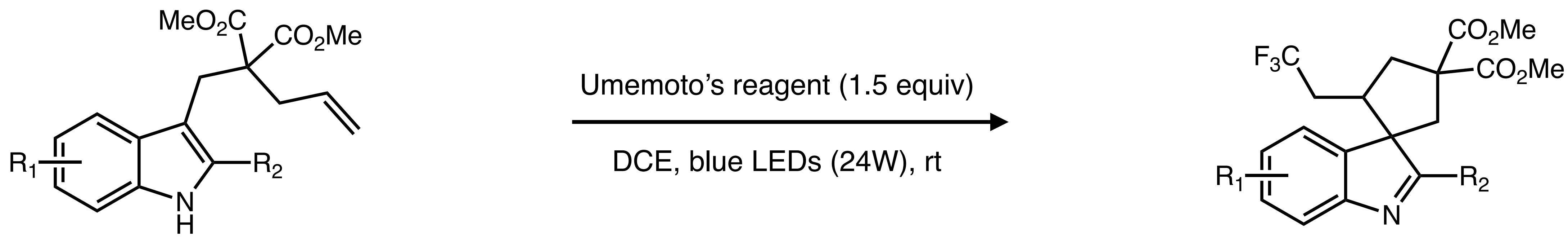

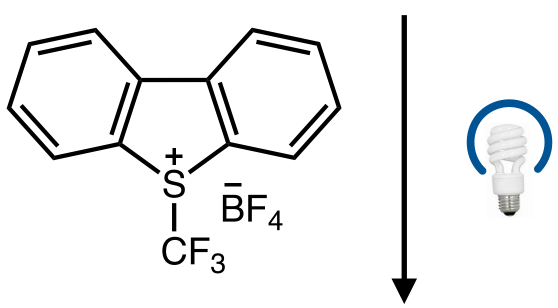

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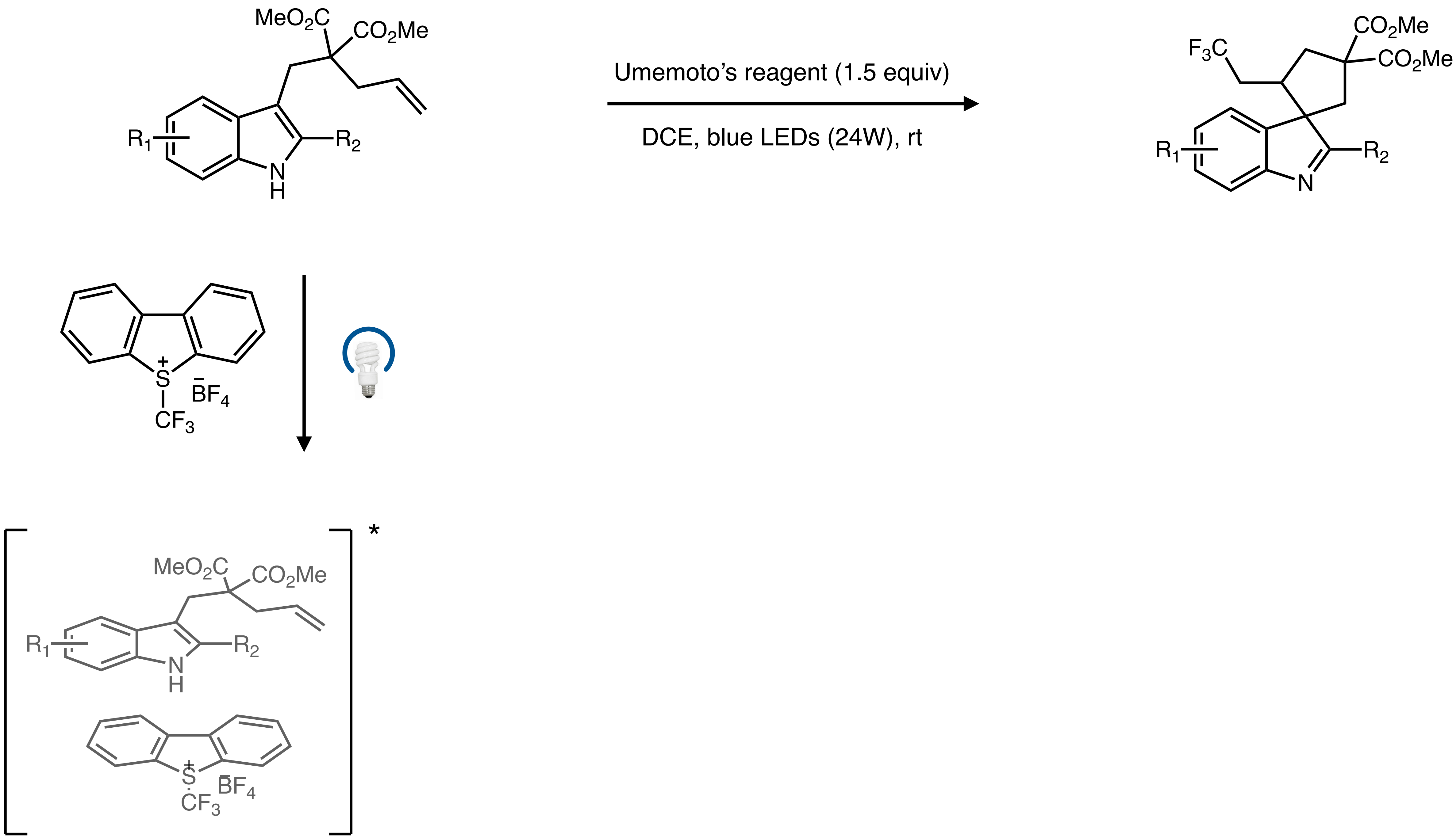

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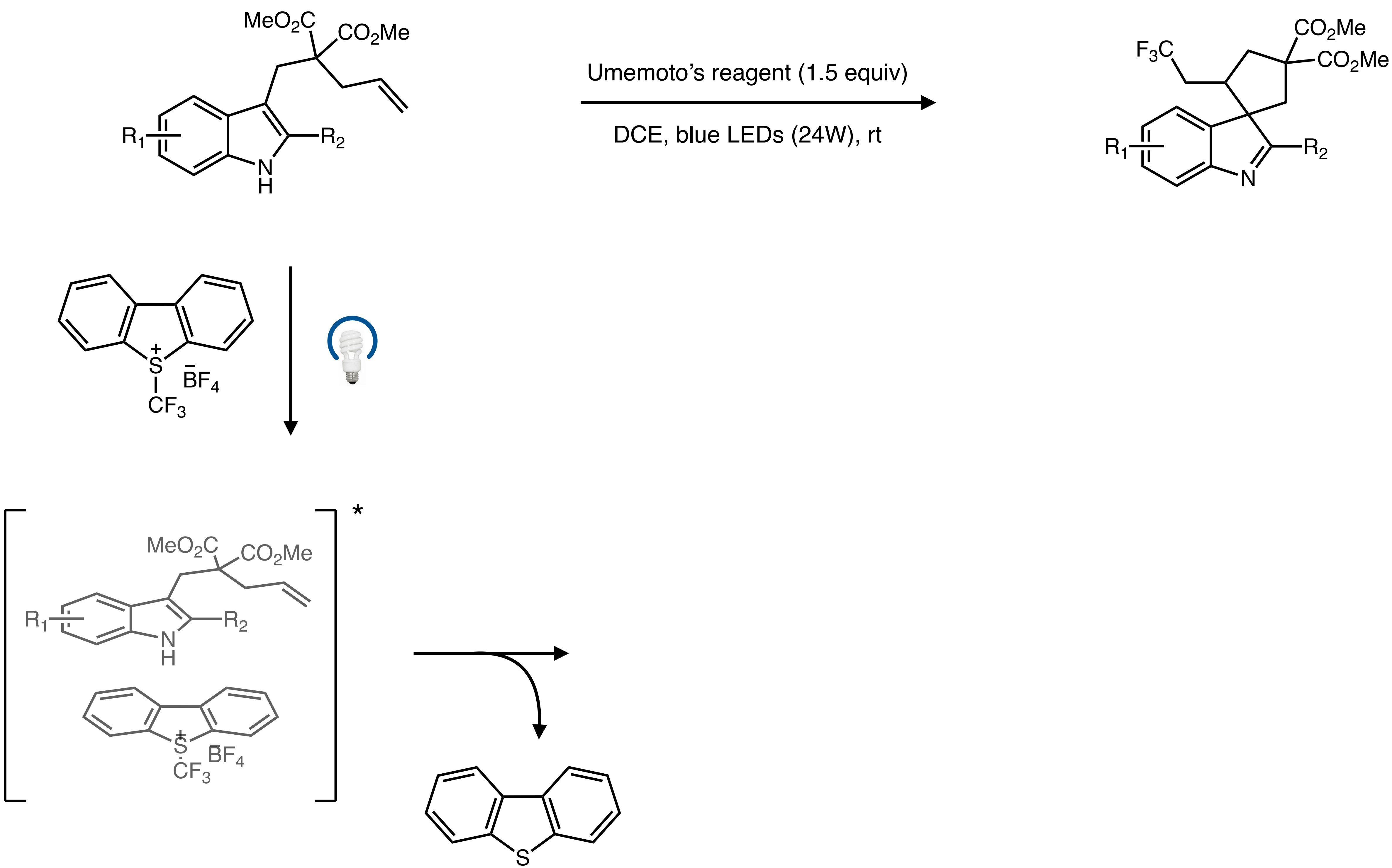

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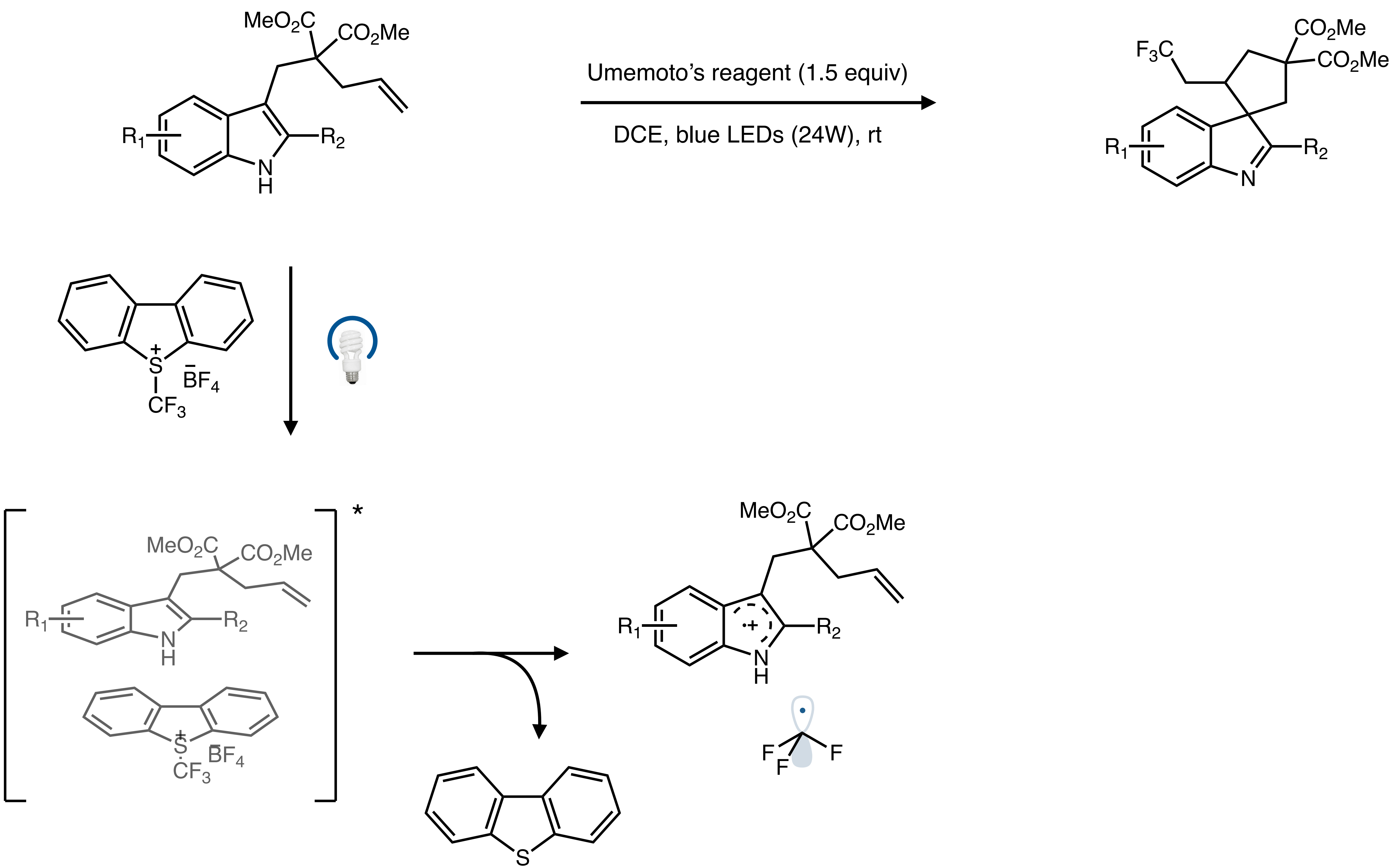

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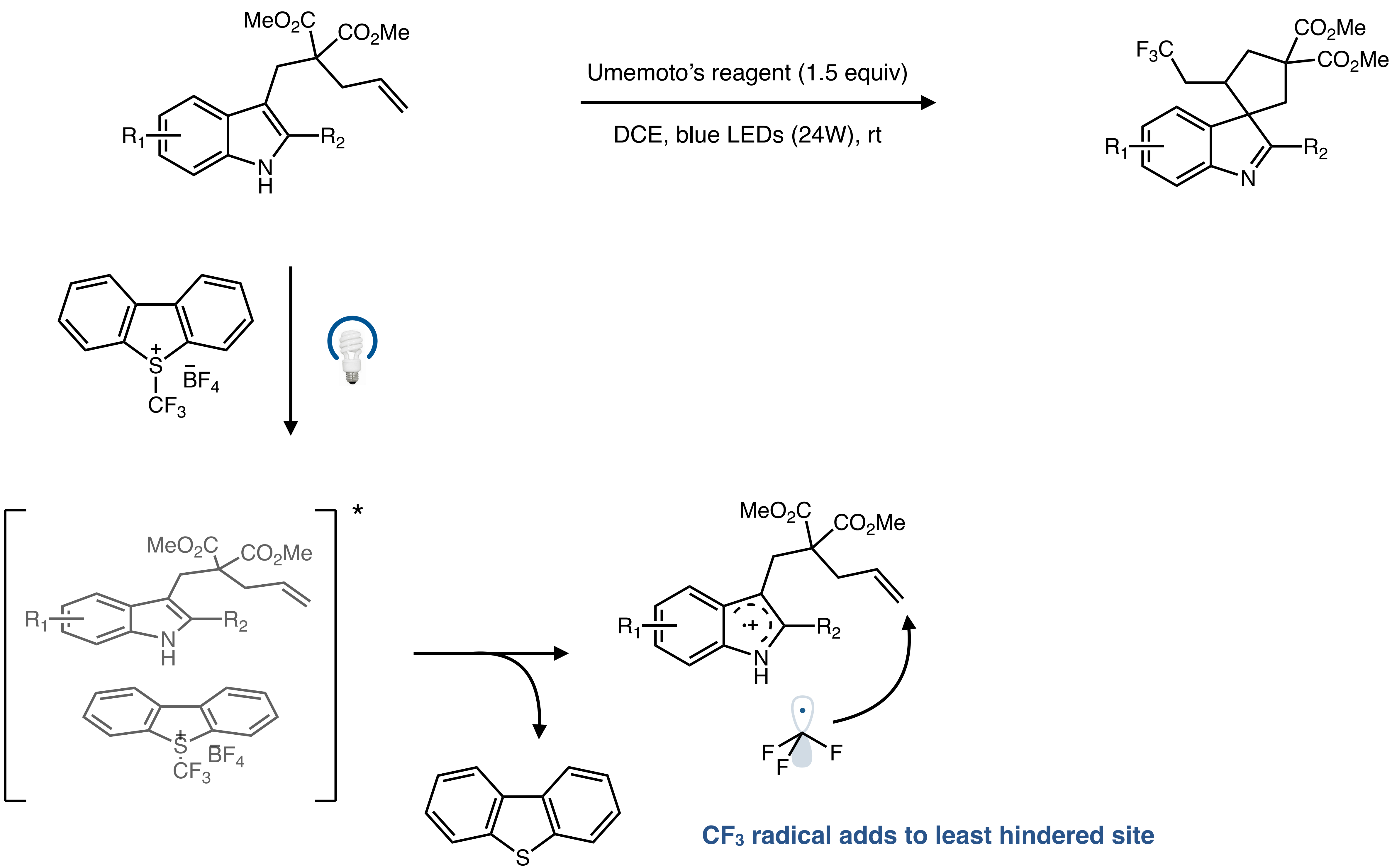

CF_3 radical adds to least hindered site

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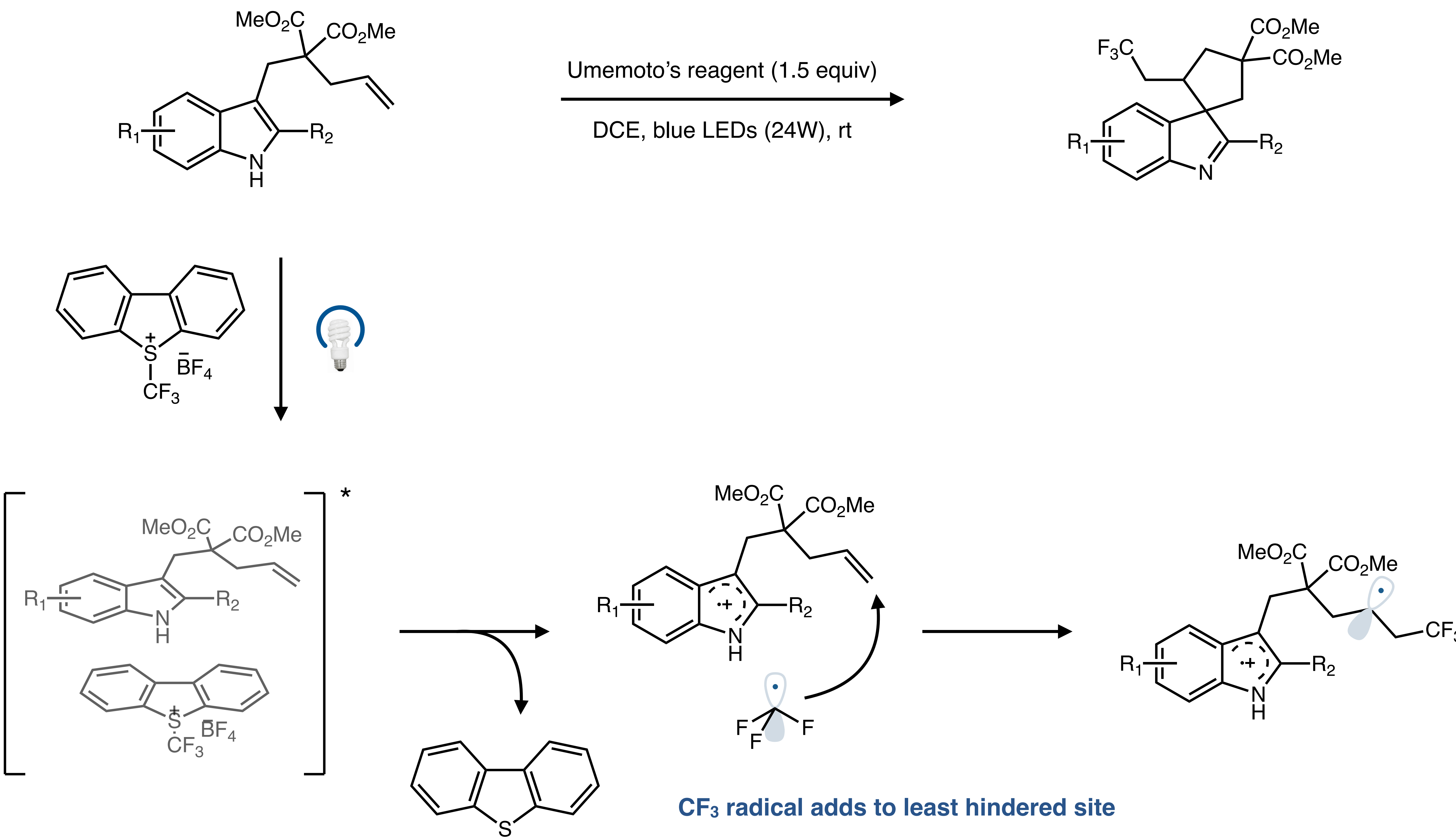

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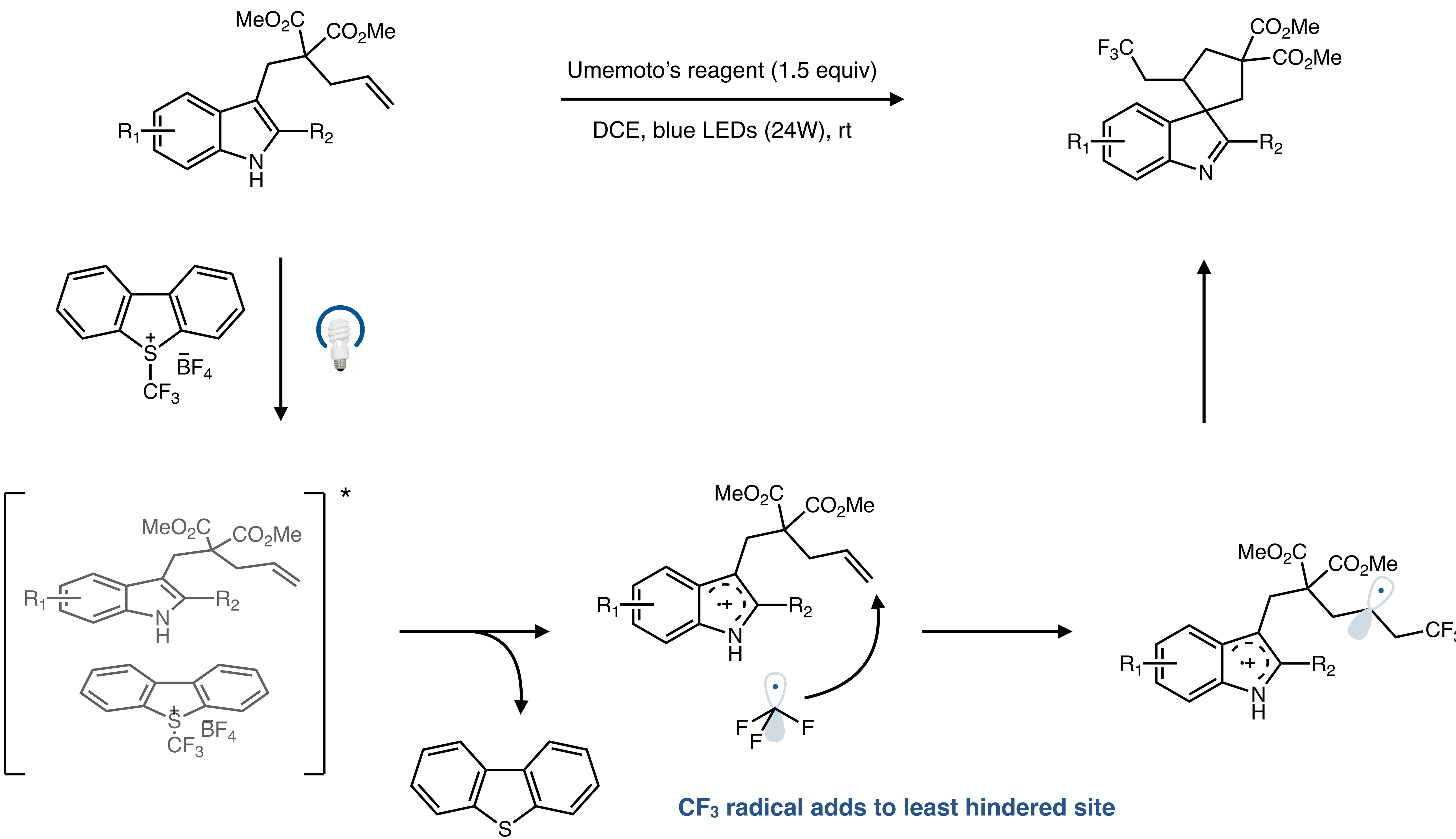

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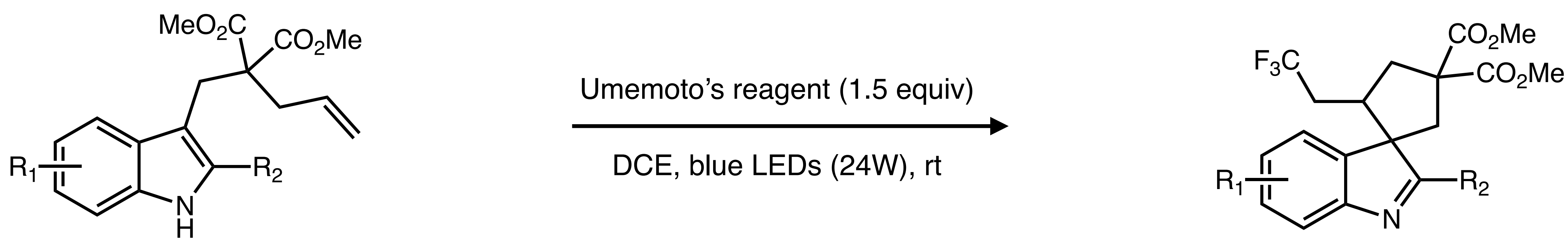

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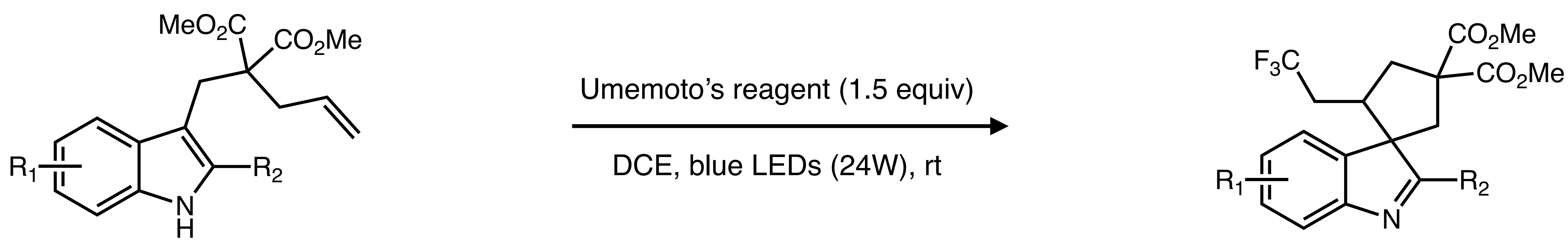
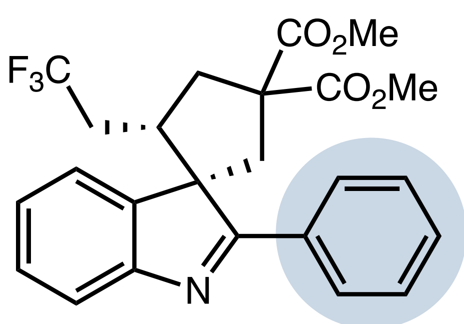
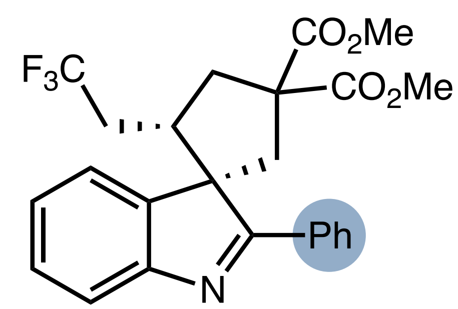




Yields (dr)

70% (1.4:1)



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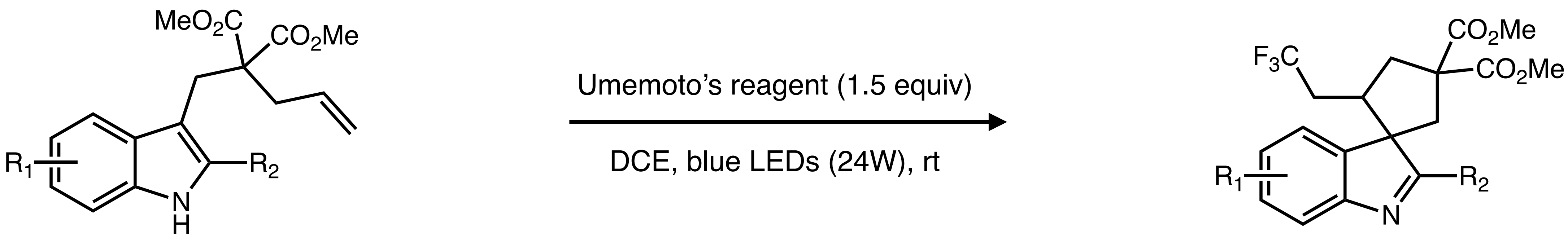

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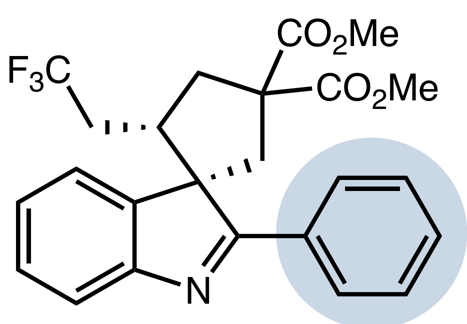

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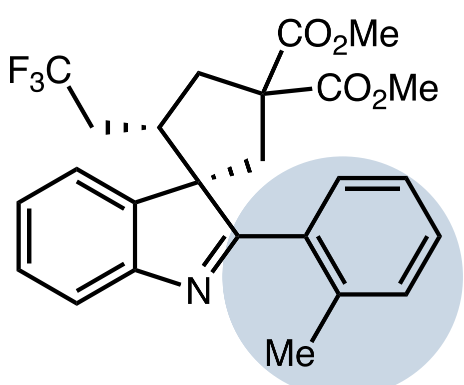
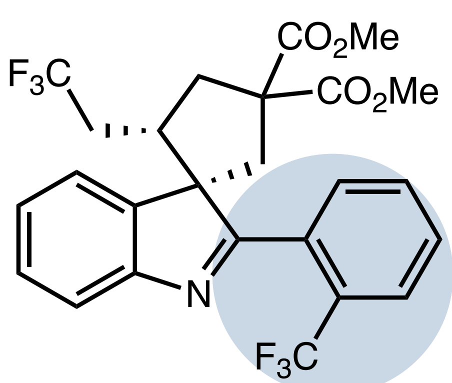
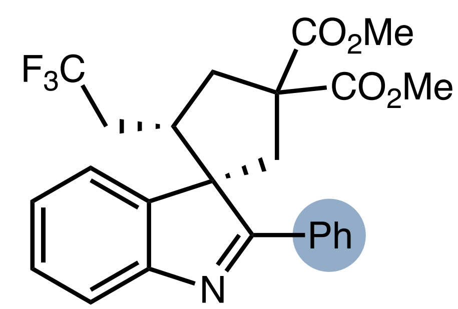


67% (5:1)



64% (6:1)



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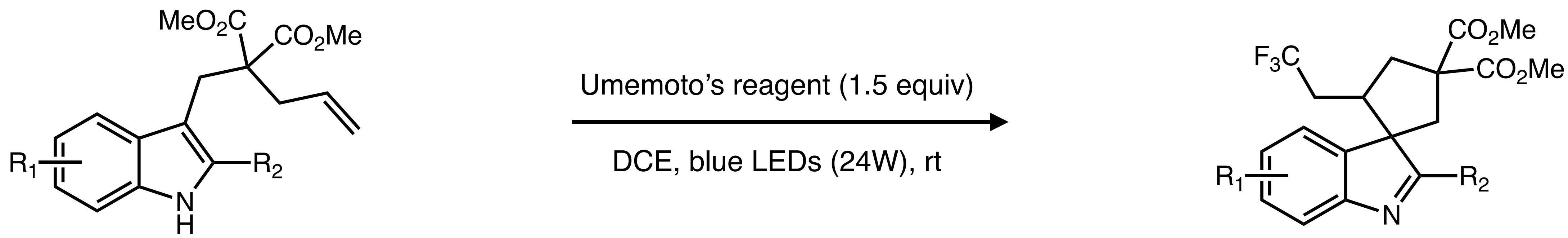
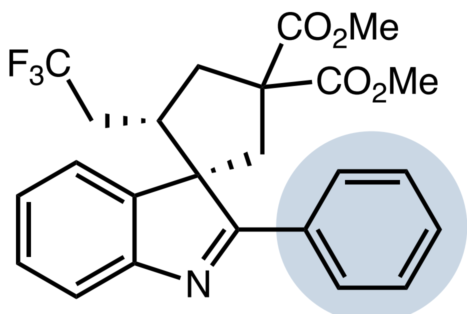
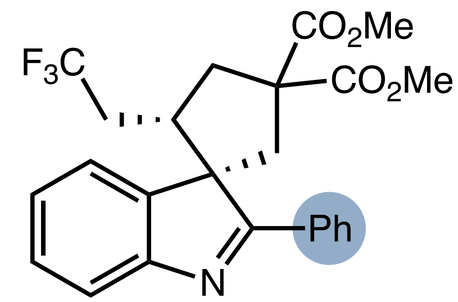
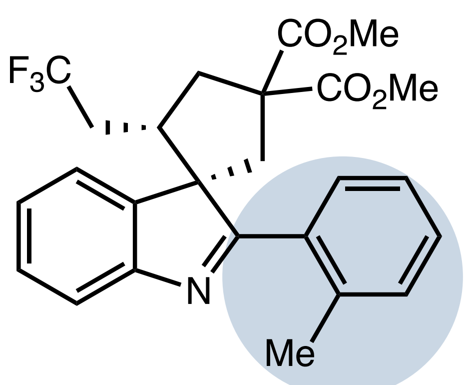
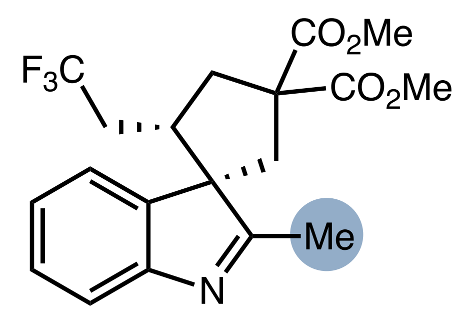
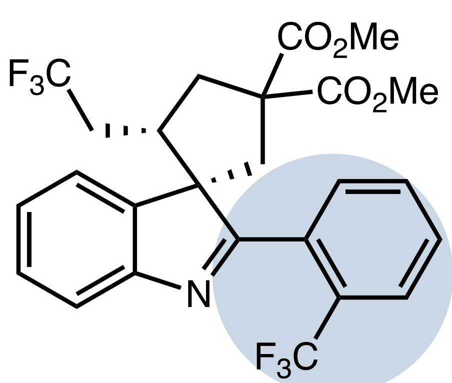
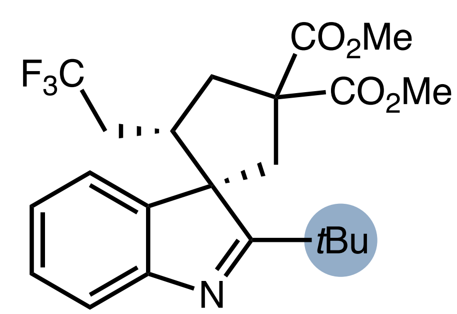
Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - oxidation



	Yields (dr)		Yields (dr)
	**70% (1.4:1)**		**70% (1.4:1)**
	**67% (5:1)**		**58% (2:1)**
	**64% (6:1)**		**55% (7:1)**

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Outline

Radical approach

Traditional radical generation — Birch & SmI_2

Photochemical

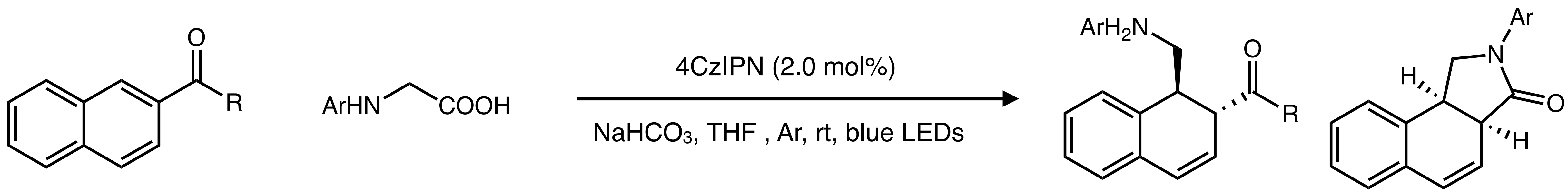
- **Single electron transfer**
  - Radical addition
  - Oxidation
  - Reduction
- **Energy transfer**
  - Direct excitation
  - Sensitization

Transition-metal

- **Mediated**
  - *η^2*
  - *η^6*
- **Catalyzed** — *Pd*

Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - reduction



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Radical Approach to Dearomatization

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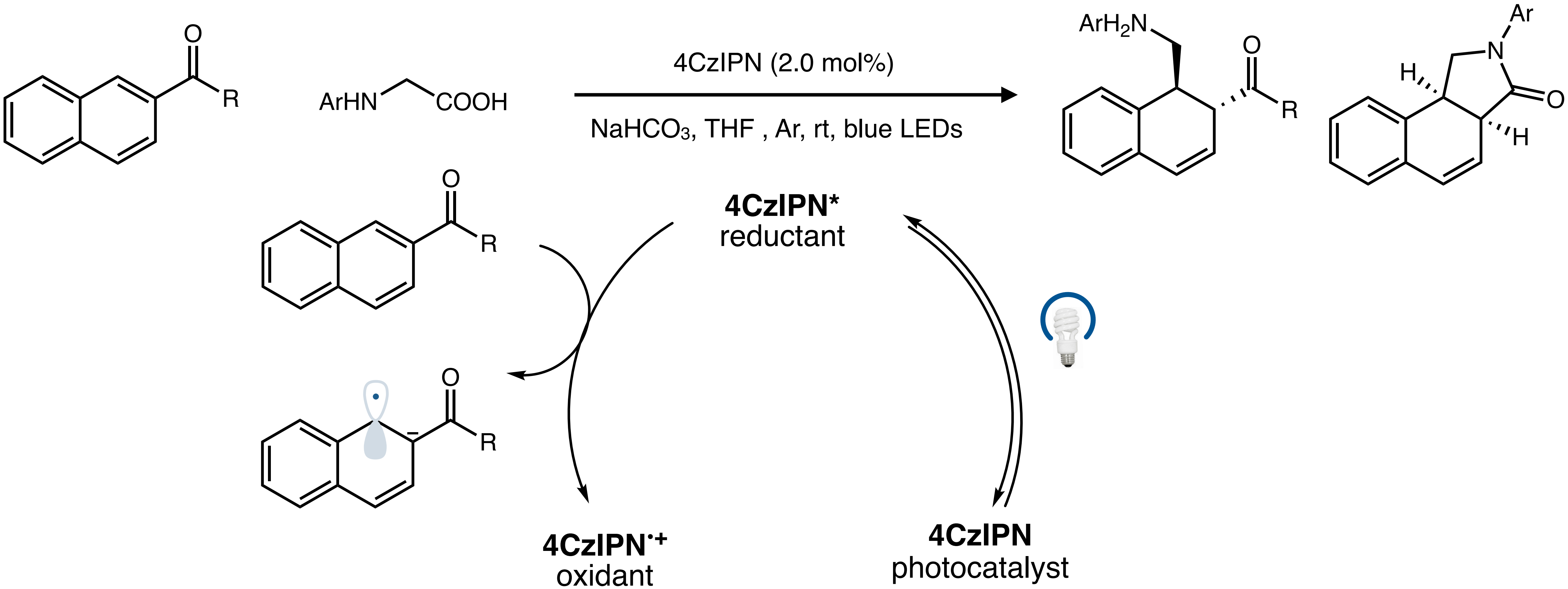

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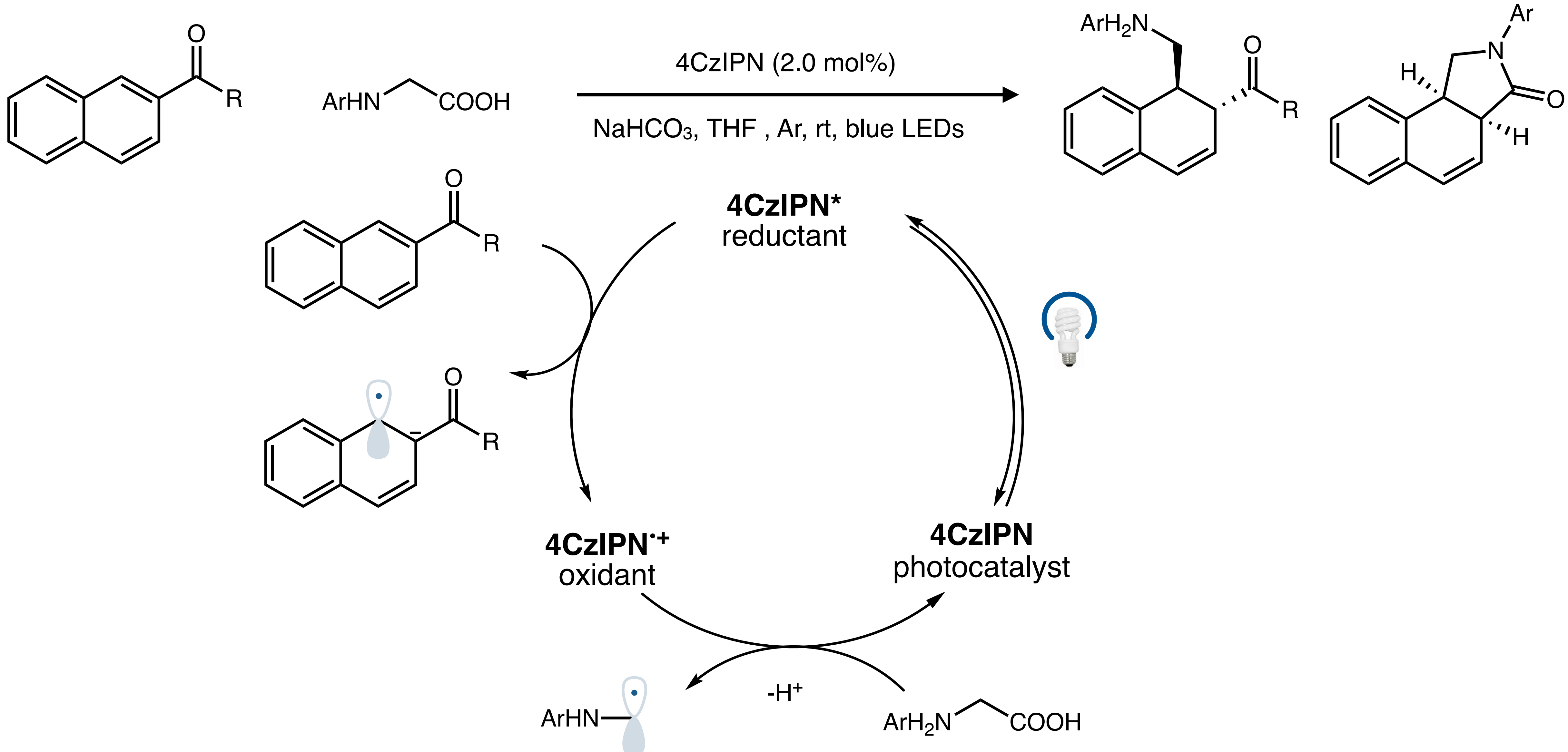

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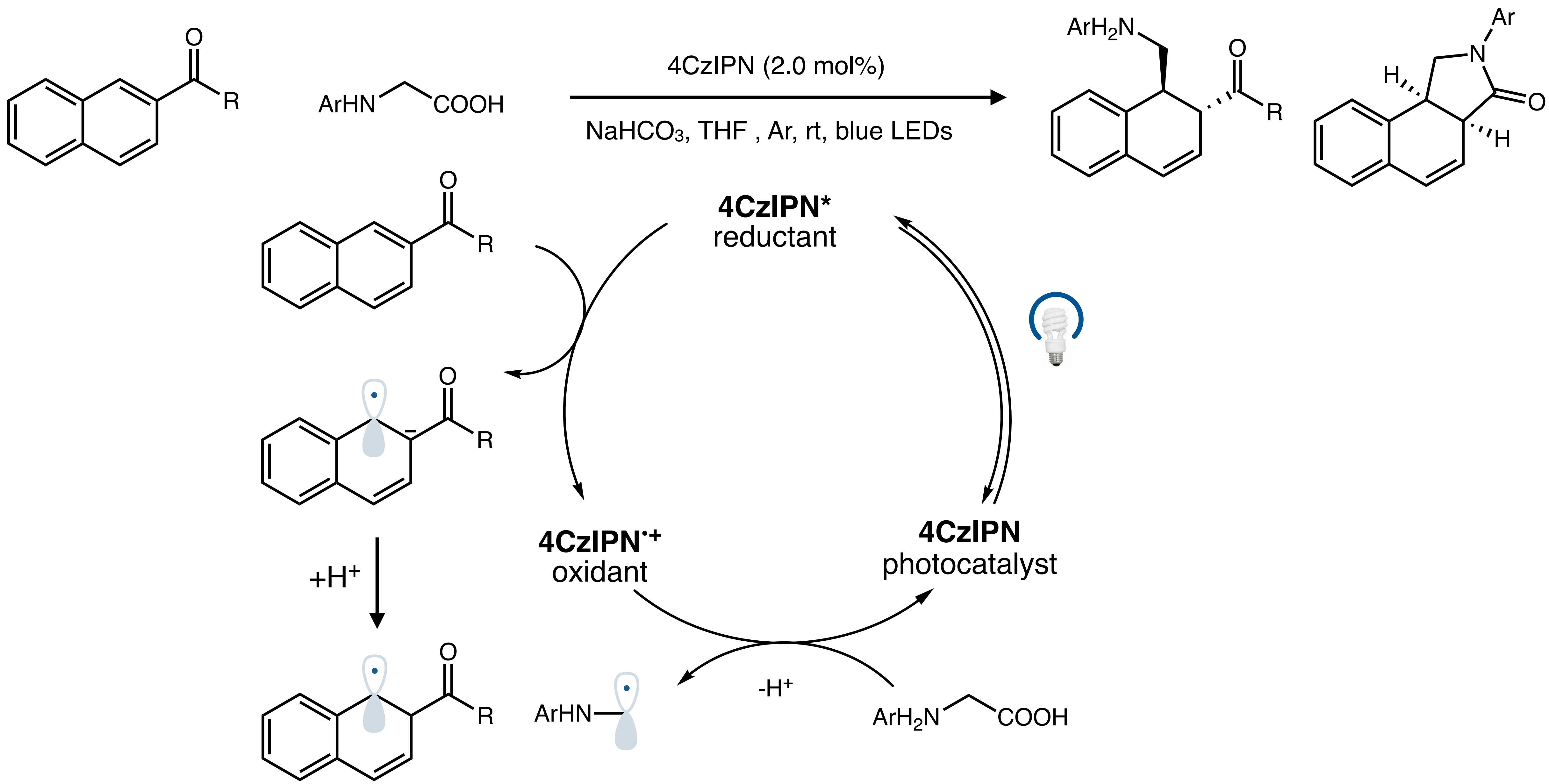

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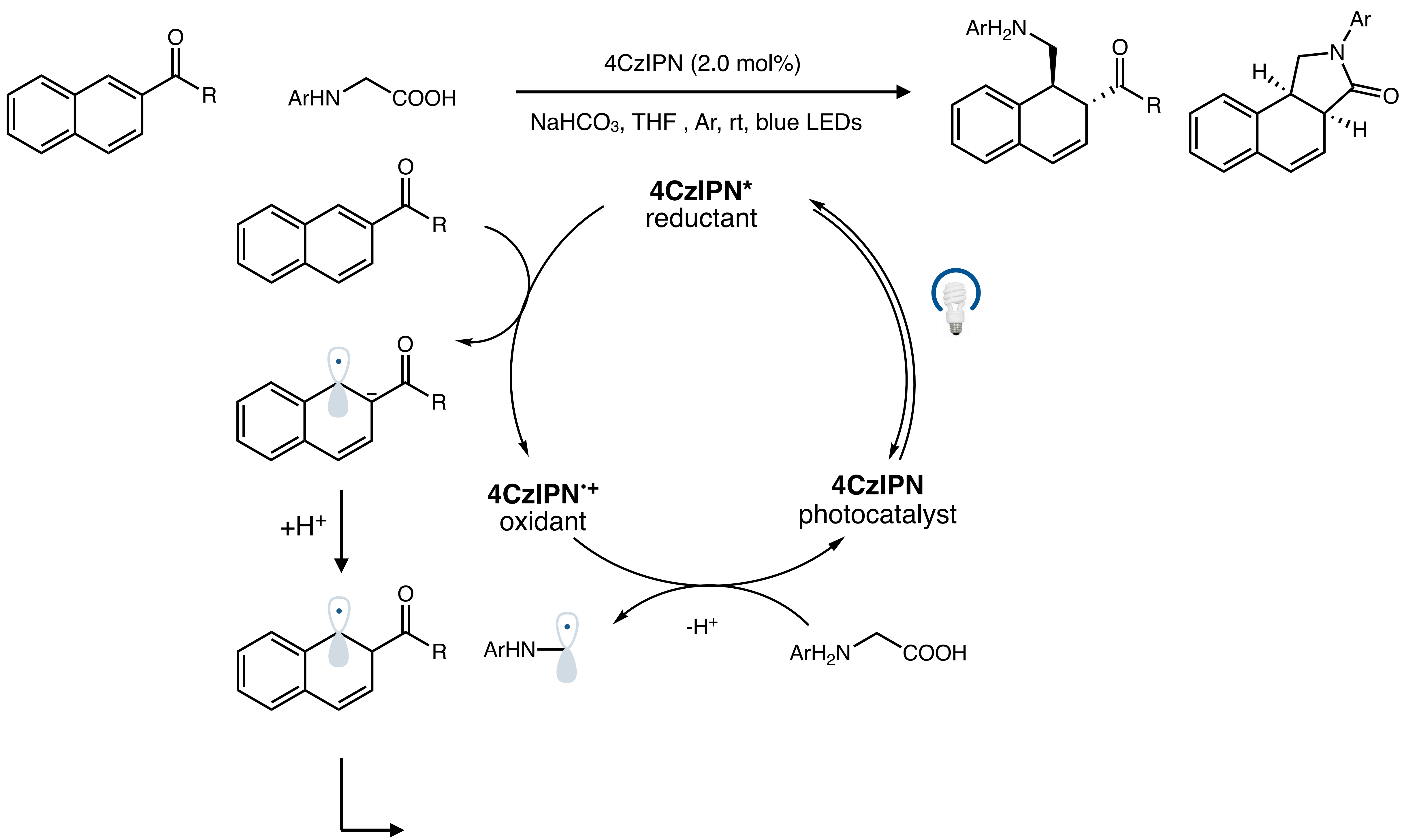

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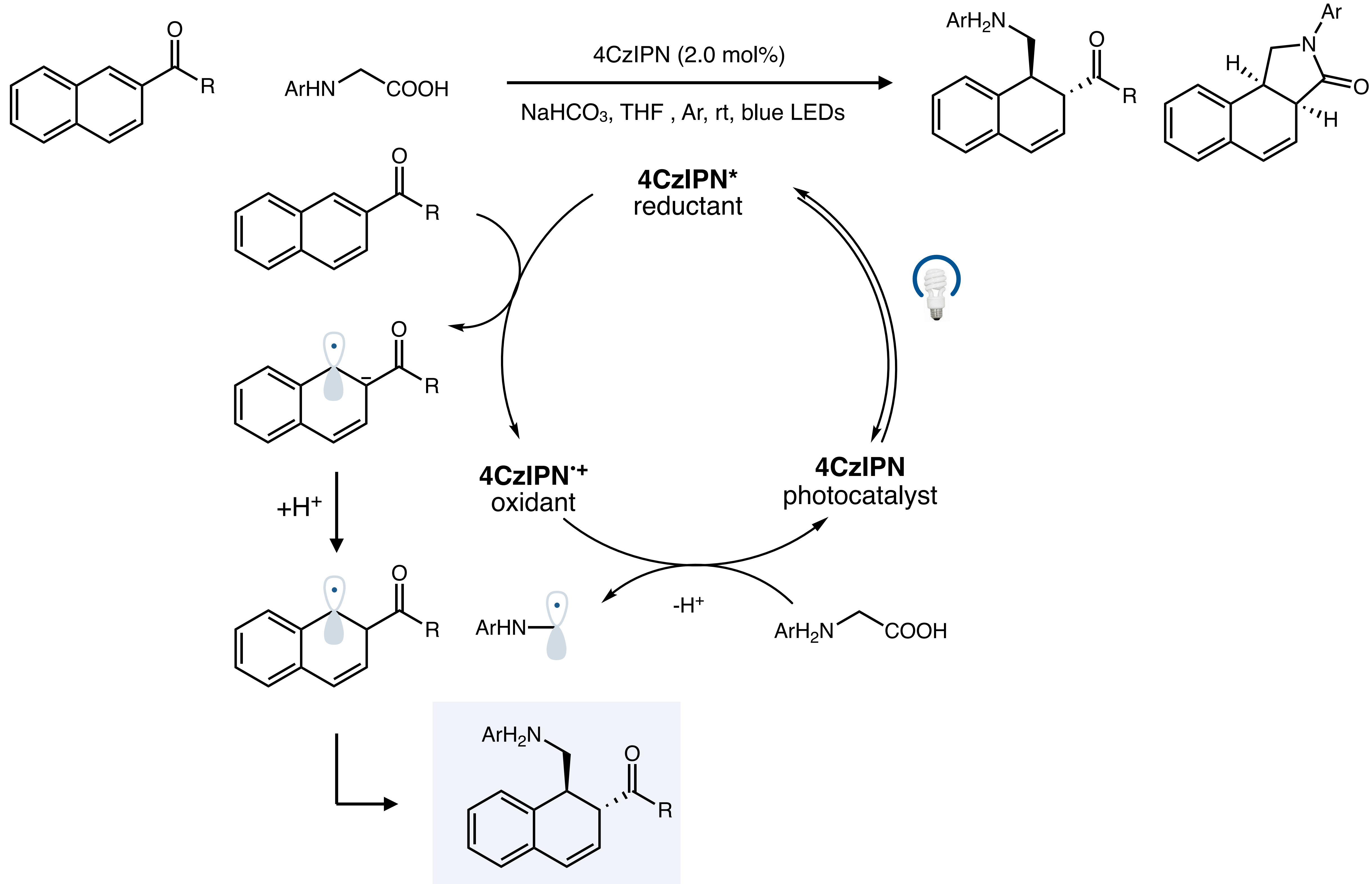

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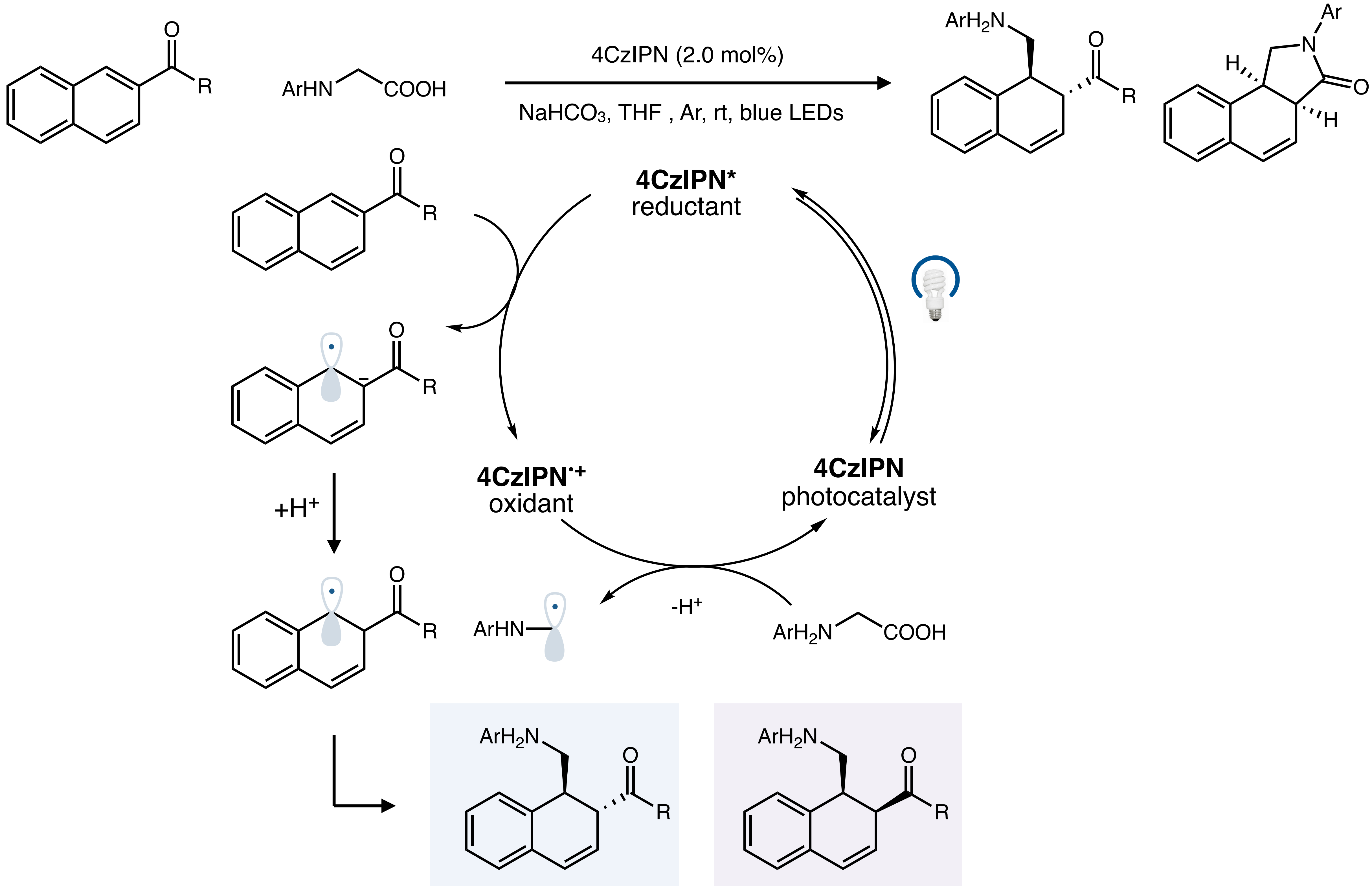

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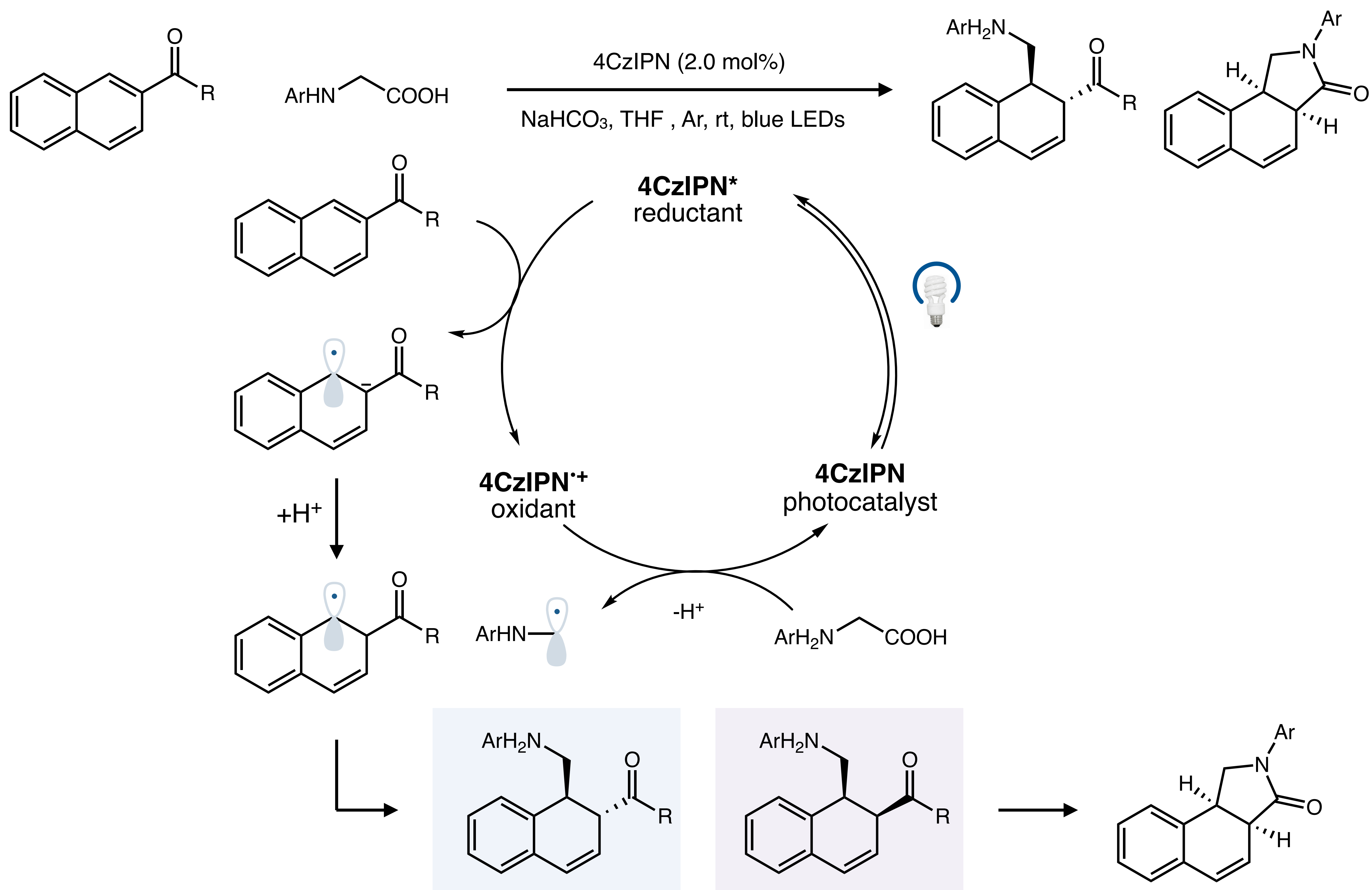

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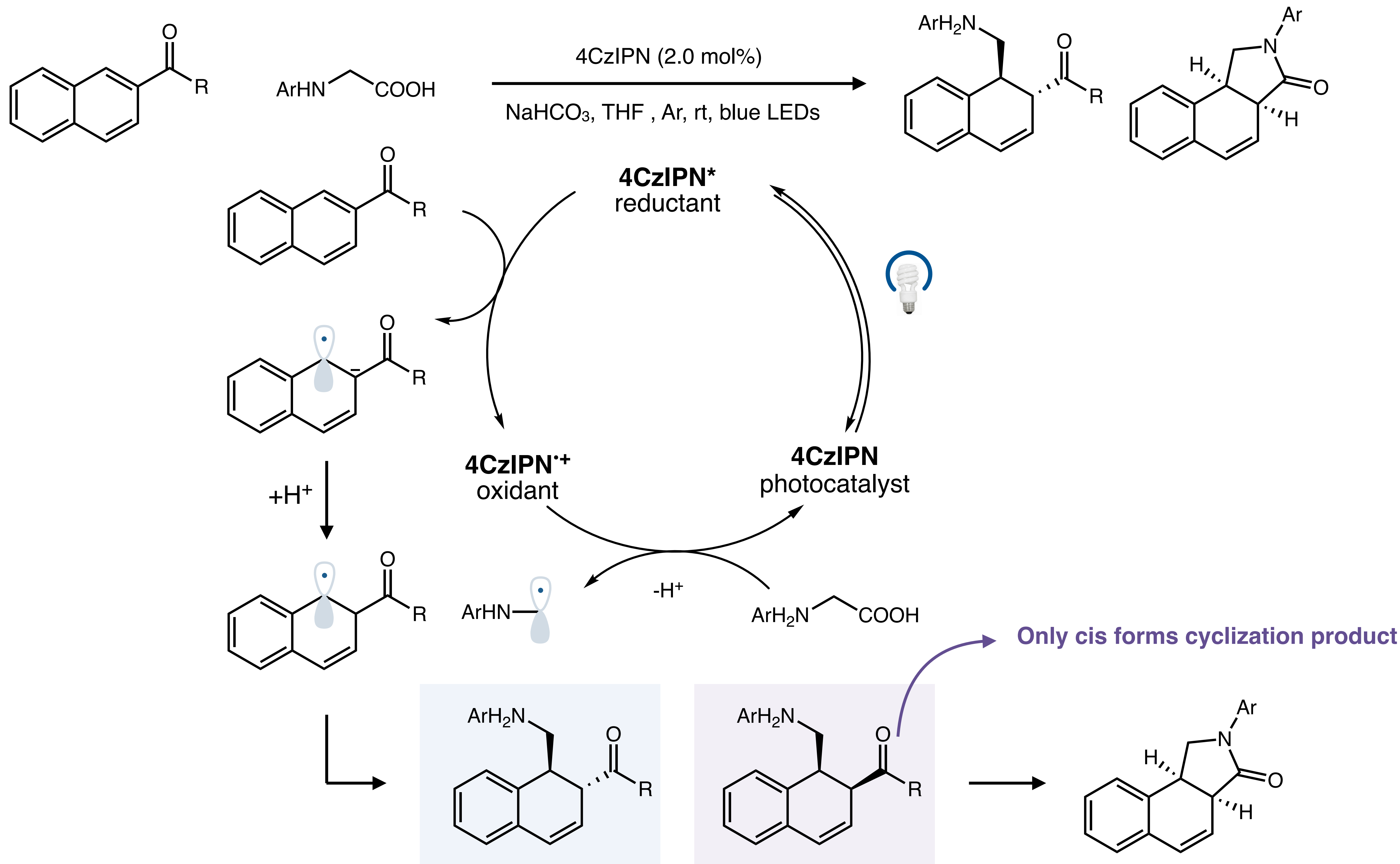

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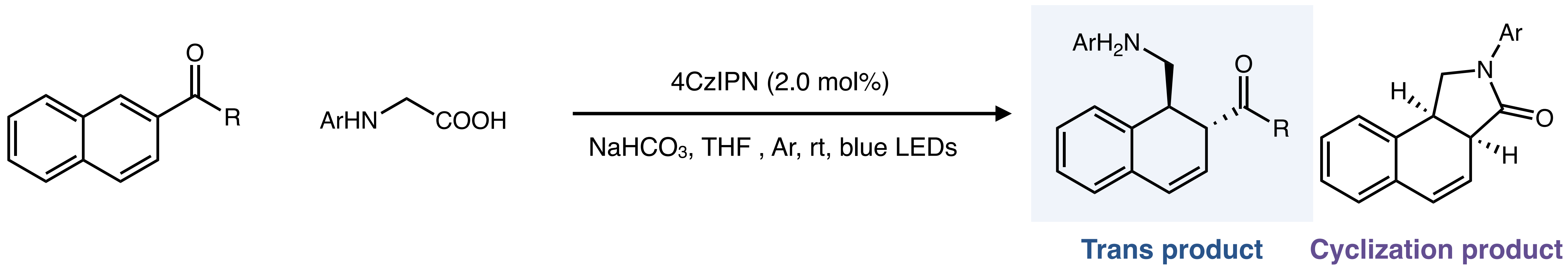
Radical Approach to Dearomatization

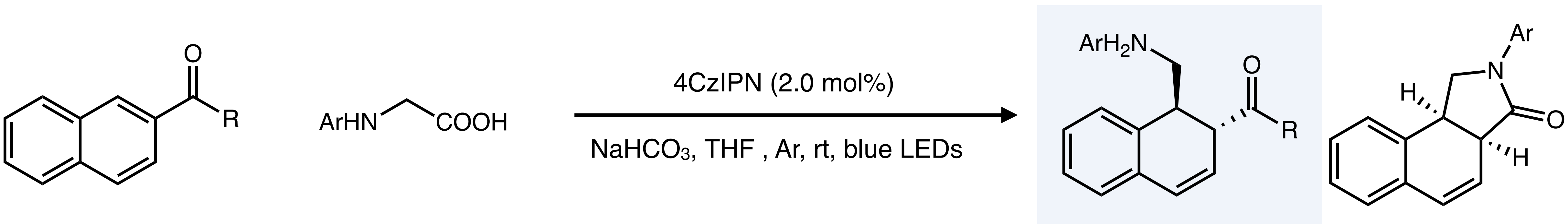
Photochemistry via visible light - single electron transfer - reduction



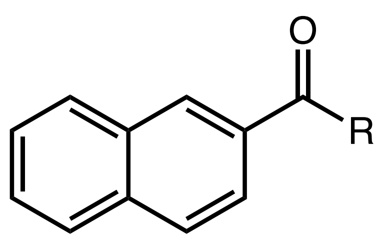
Cheng, Y. Z.; Huang, X. L.; Zhuang, W. H.; Zhao, Q. R.; Zhang, X.; Mei, T. S.; You, S. L. *Angew Chem Int Ed Engl* **2020**, *59* (41), 18062-18067.

Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - reduction



Trans product **Cyclization product**



Trans **Cyclization**

R group

Cheng, Y. Z.; Huang, X. L.; Zhuang, W. H.; Zhao, Q. R.; Zhang, X.; Mei, T. S.; You, S. L. *Angew Chem Int Ed Engl* **2020**, *59* (41), 18062-18067.

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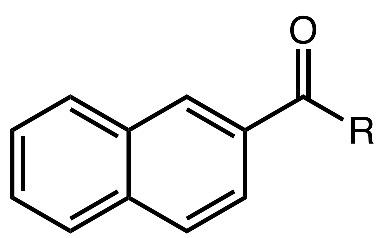
Photochemistry via visible light - single electron transfer - reduction

Trans product **Cyclization product**



Trans **Cyclization**

R group

OMe (87%)

OEt (78%)

O^{i}Pr (61%)

Cheng, Y. Z.; Huang, X. L.; Zhuang, W. H.; Zhao, Q. R.; Zhang, X.; Mei, T. S.; You, S. L. *Angew Chem Int Ed Engl* **2020**, *59* (41), 18062-18067.

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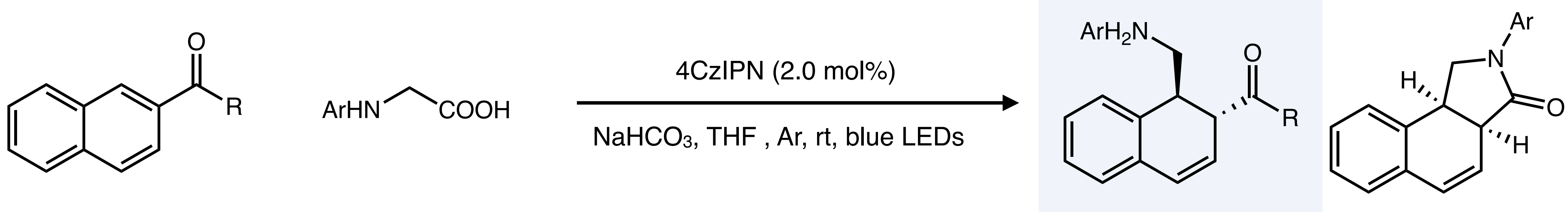
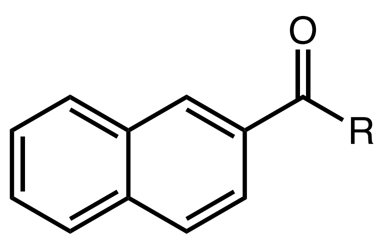


Trans product **Cyclization product**

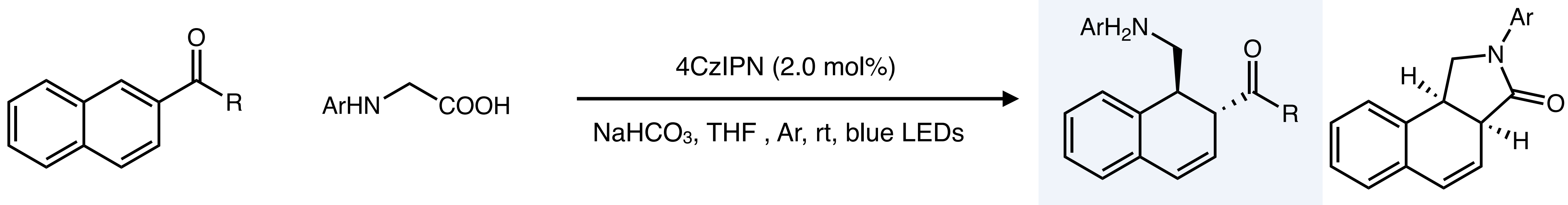


R group	Trans	Cyclization
OMe (87%)	2	1
OEt (78%)	2	1
O^{i}Pr (61%)	4	1

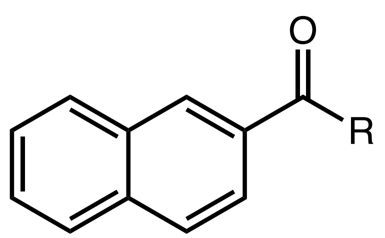
Cheng, Y. Z.; Huang, X. L.; Zhuang, W. H.; Zhao, Q. R.; Zhang, X.; Mei, T. S.; You, S. L. *Angew Chem Int Ed Engl* **2020**, *59* (41), 18062-18067.

Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - reduction



Trans product **Cyclization product**



R group	Trans	Cyclization
OMe (87%)	2	1
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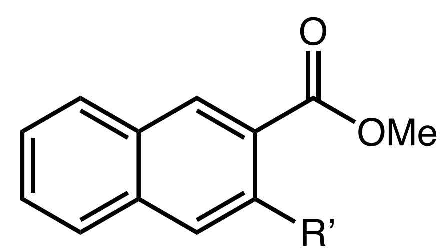
O^{i}Pr (61%)	4	1

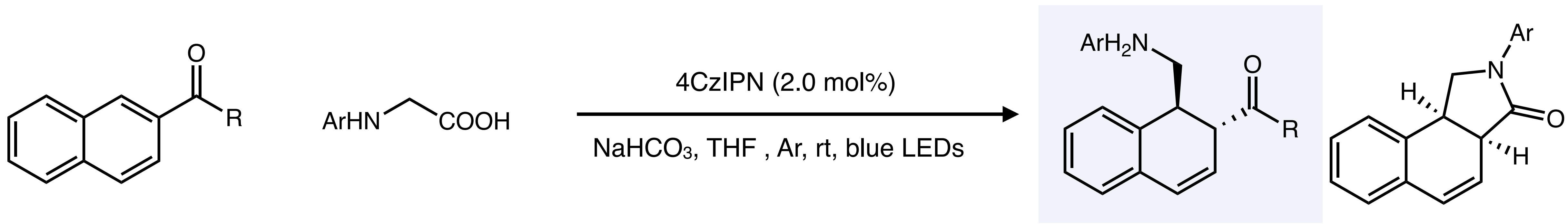


R' group	Trans	Cyclization

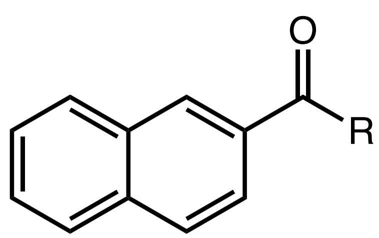
Cheng, Y. Z.; Huang, X. L.; Zhuang, W. H.; Zhao, Q. R.; Zhang, X.; Mei, T. S.; You, S. L. *Angew Chem Int Ed Engl* **2020**, *59* (41), 18062-18067.

Radical Approach to Dearomatization

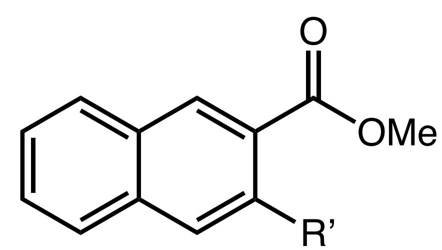
Photochemistry via visible light - single electron transfer - reduction

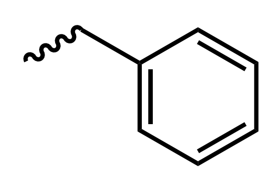
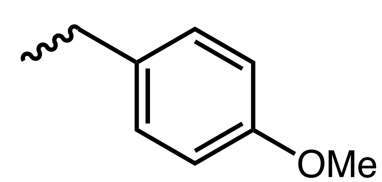


Trans product **Cyclization product**



R group	Trans	Cyclization
OMe (87%)	2	1
OEt (78%)	2	1
O^{i}Pr (61%)	4	1



R' group	Trans	Cyclization
 79%		
 85%		

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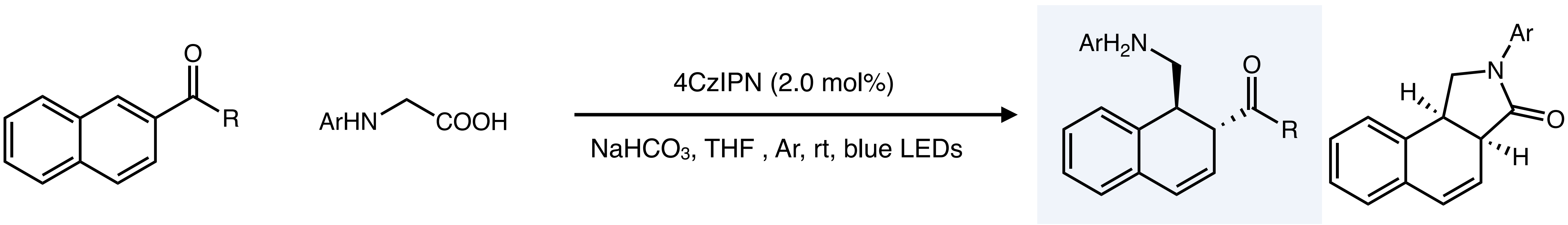
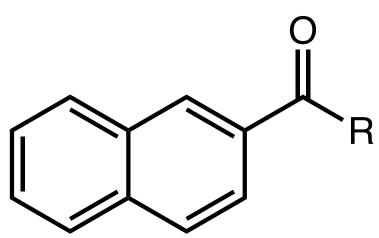
Radical Approach to Dearomatization

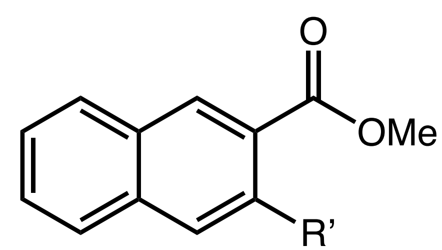
Photochemistry via visible light - single electron transfer - reduction

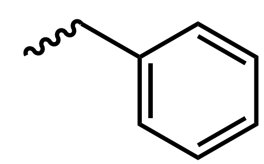
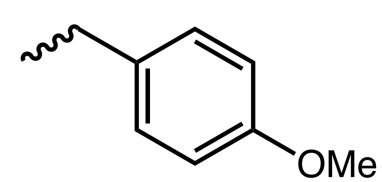


Trans product **Cyclization product**



R group	Trans	Cyclization
OMe (87%)	2	1
OEt (78%)	2	1
O^{i}Pr (61%)	4	1



R' group	Trans	Cyclization
 79%	9.6	1
 85%	10	1

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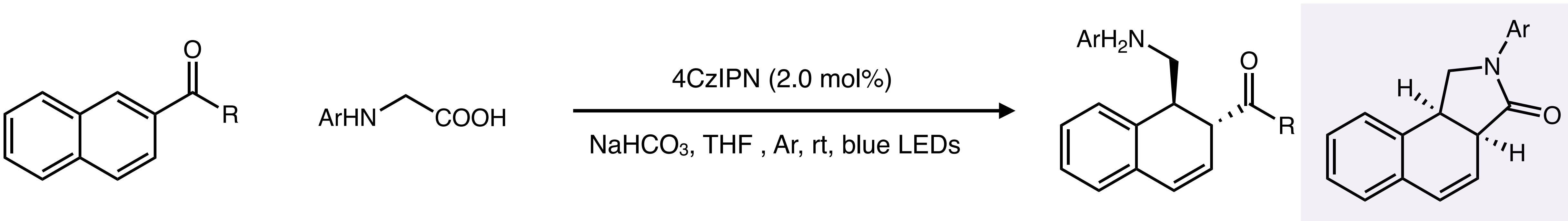
Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - reduction



Trans product **Cyclization product**

Cheng, Y. Z.; Huang, X. L.; Zhuang, W. H.; Zhao, Q. R.; Zhang, X.; Mei, T. S.; You, S. L. *Angew Chem Int Ed Engl* **2020**, *59* (41), 18062-18067.

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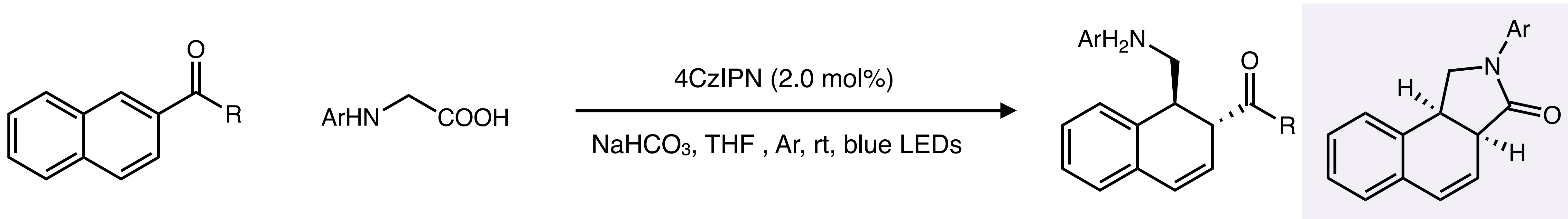
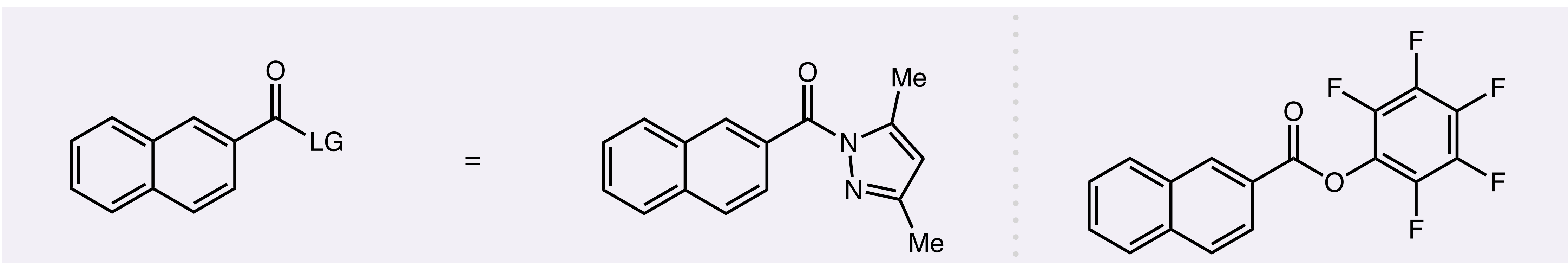


Trans product **Cyclization product**



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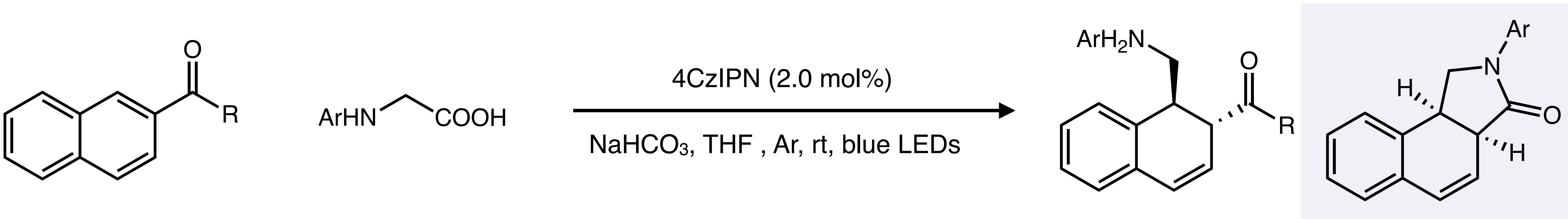
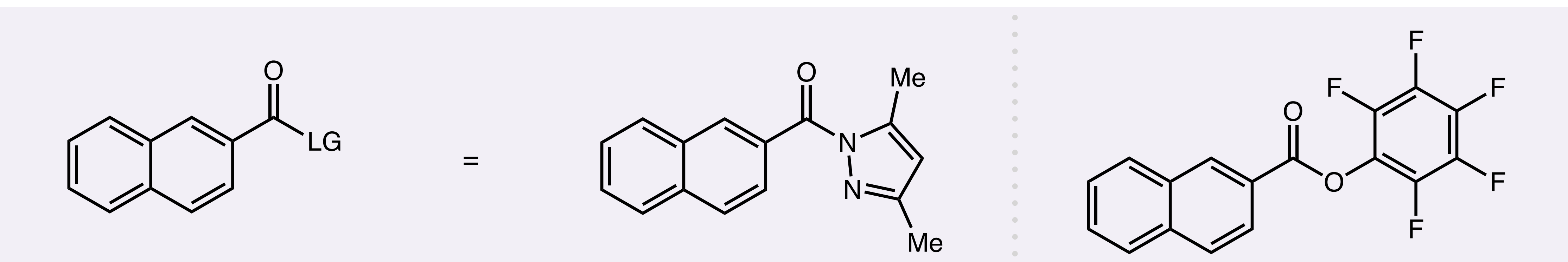
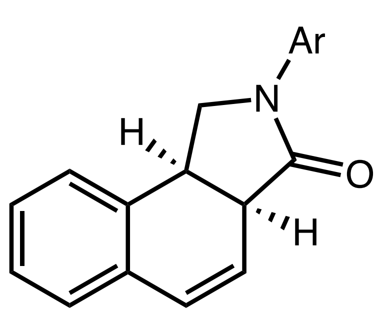
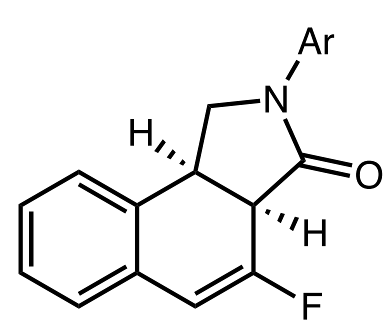


Trans product **Cyclization product**

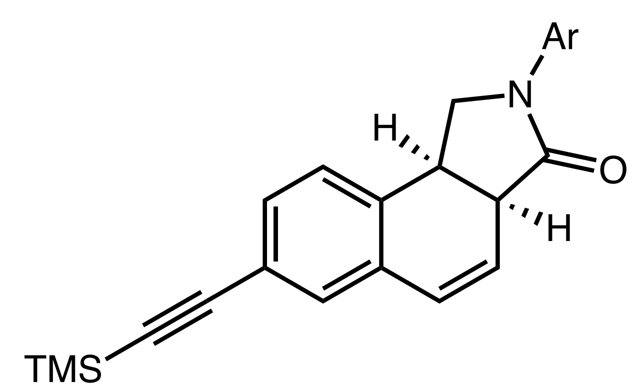




91% yield



72% yield



77% yield

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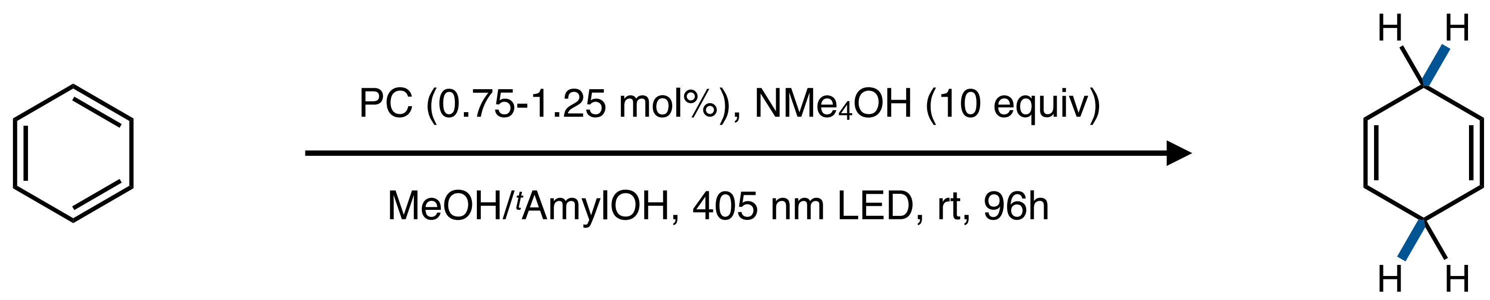
Radical Approach to Dearomatization

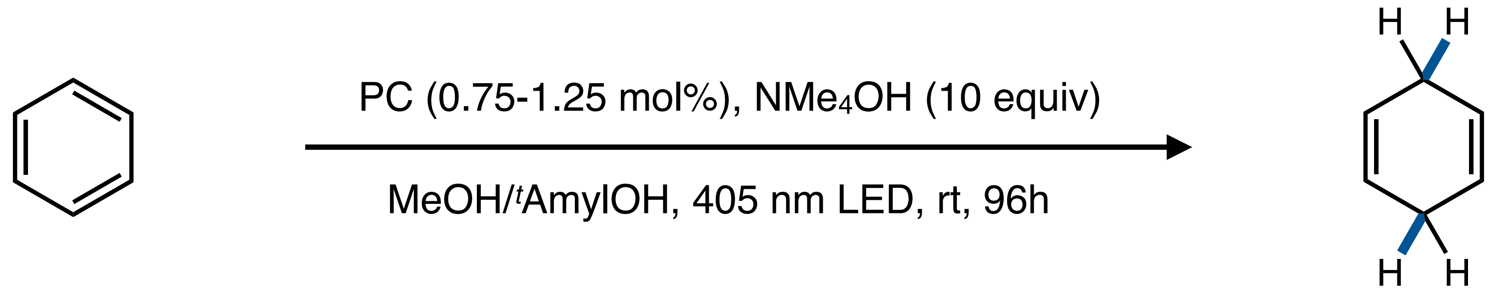
Photochemistry via visible light - single electron transfer - reduction



Cole, J. P.; Chen, D. F.; Kudisch, M.; Pearson, R. M.; Lim, C. H.; Miyake, G. M. *J Am Chem Soc* **2020**, *142* (31), 13573-13581.

Radical Approach to Dearomatization

Photochemistry via visible light - single electron transfer - reduction



Consecutive
photoinduced
electron transfer
(ConPET)

Cole, J. P.; Chen, D. F.; Kudisch, M.; Pearson, R. M.; Lim, C. H.; Miyake, G. M. *J Am Chem Soc* **2020**, *142* (31), 13573-13581.

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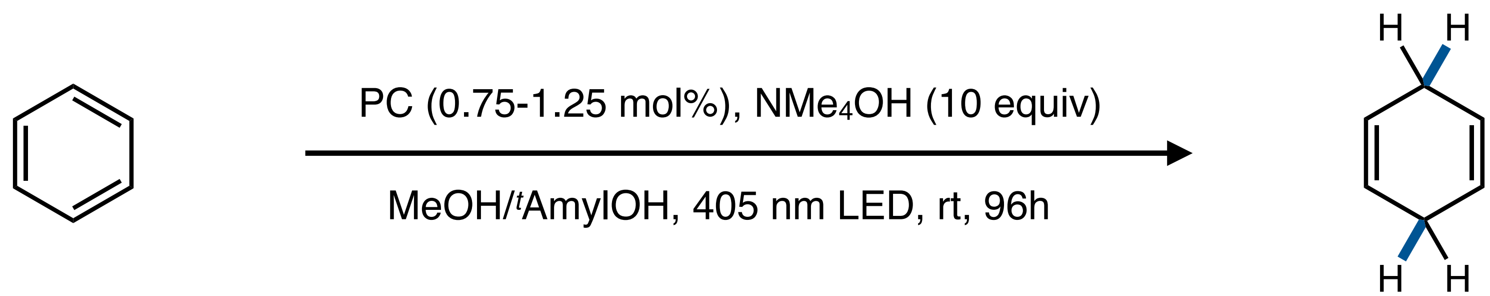
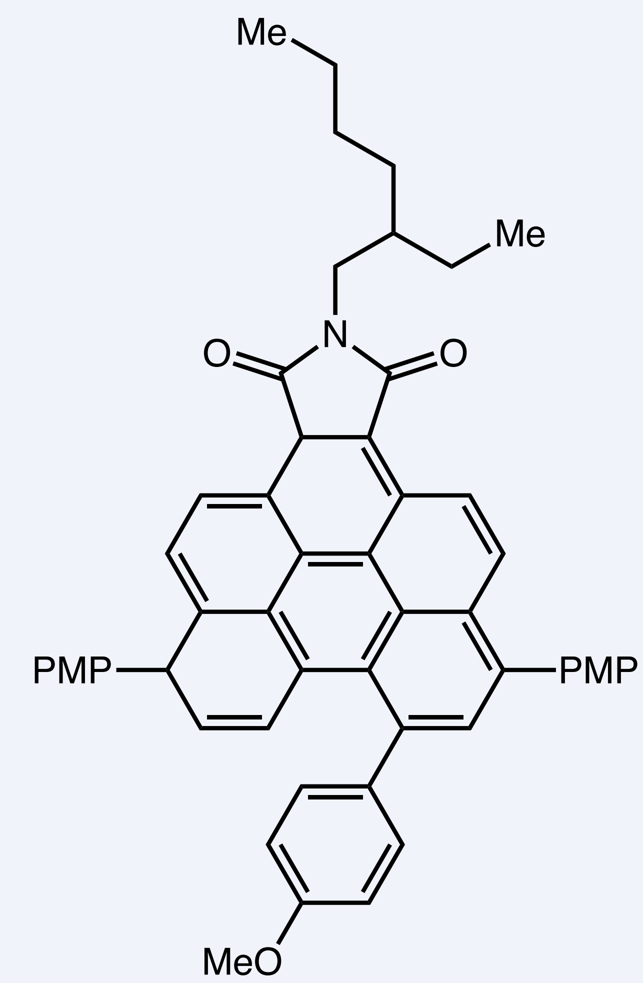


Consecutive photoinduced electron transfer (ConPET)



PC

Cole, J. P.; Chen, D. F.; Kudisch, M.; Pearson, R. M.; Lim, C. H.; Miyake, G. M. *J Am Chem Soc* **2020**, *142* (31), 13573-13581.

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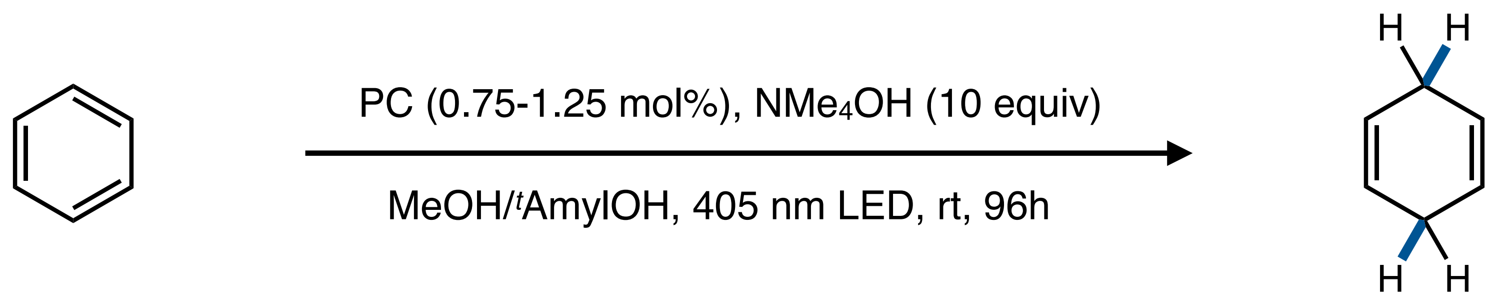
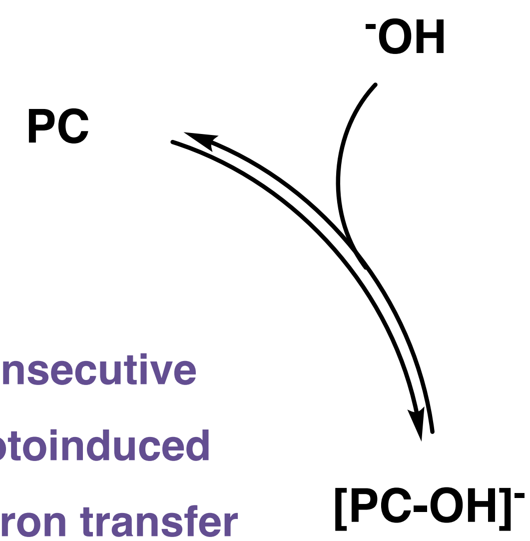
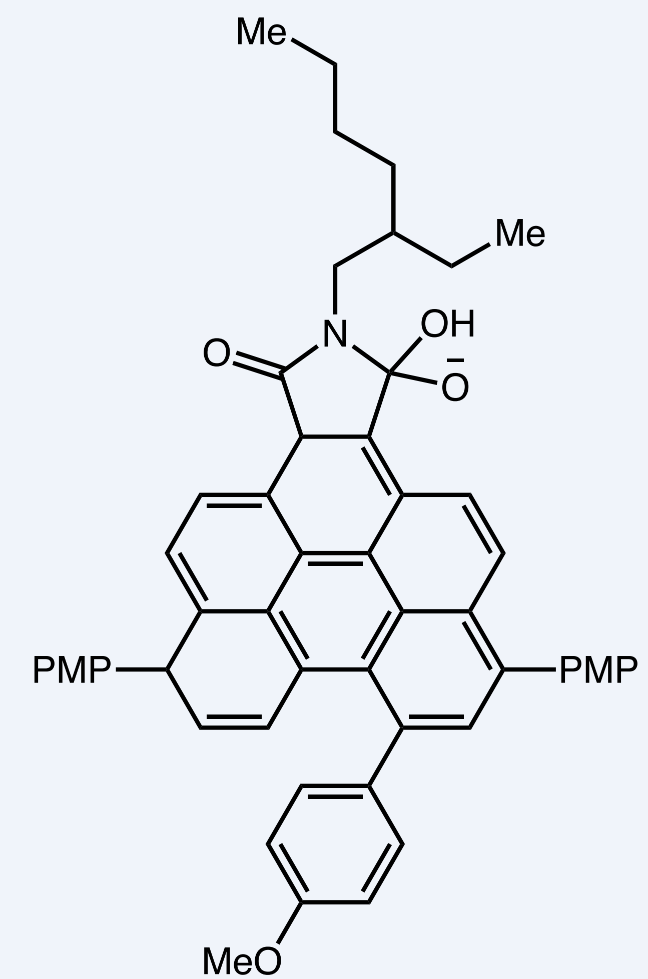
Photochemistry via visible light - single electron transfer - reduction





Consecutive photoinduced electron transfer (ConPET)



$[PC\text{-}OH]^-$

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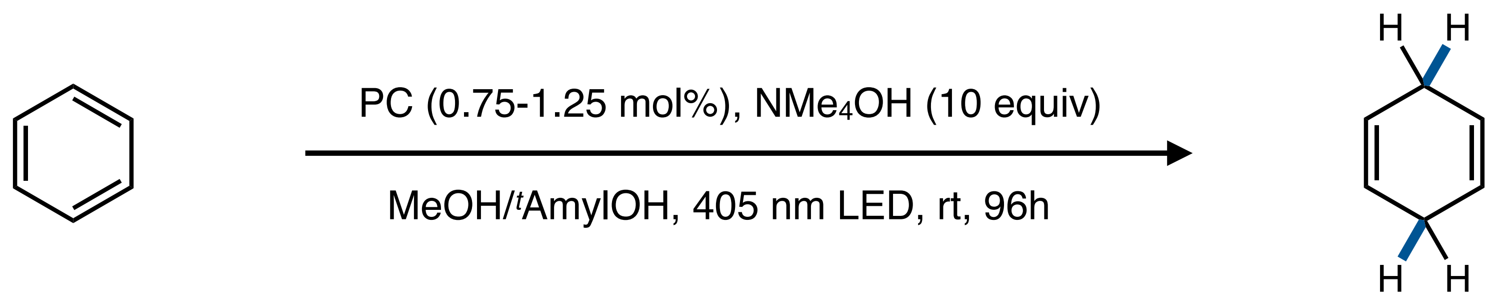

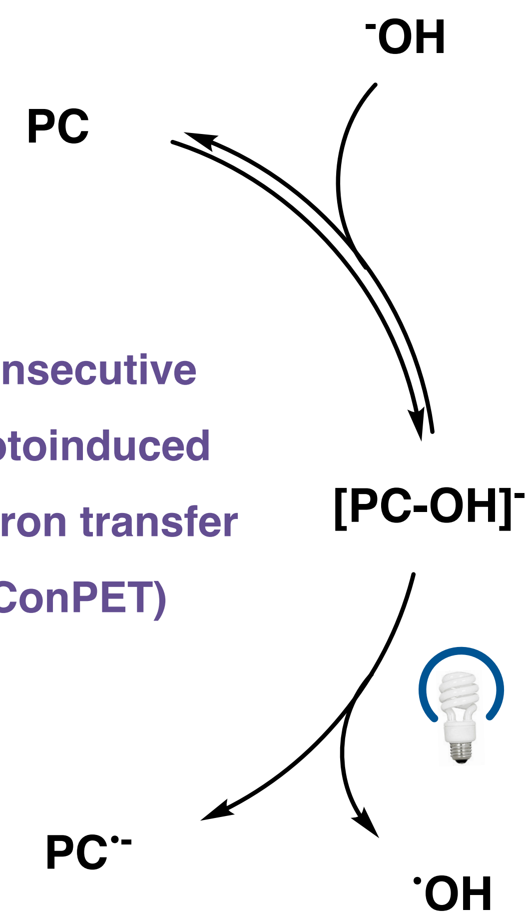

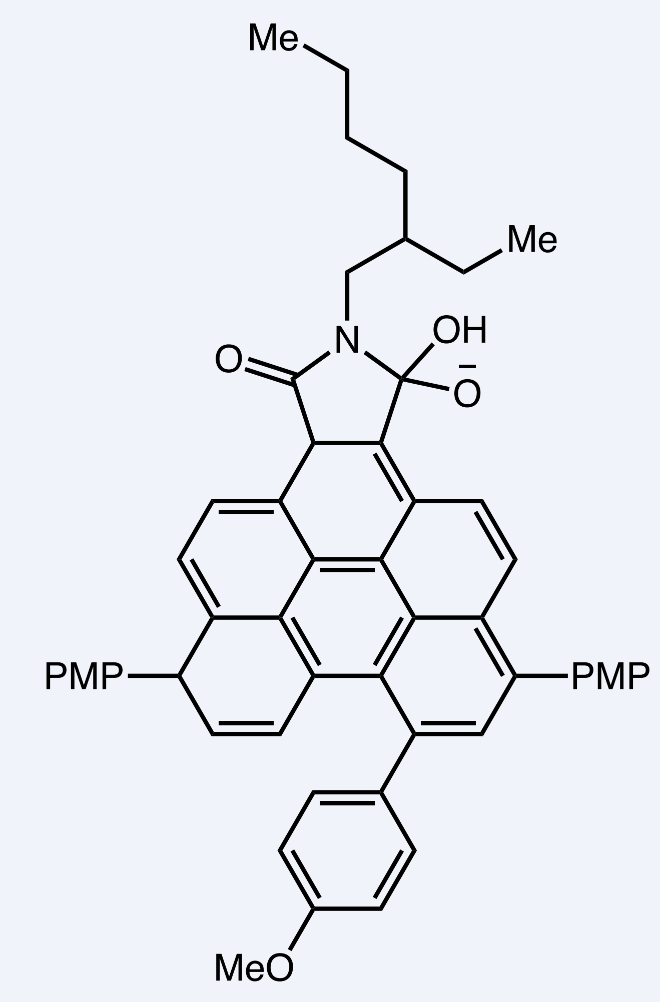

[PC-OH]$^-$

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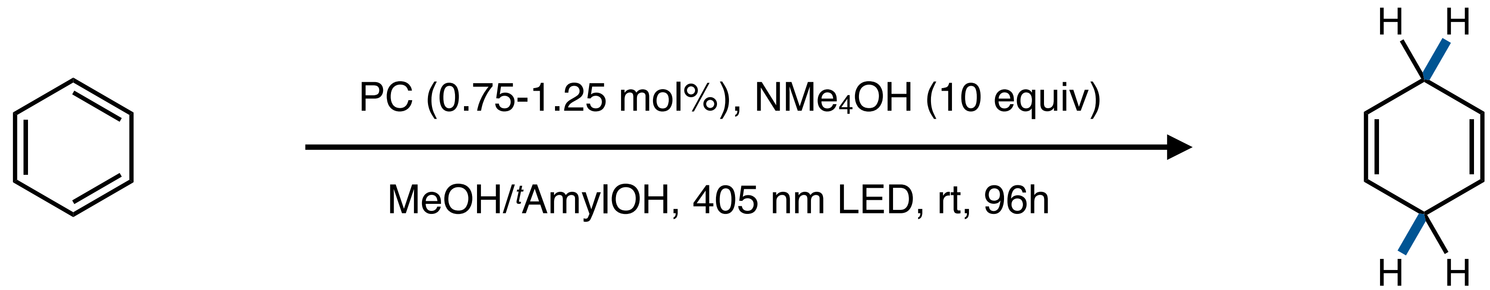

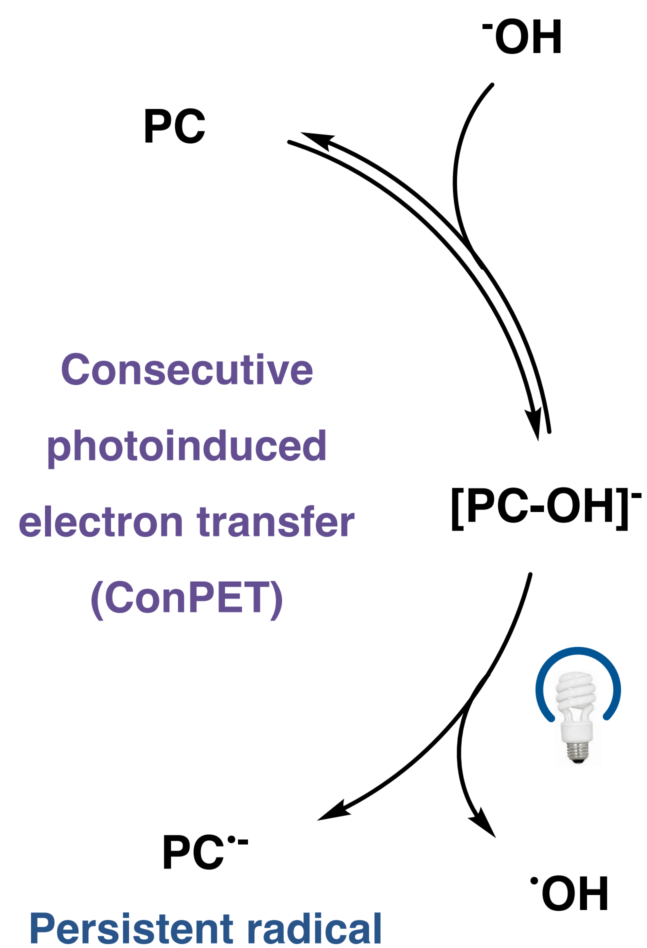

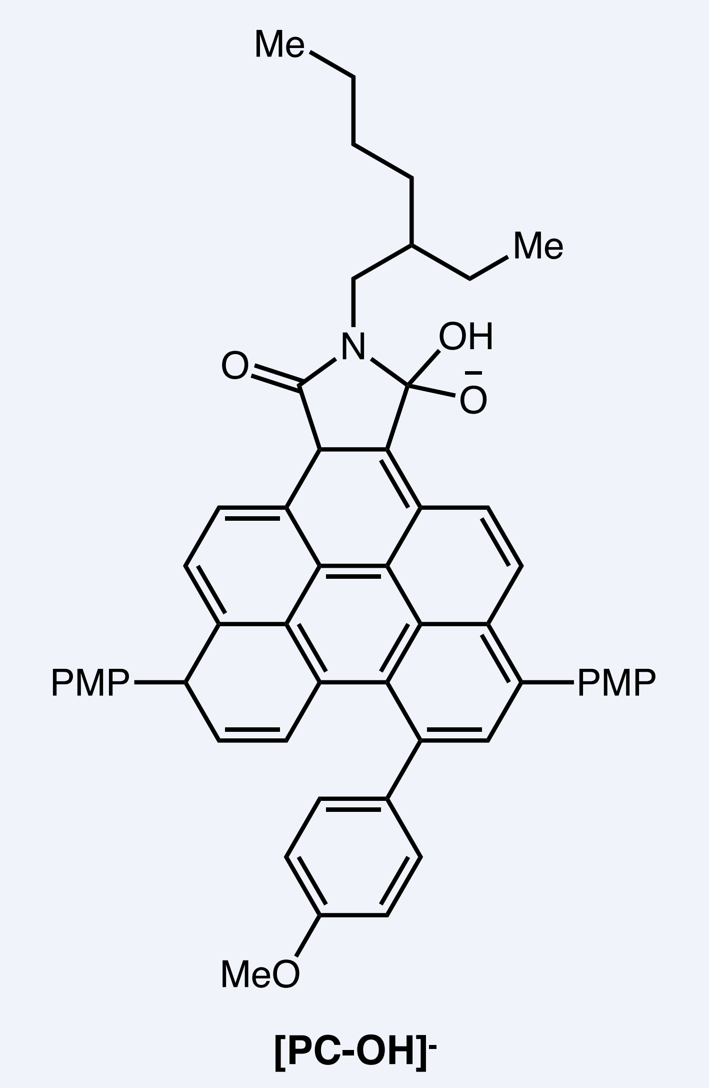

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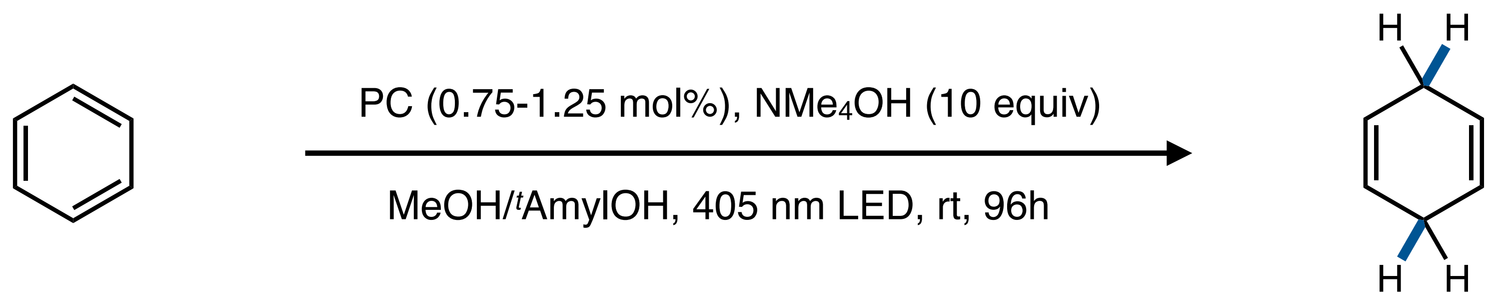

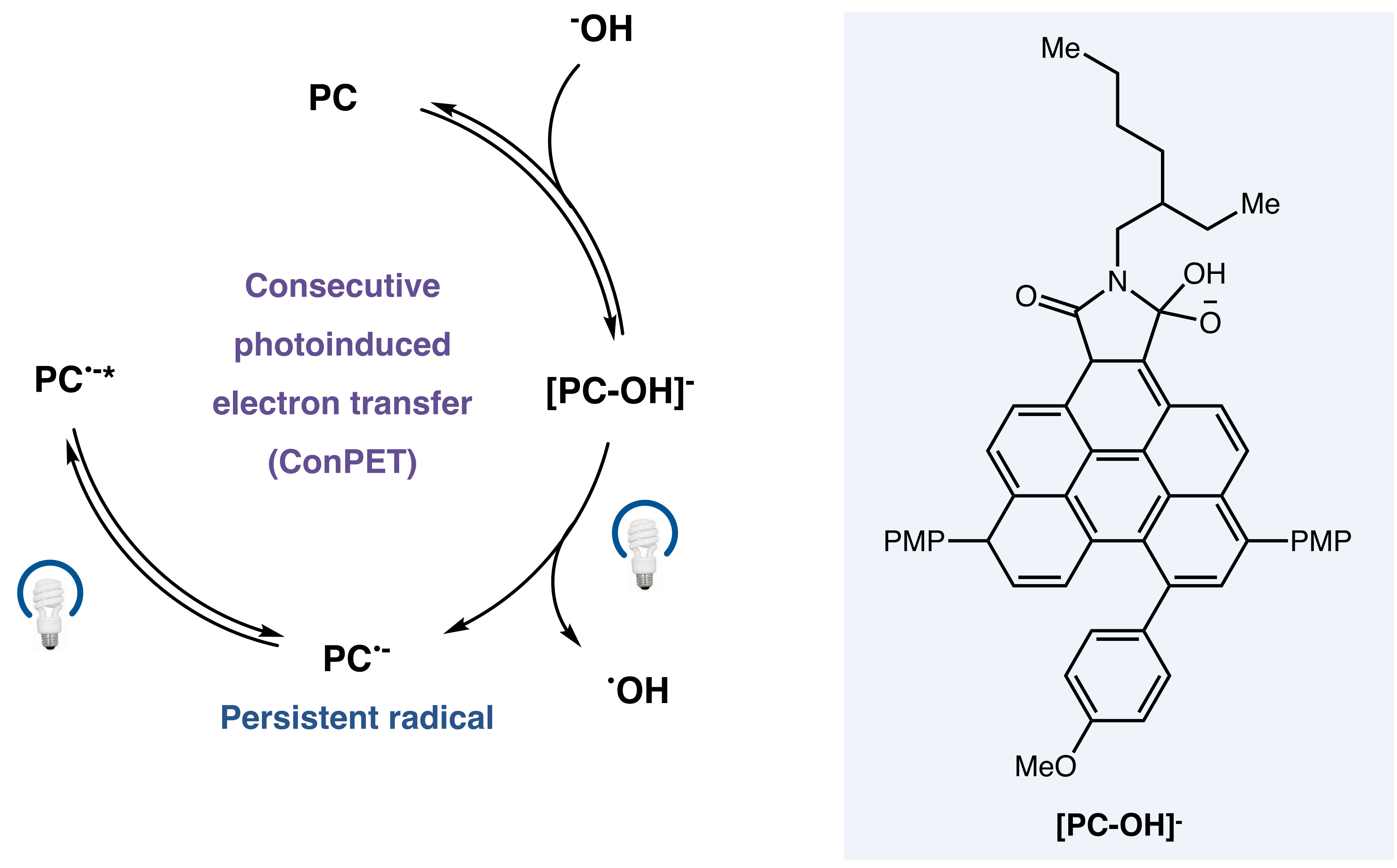

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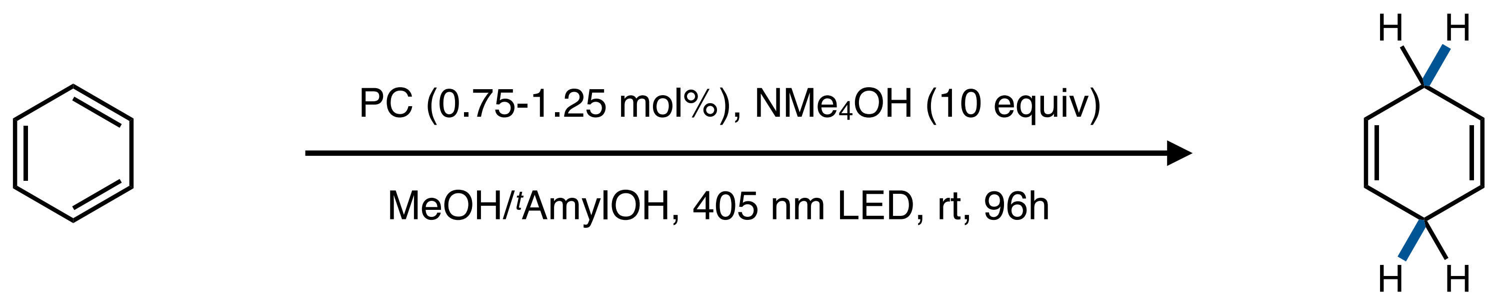

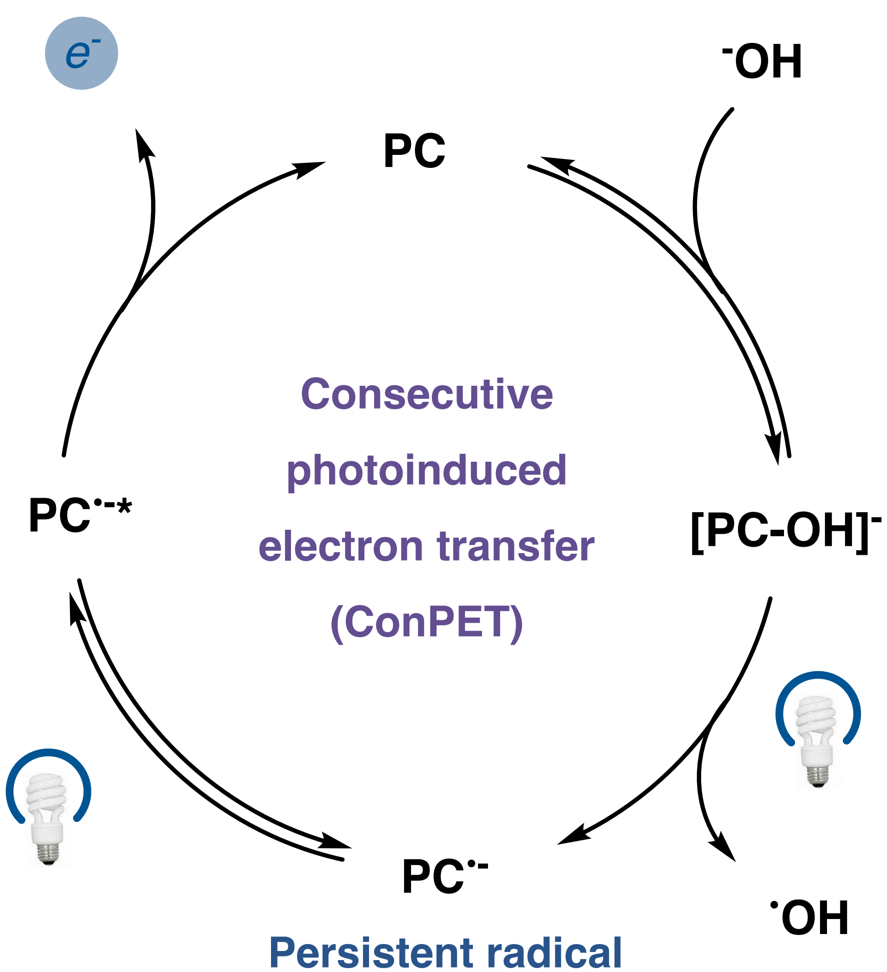

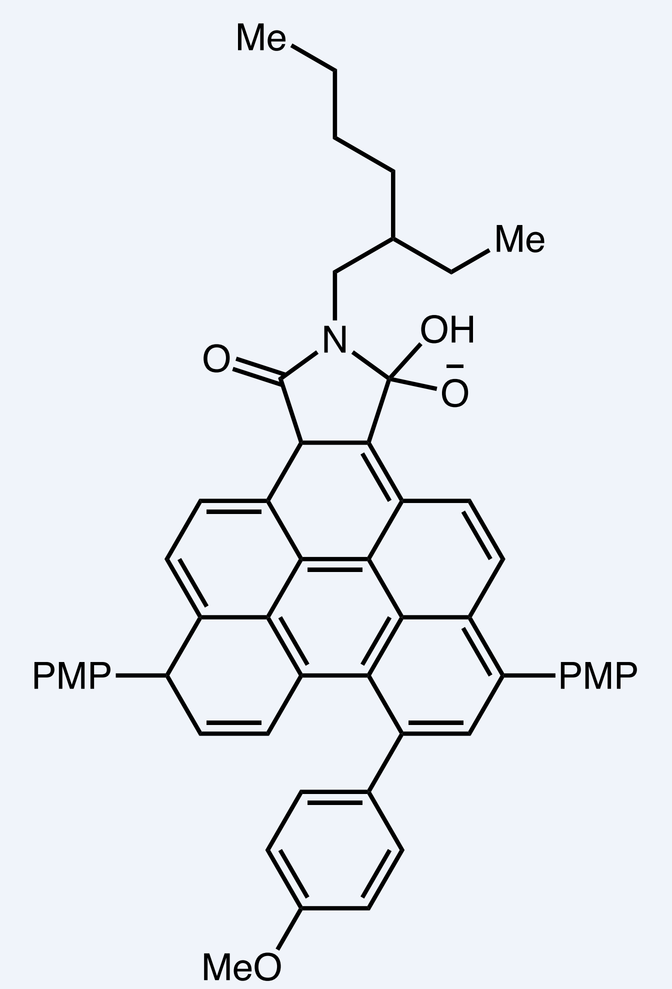

[PC-OH]-

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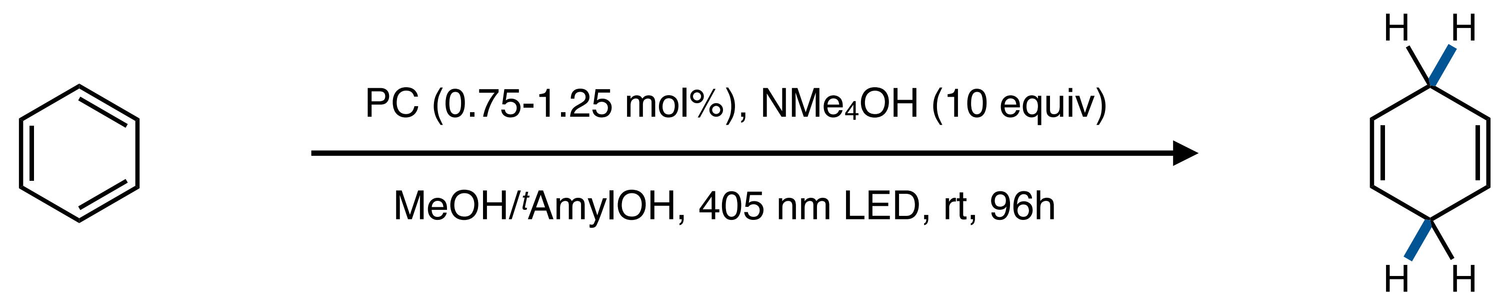

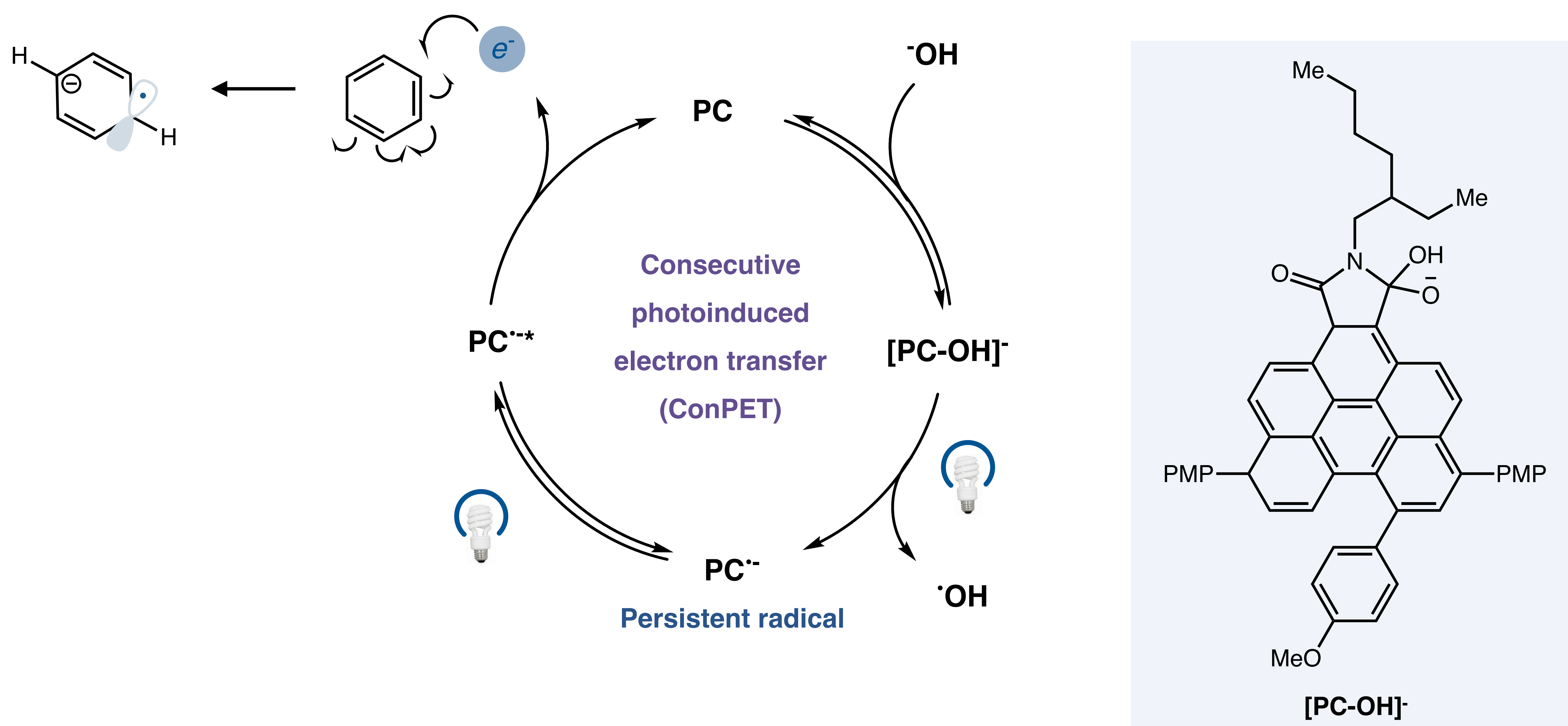

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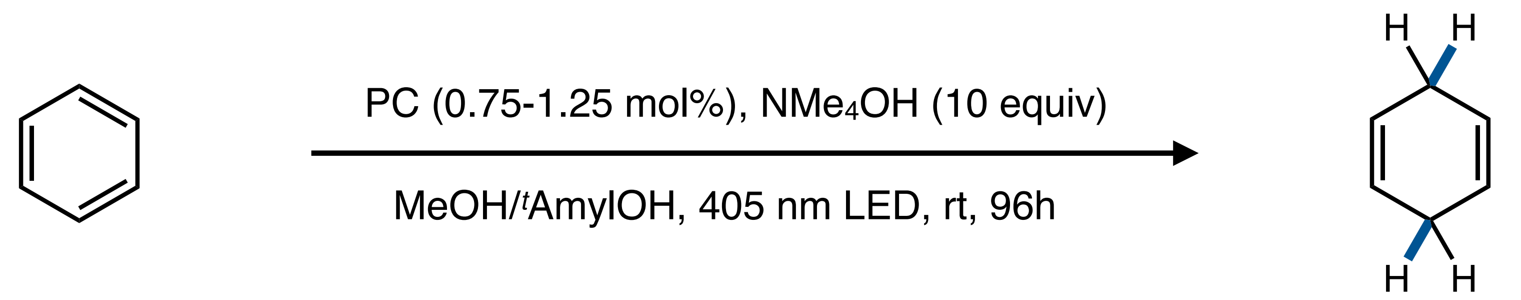

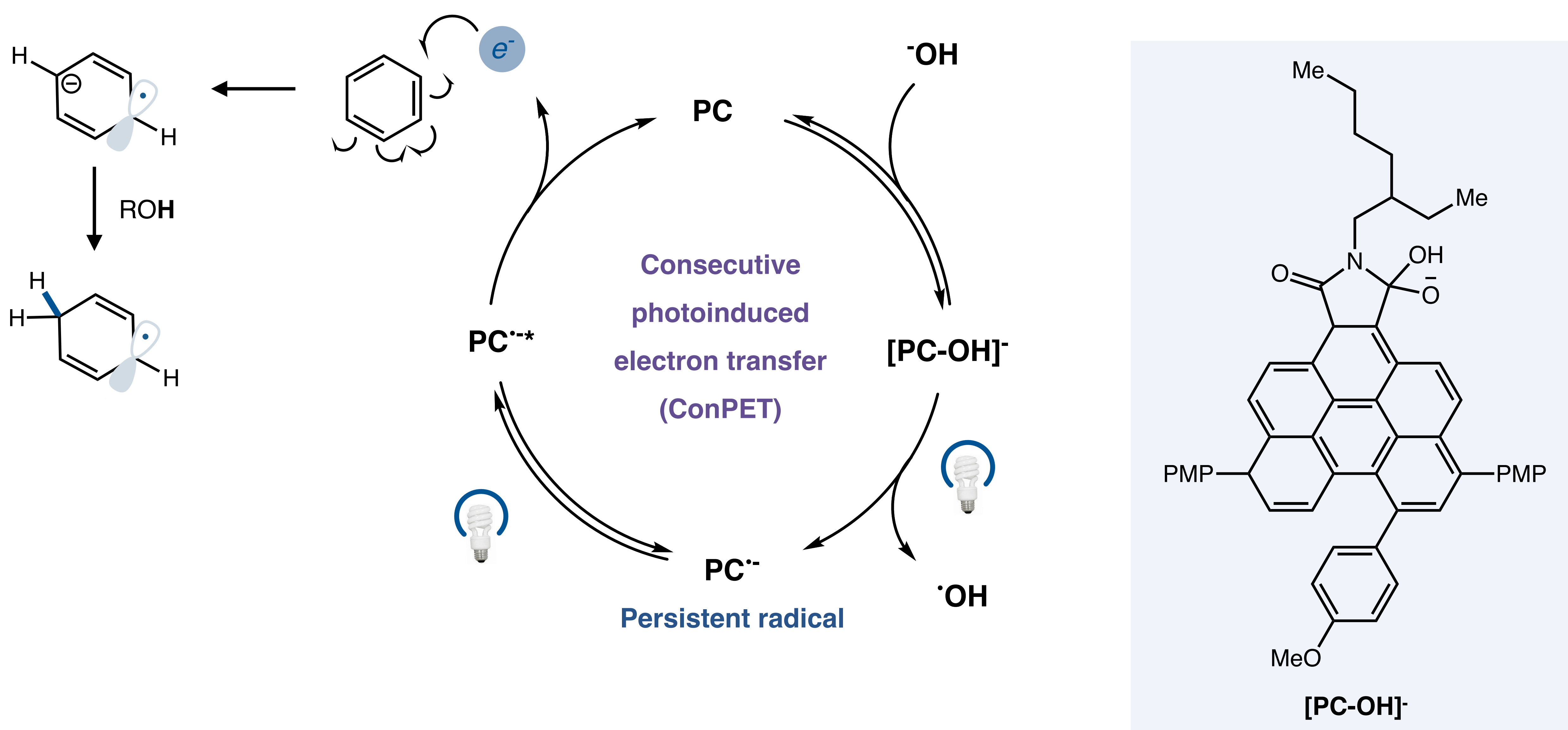

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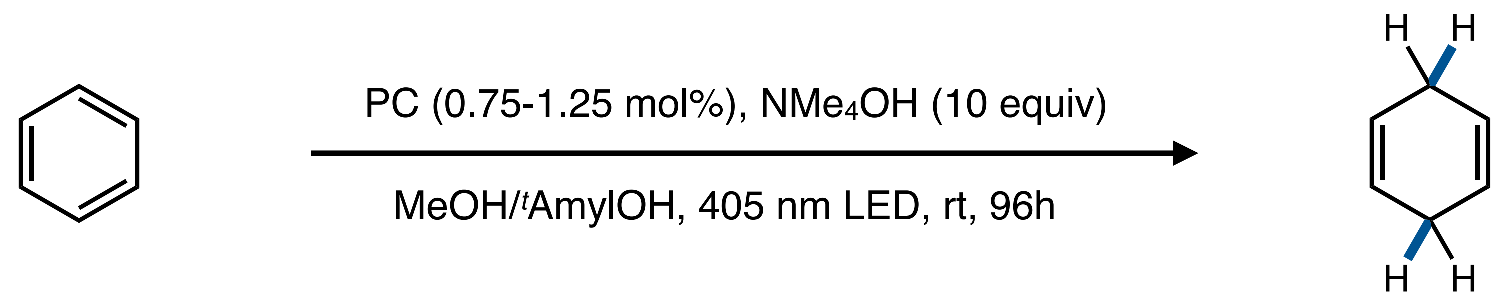

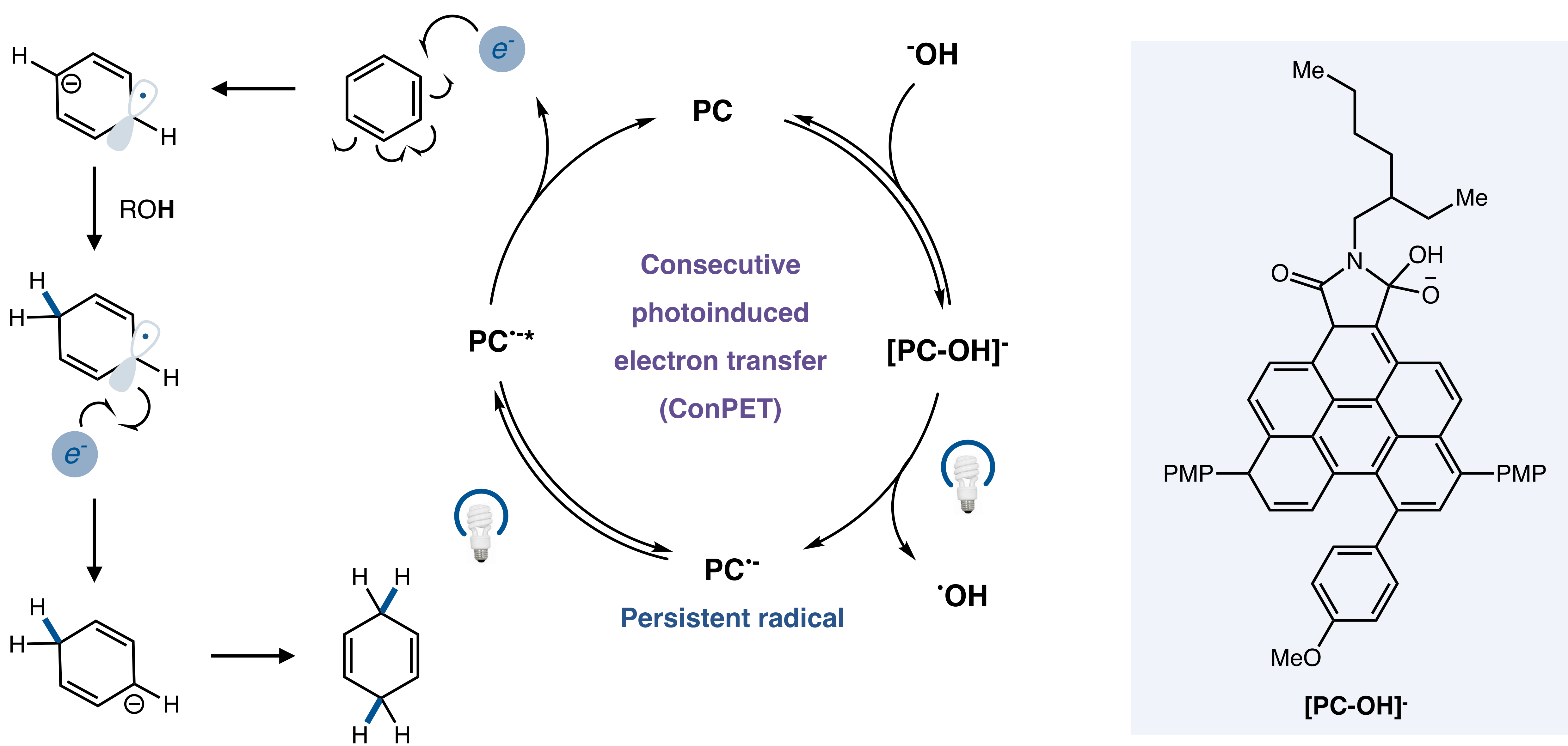

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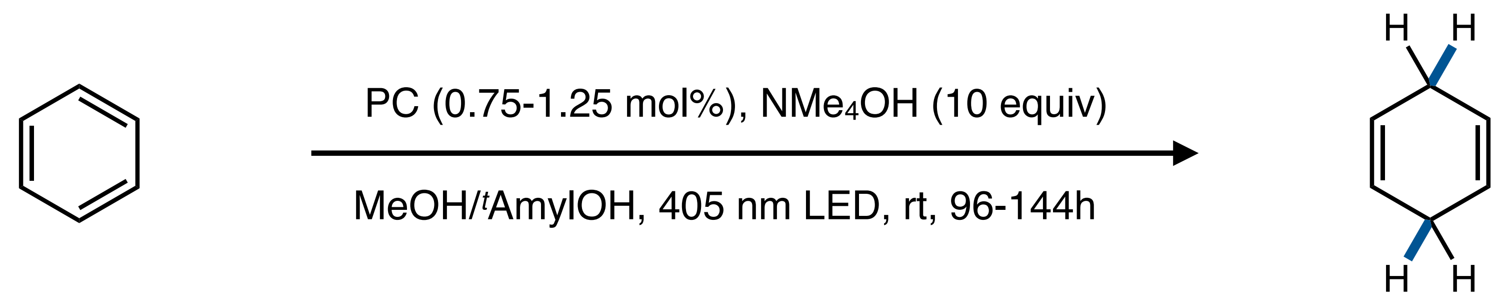

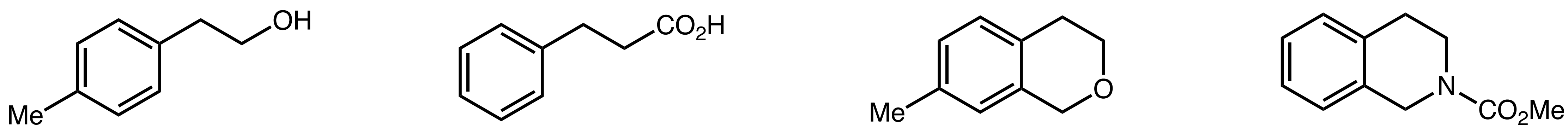

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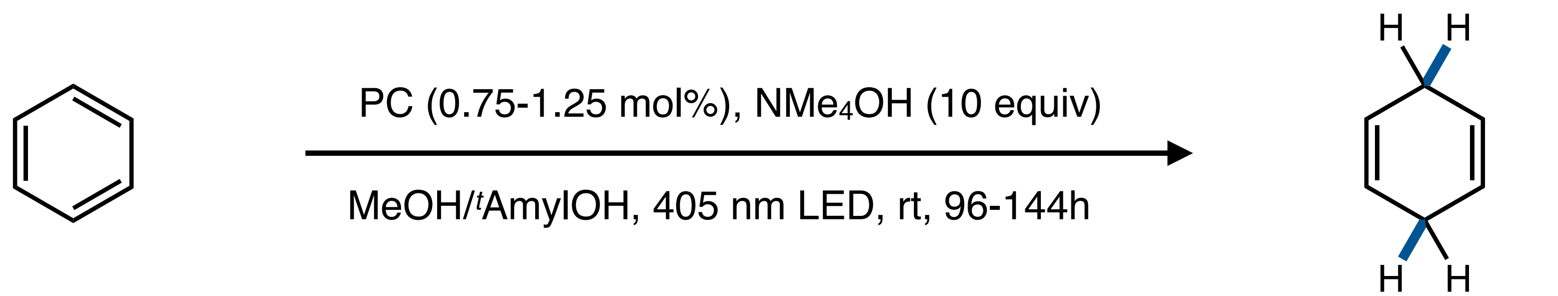
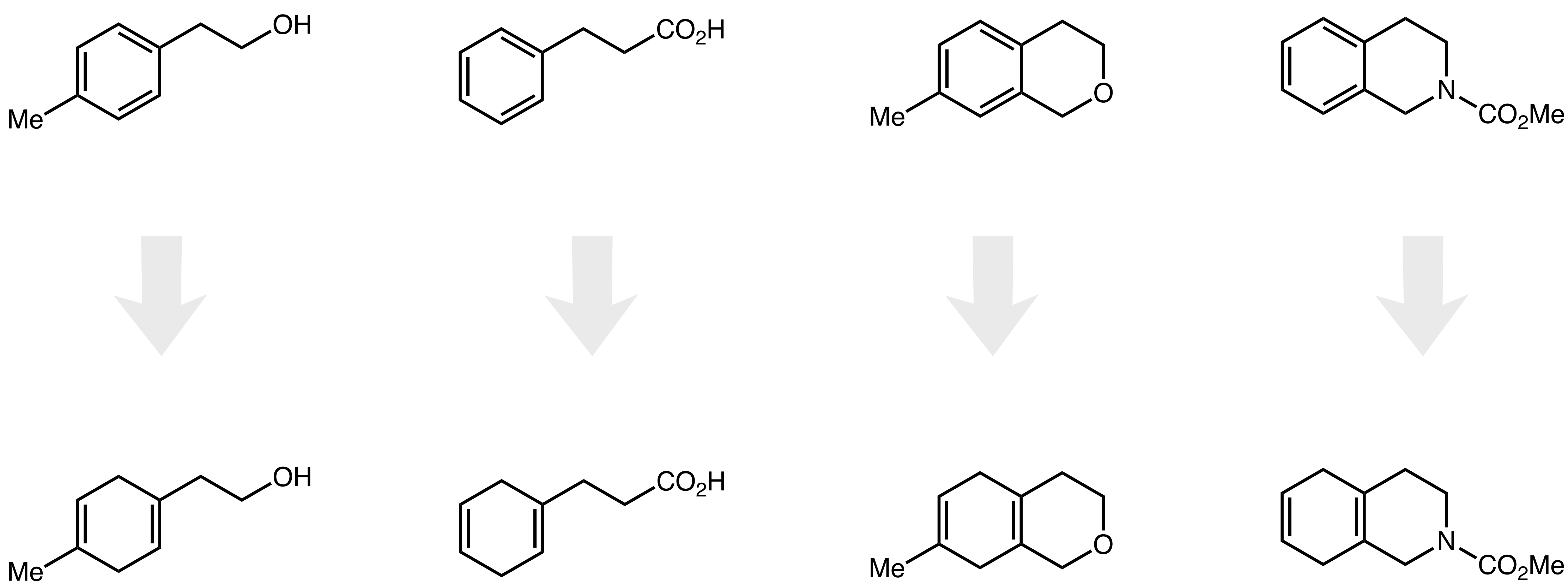




48% yield | **63% yield** | **72% yield** | **40% yield**

Cole, J. P.; Chen, D. F.; Kudisch, M.; Pearson, R. M.; Lim, C. H.; Miyake, G. M. *J Am Chem Soc* **2020**, *142* (31), 13573-13581.

Outline

Radical approach

Traditional radical generation

Birch & SmI_2

Radical addition

Single electron transfer

Oxidation

Reduction

Photochemical

Direct excitation

Energy transfer

Sensitization

Transition-metal

η^2

Mediated

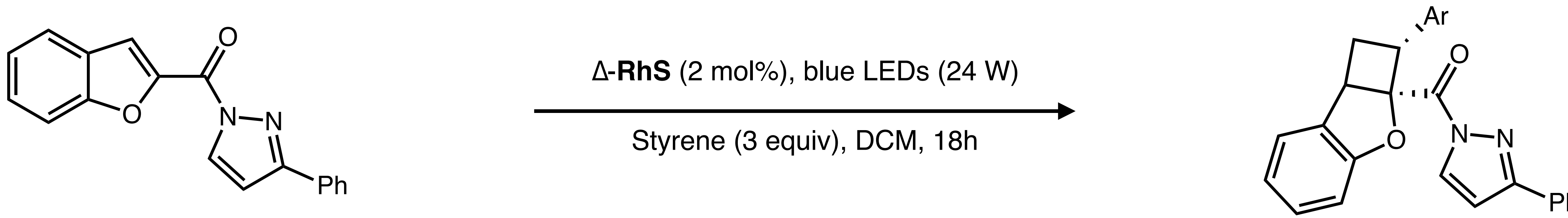
η^6

Catalyzed

Pd

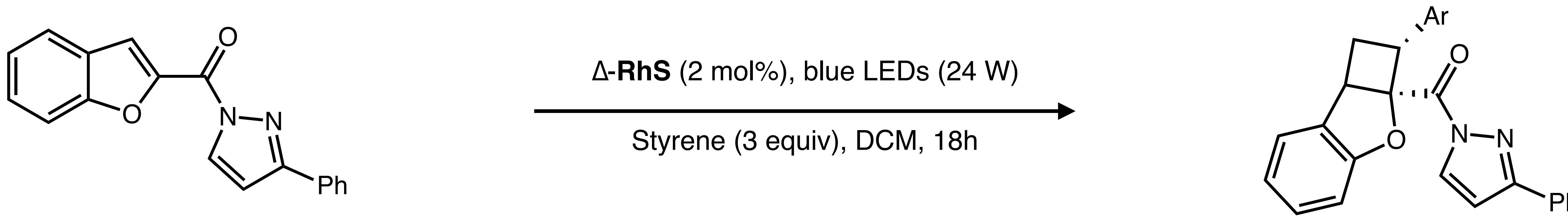
Radical Approach to Dearomatization

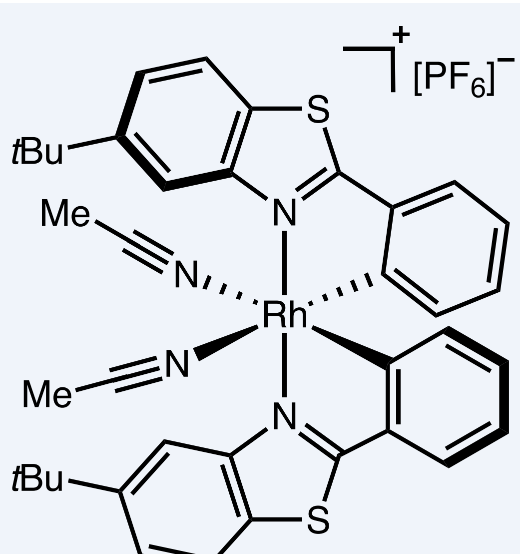
Photochemistry via visible light - energy transfer - direct excitation



Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation

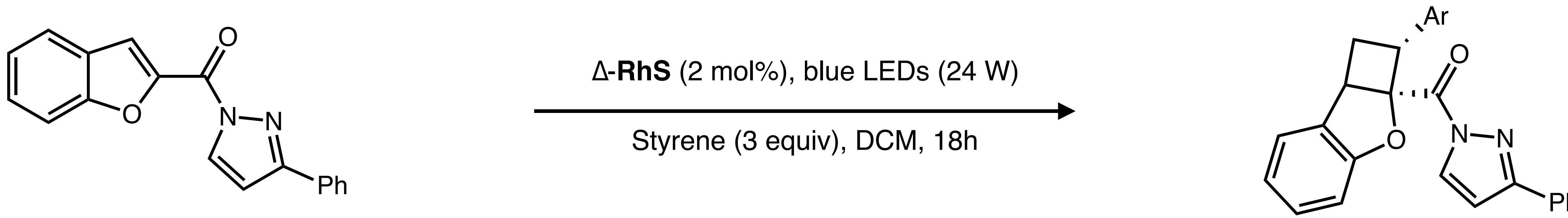


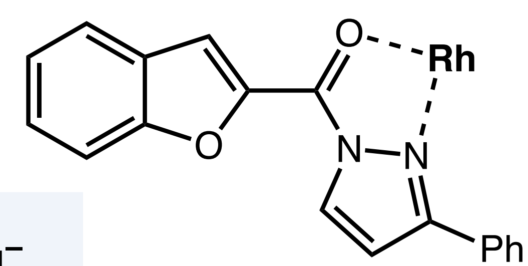


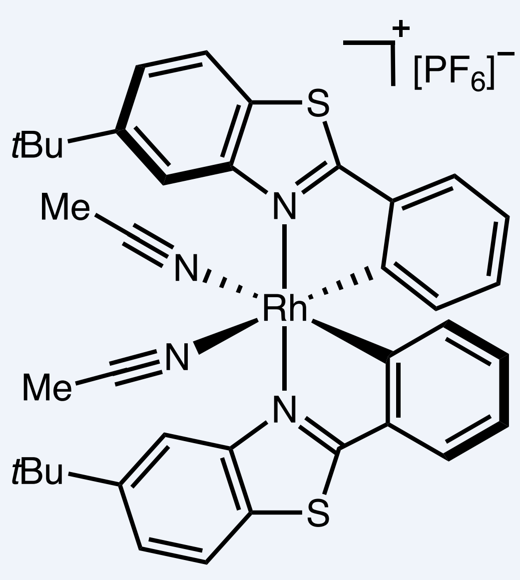
Δ-**RhS**

Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



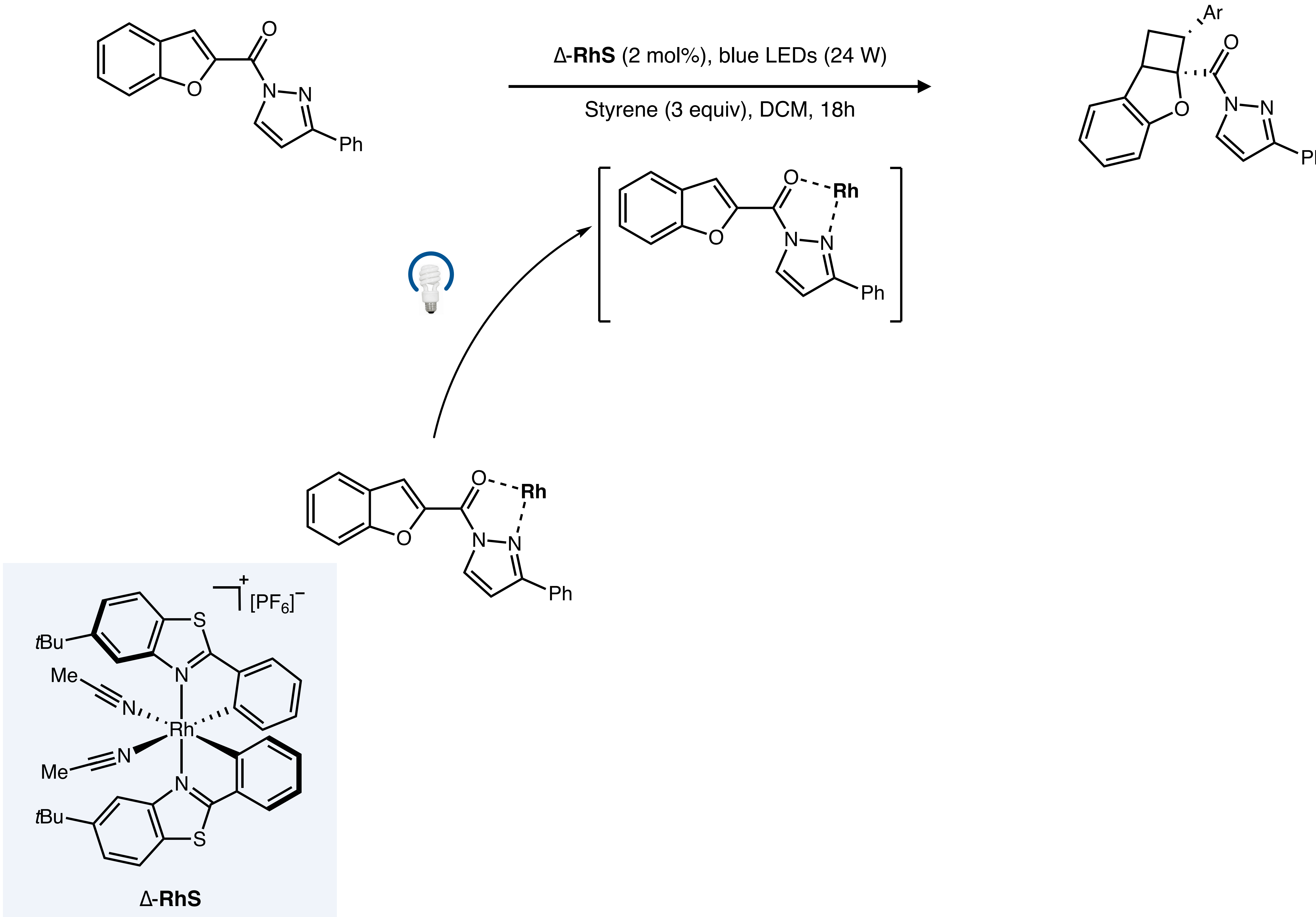




Δ-RhS

Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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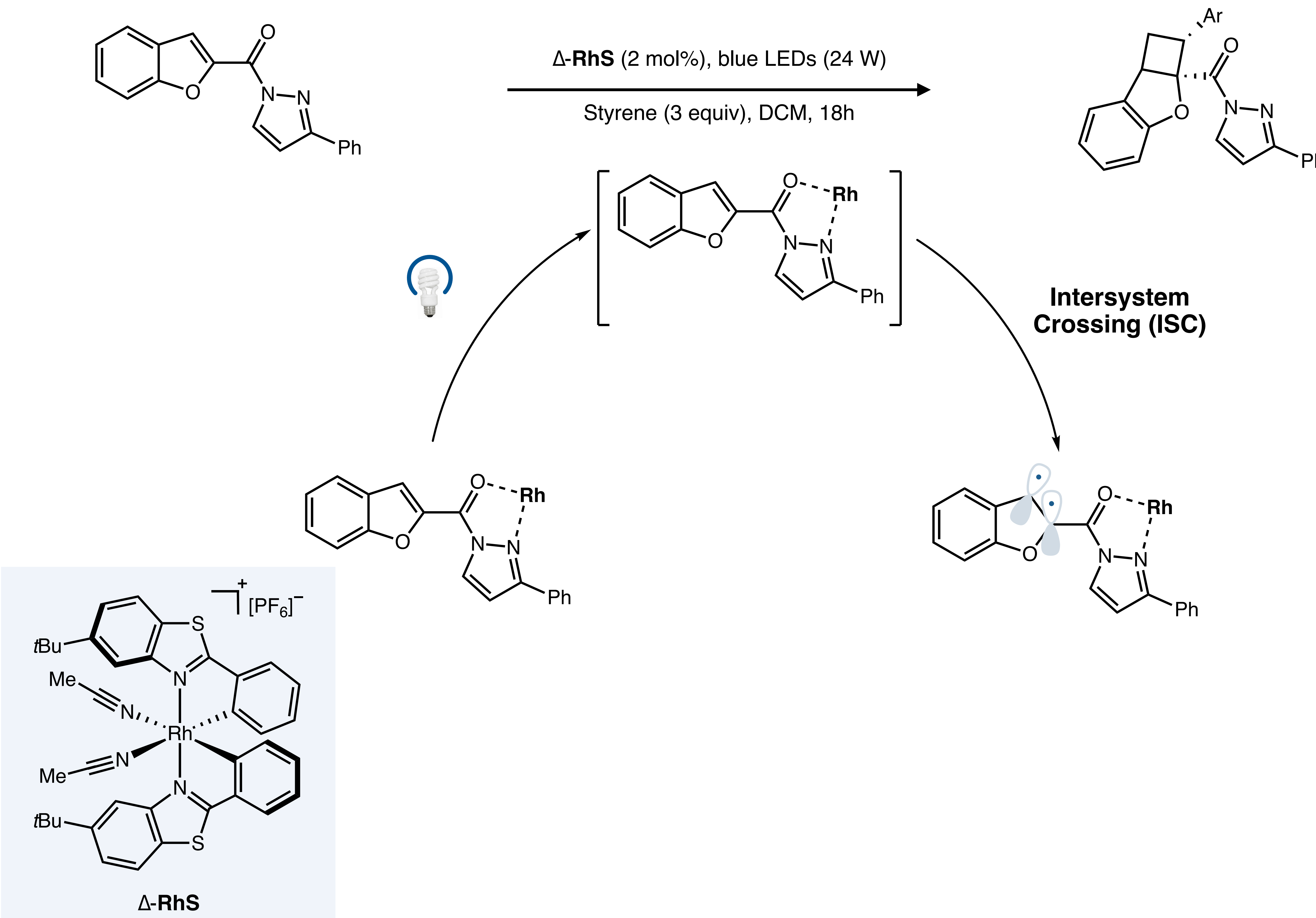
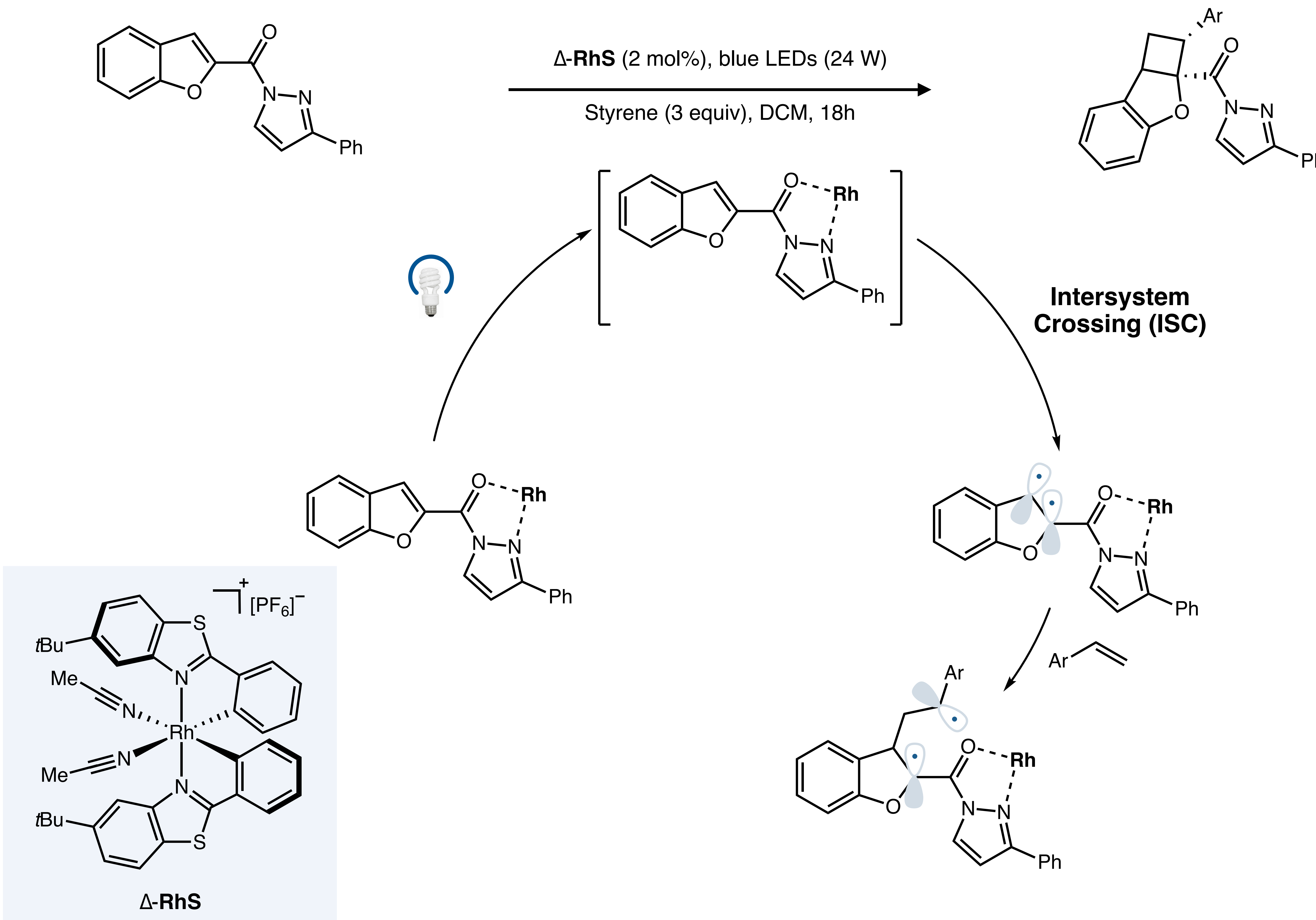
Photochemistry via visible light - energy transfer - direct excitation



Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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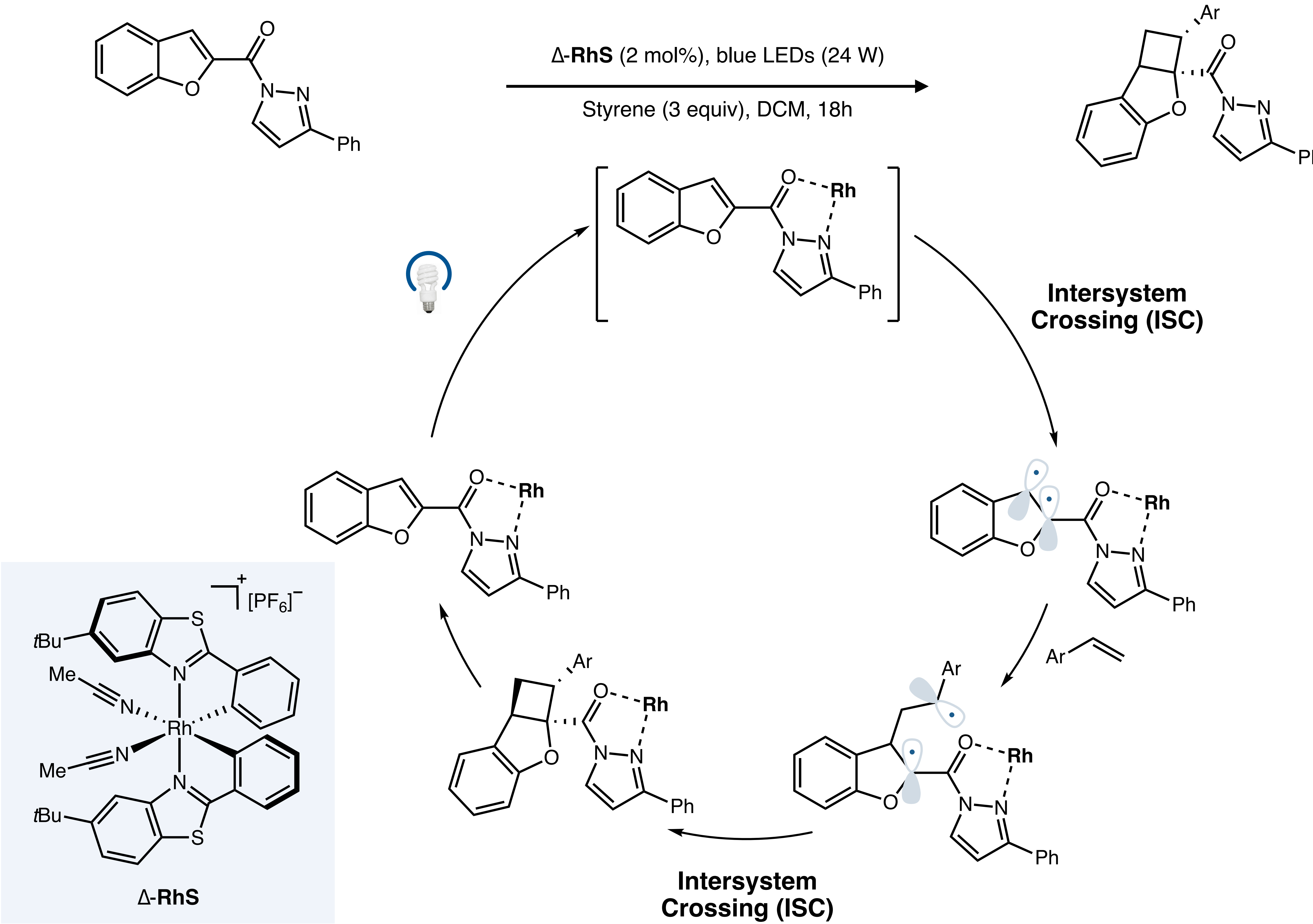
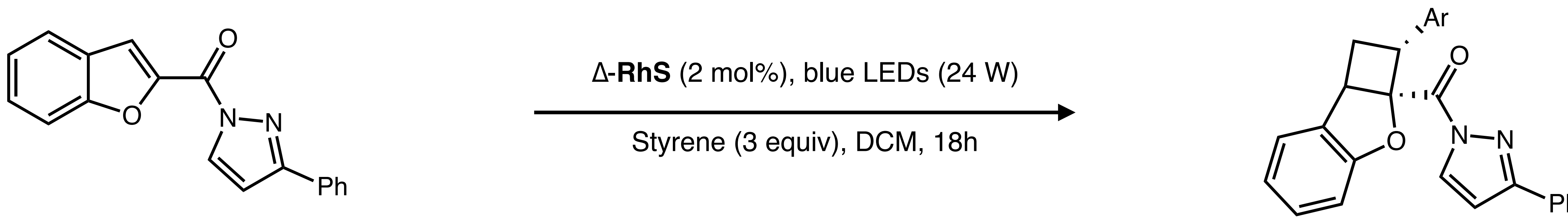
Photochemistry via visible light - energy transfer - direct excitation



Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation

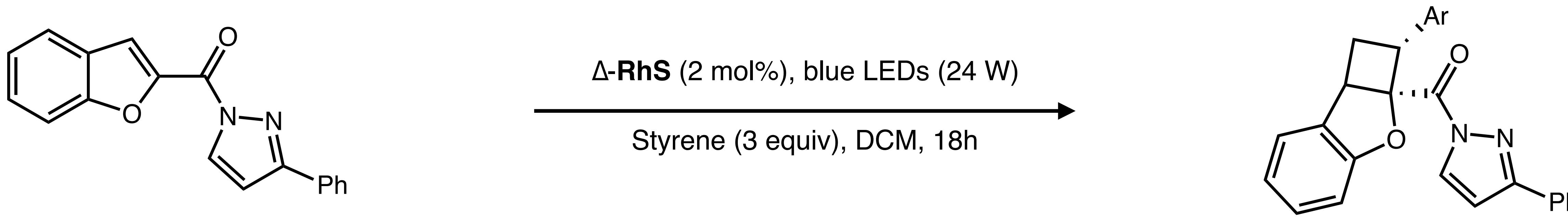


- Regioselectivity

Hu, N.; Jung, H.; Zheng, Y.; Lee, J.; Zhang, L.; Ullah, Z.; Xie, X.; Harms, K.; Baik, M. H.; Meggers, E. *Angew Chem Int Ed Engl* **2018**, *57* (21), 6242-6246.

Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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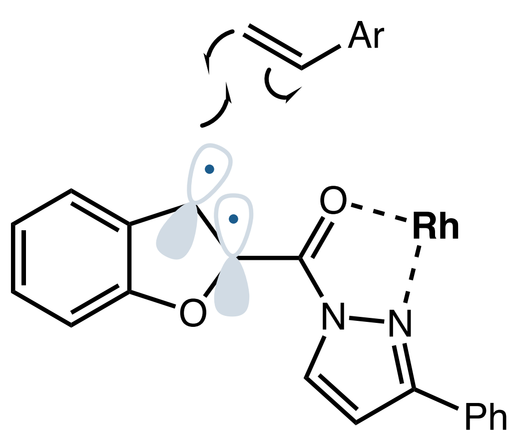

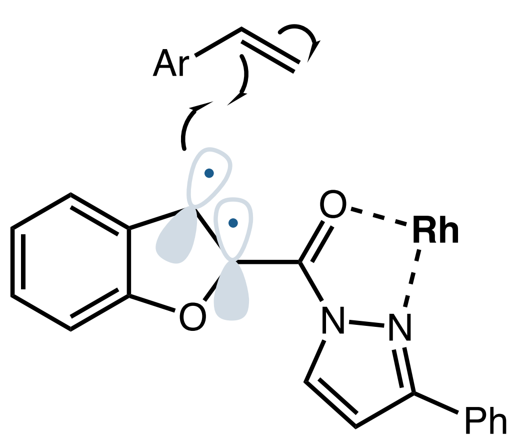

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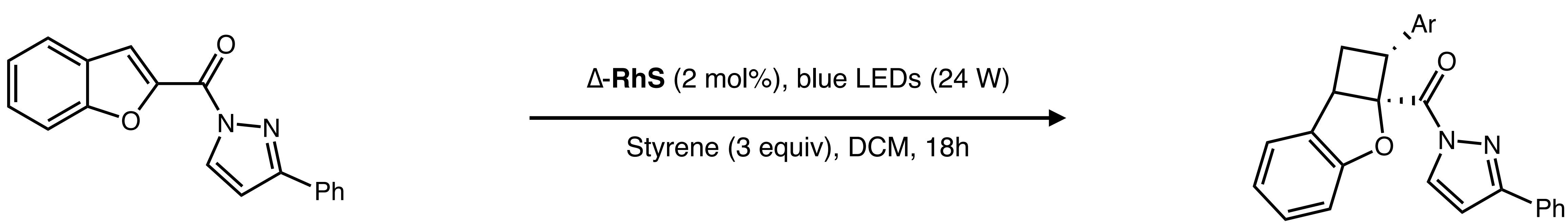
Photochemistry via visible light - energy transfer - direct excitation



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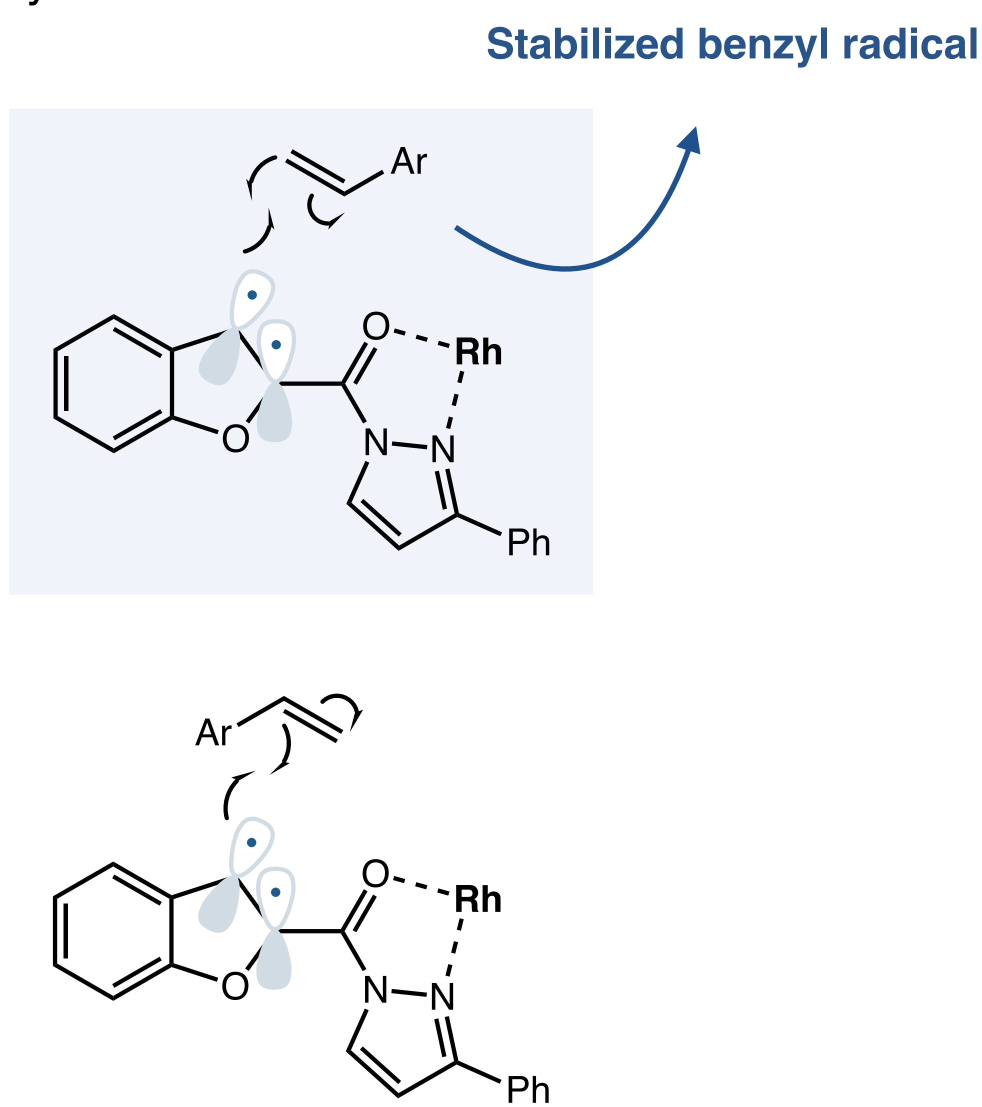

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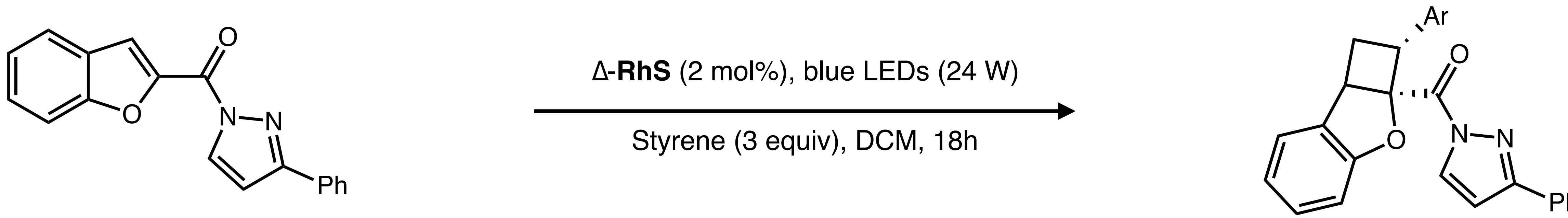

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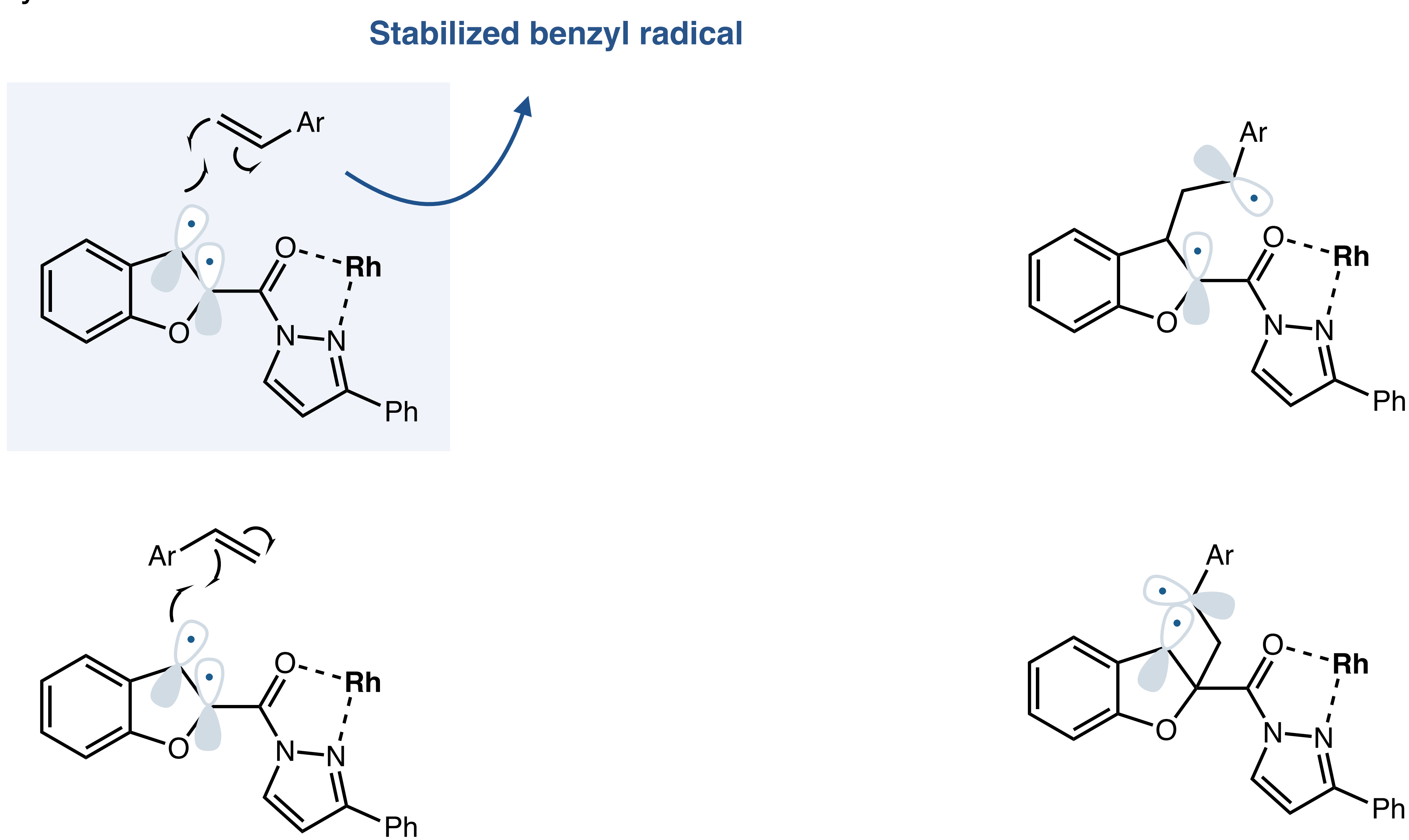

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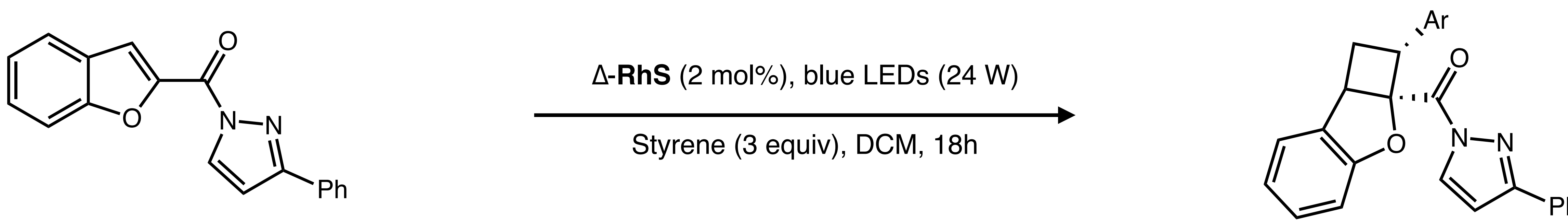

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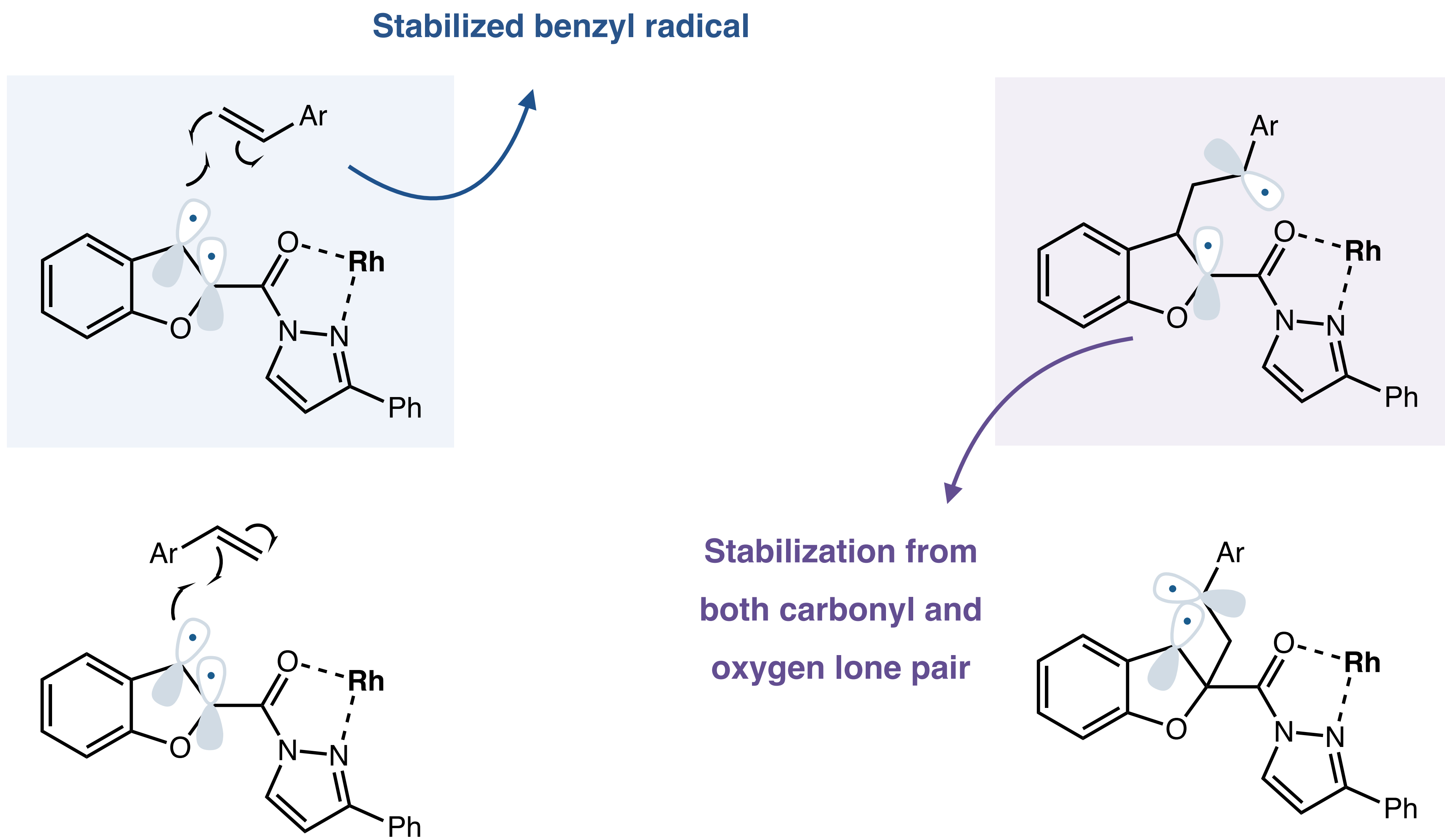

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Radical Approach to Dearomatization

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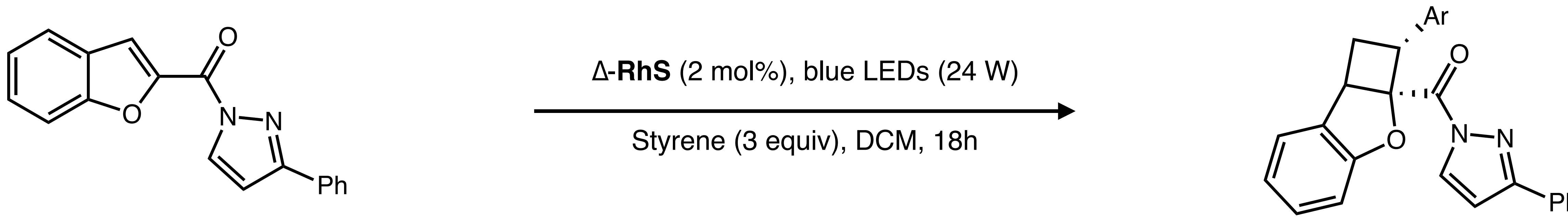

- Stereoselectivity

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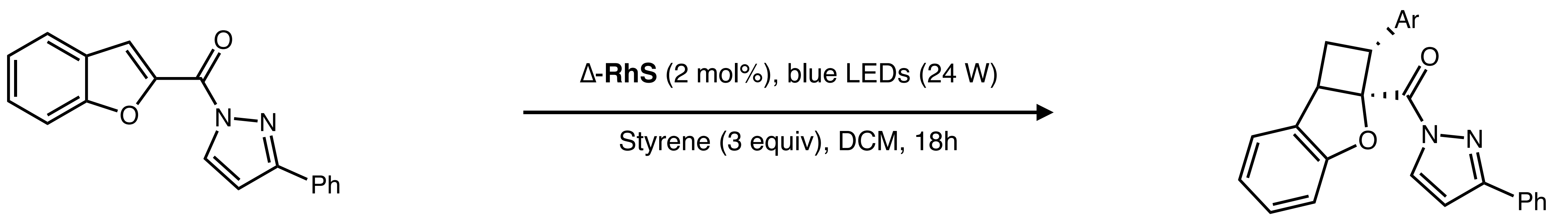
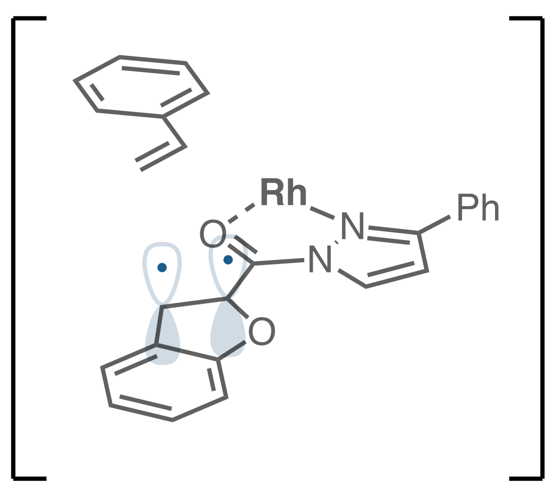


- Stereoselectivity



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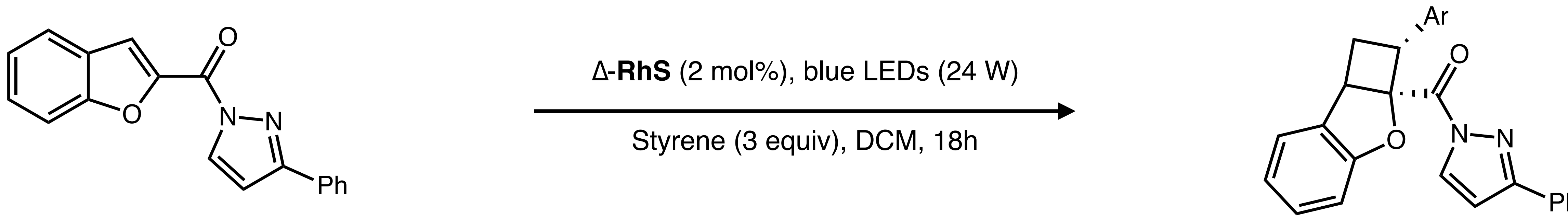

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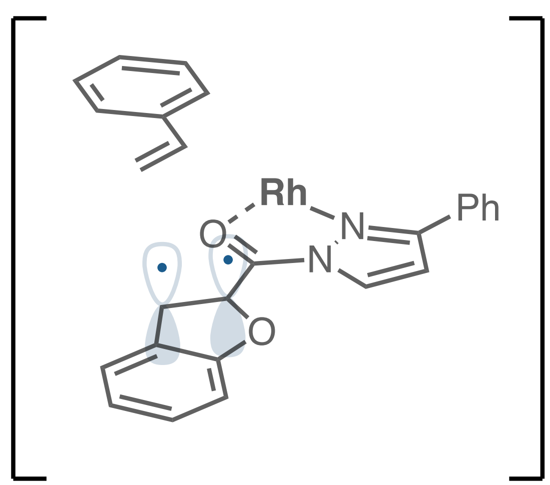

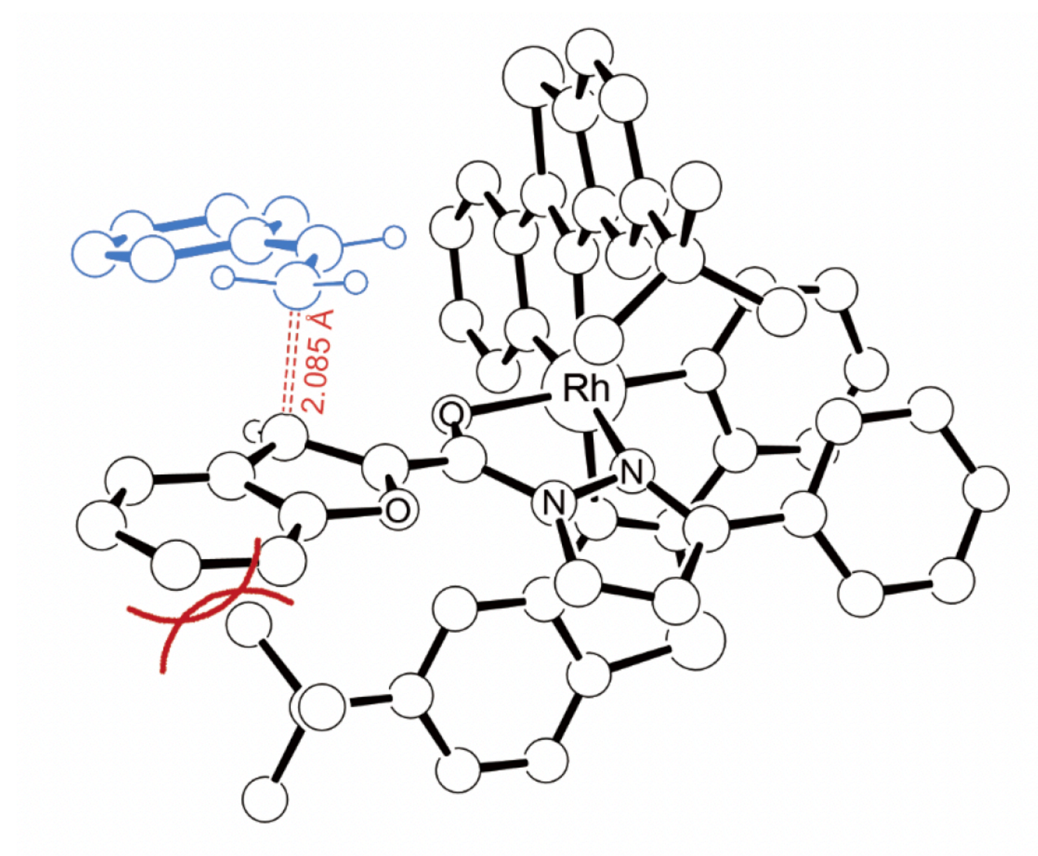

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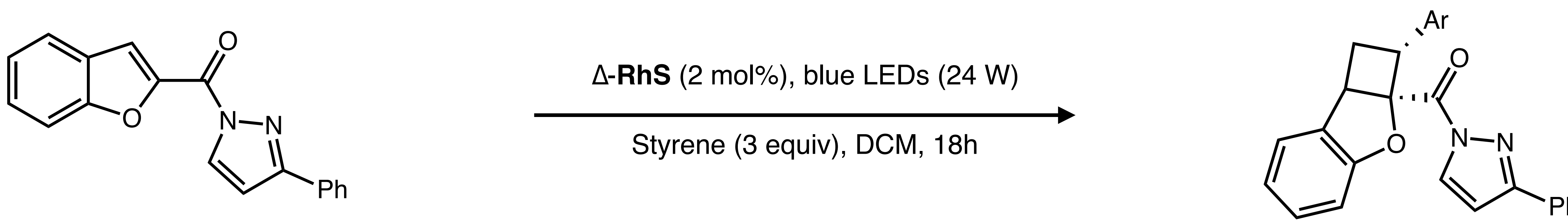
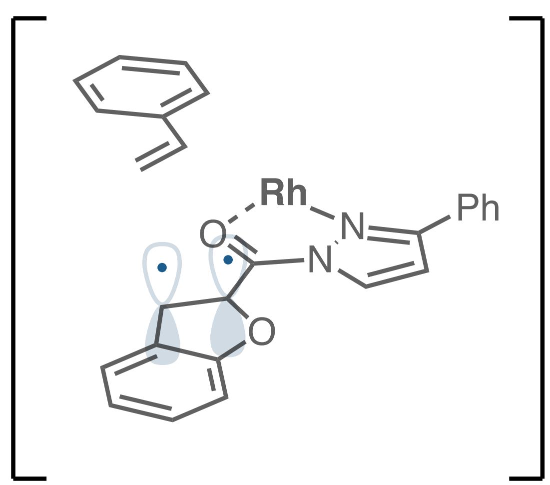
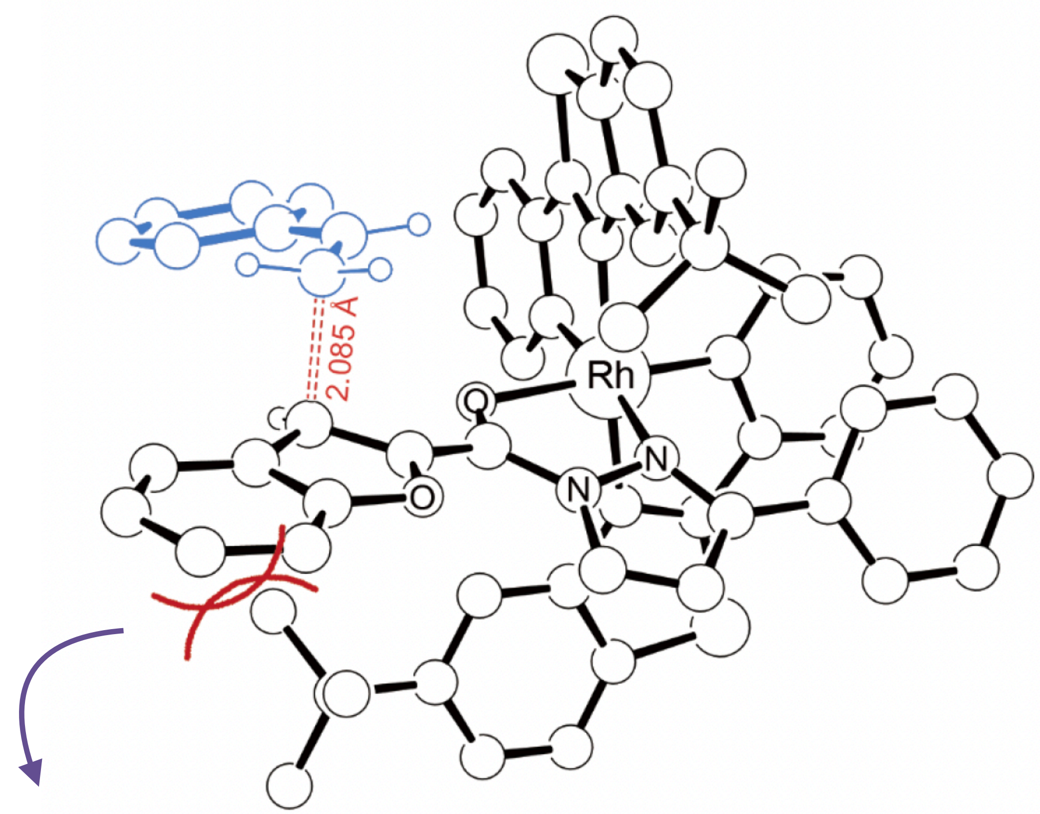


■ Stereoselectivity



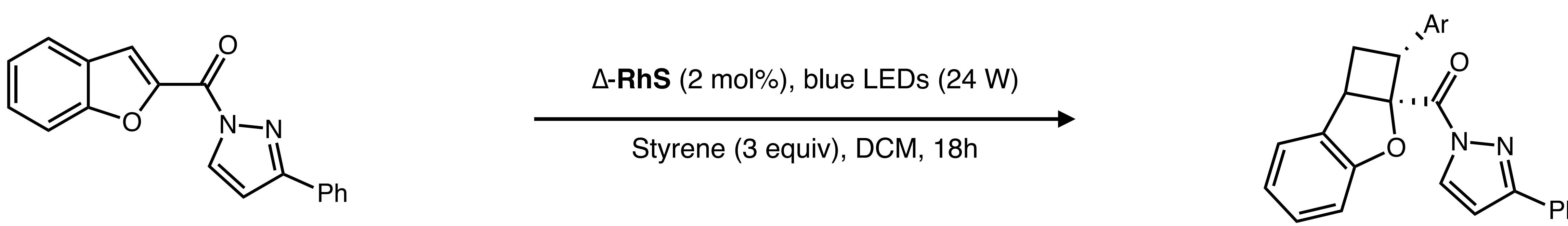


Blocking the attack from the bottom side

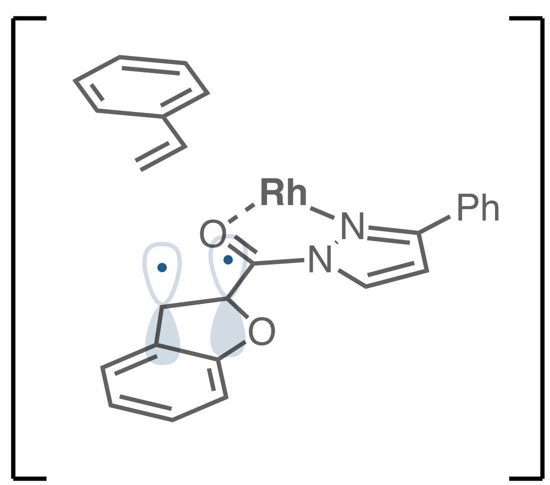
Hu, N.; Jung, H.; Zheng, Y.; Lee, J.; Zhang, L.; Ullah, Z.; Xie, X.; Harms, K.; Baik, M. H.; Meggers, E. *Angew Chem Int Ed Engl* **2018**, *57* (21), 6242-6246.

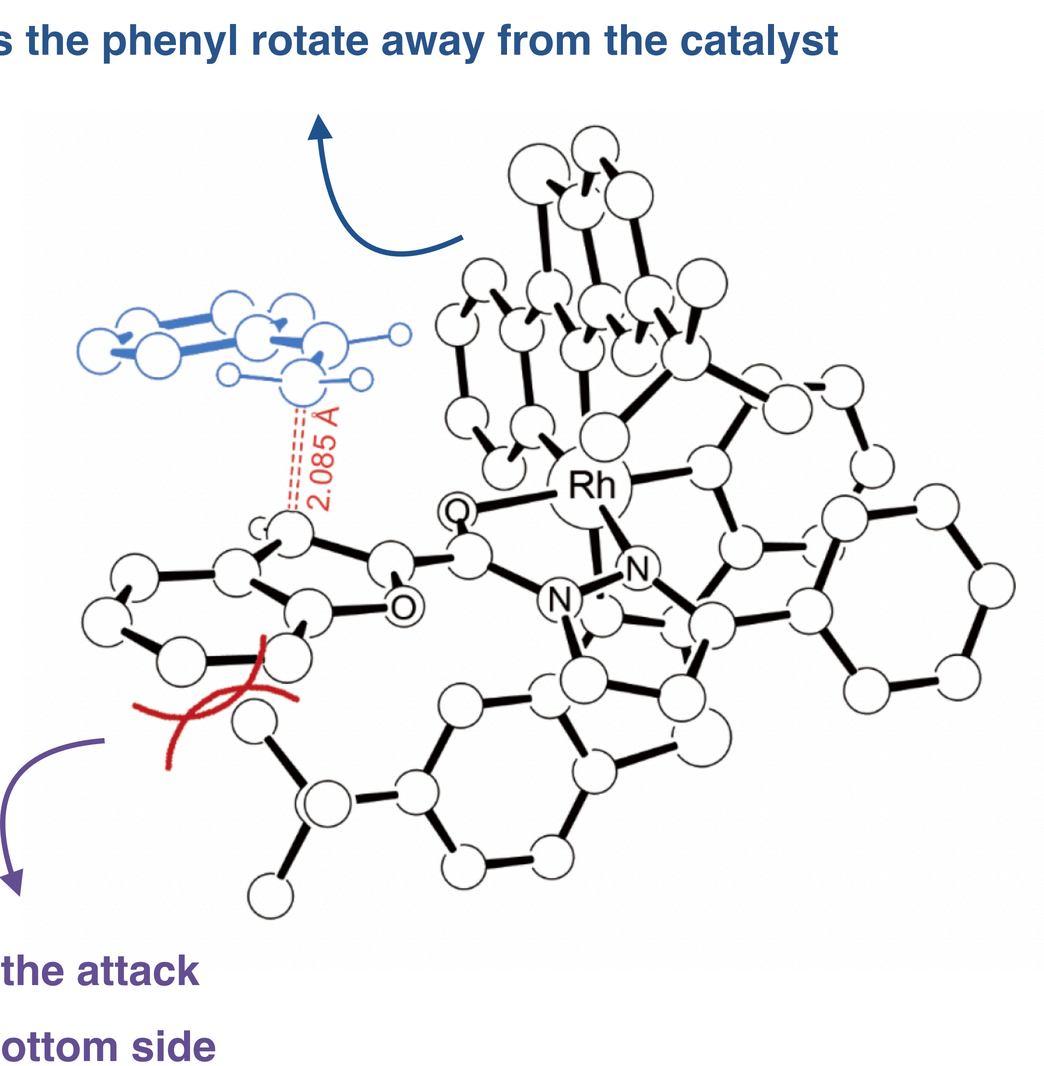
Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



- Stereoselectivity

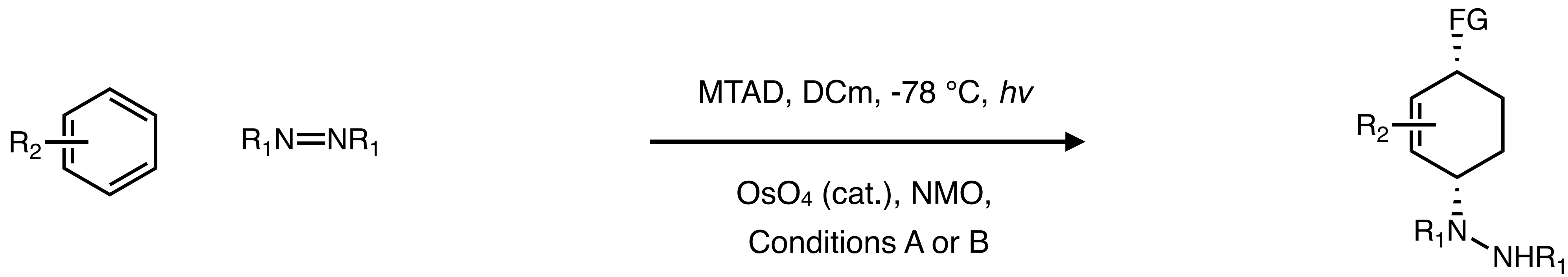




Hu, N.; Jung, H.; Zheng, Y.; Lee, J.; Zhang, L.; Ullah, Z.; Xie, X.; Harms, K.; Baik, M. H.; Meggers, E. *Angew Chem Int Ed Engl* **2018**, *57* (21), 6242-6246.

Radical Approach to Dearomatization

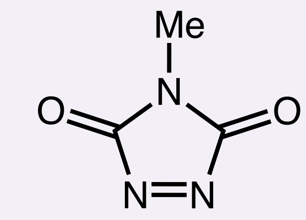
Photochemistry via visible light - energy transfer - direct excitation



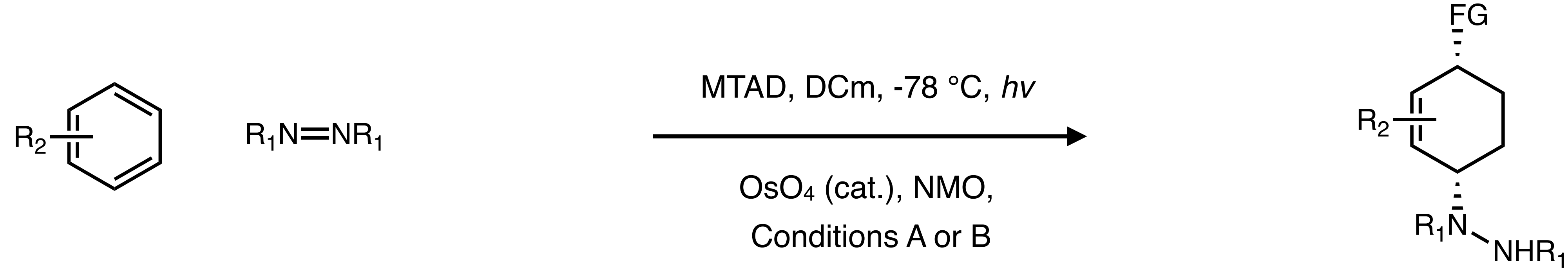
Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. *Nat Chem* **2016**, *8* (10), 922-928.

Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



MTAD



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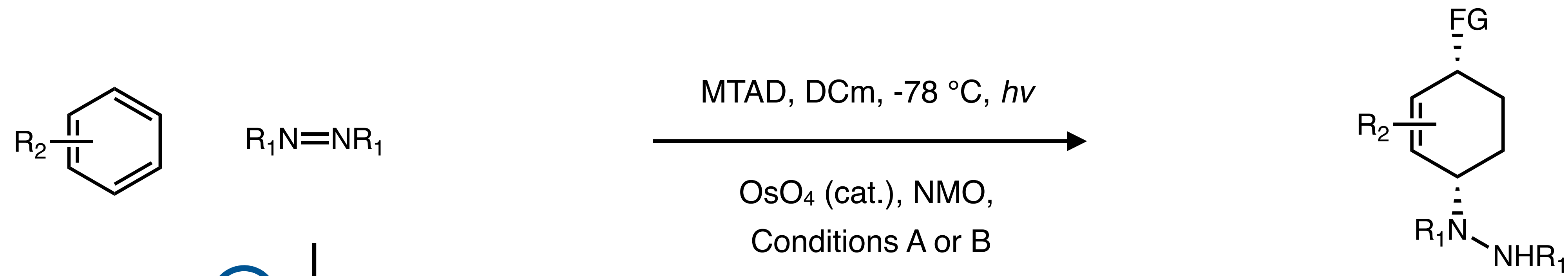
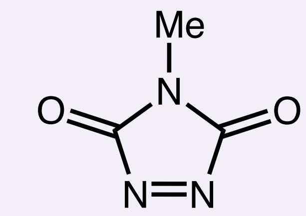
Radical Approach to Dearomatization

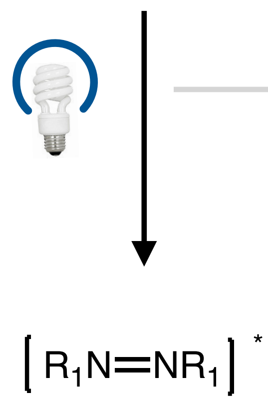
Photochemistry via visible light - energy transfer - direct excitation





MTAD

■ Mechanism



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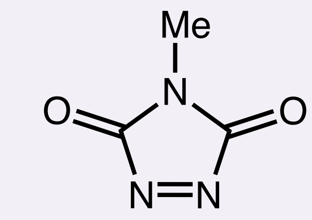
Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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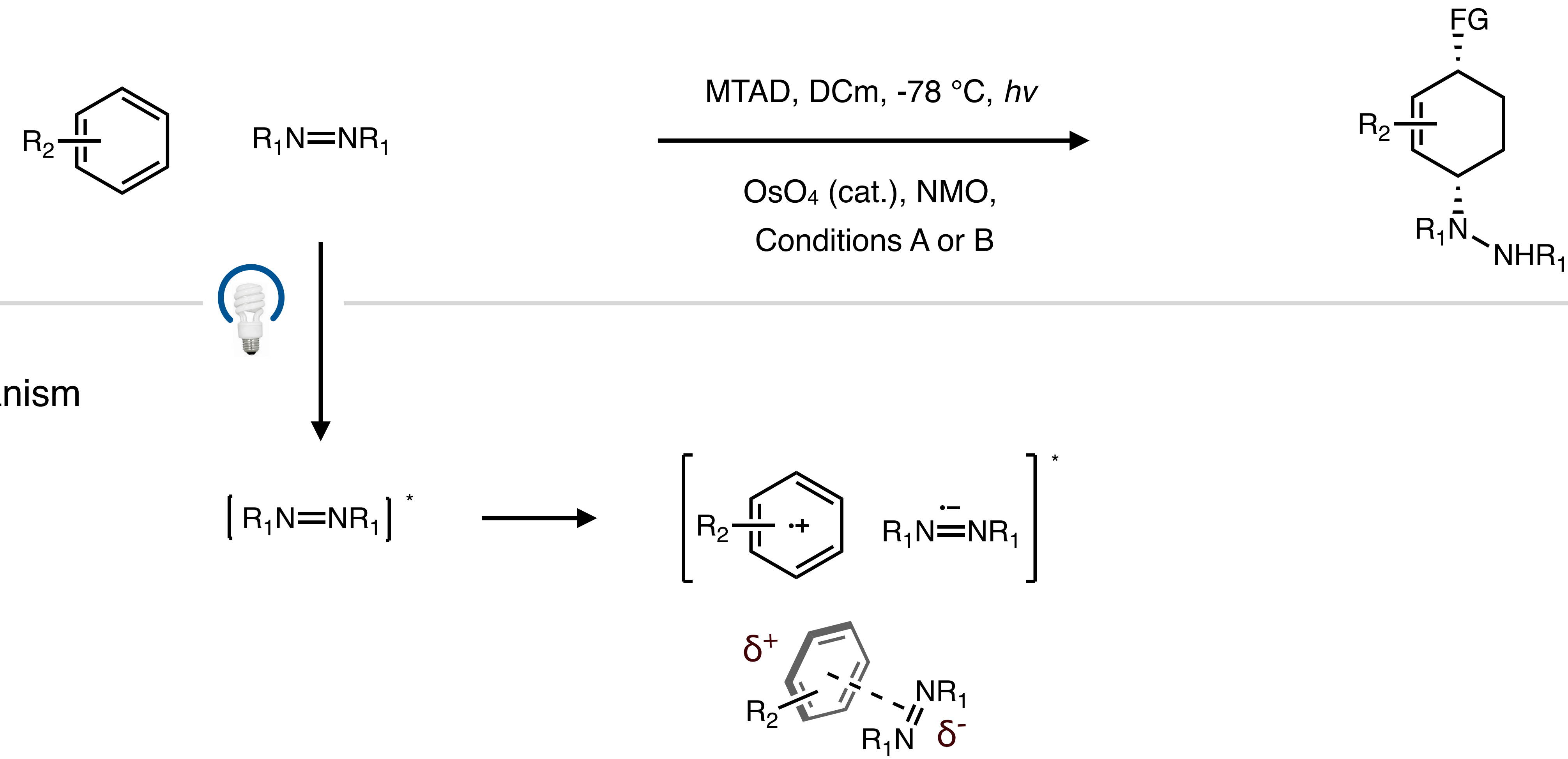

- Mechanism

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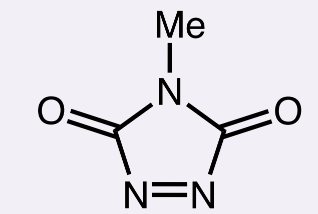
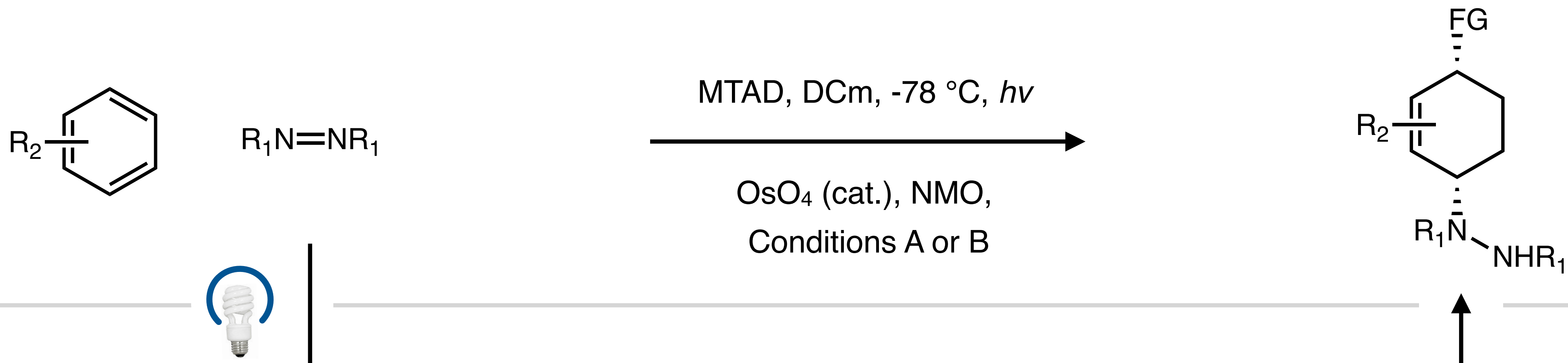
Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



MTAD



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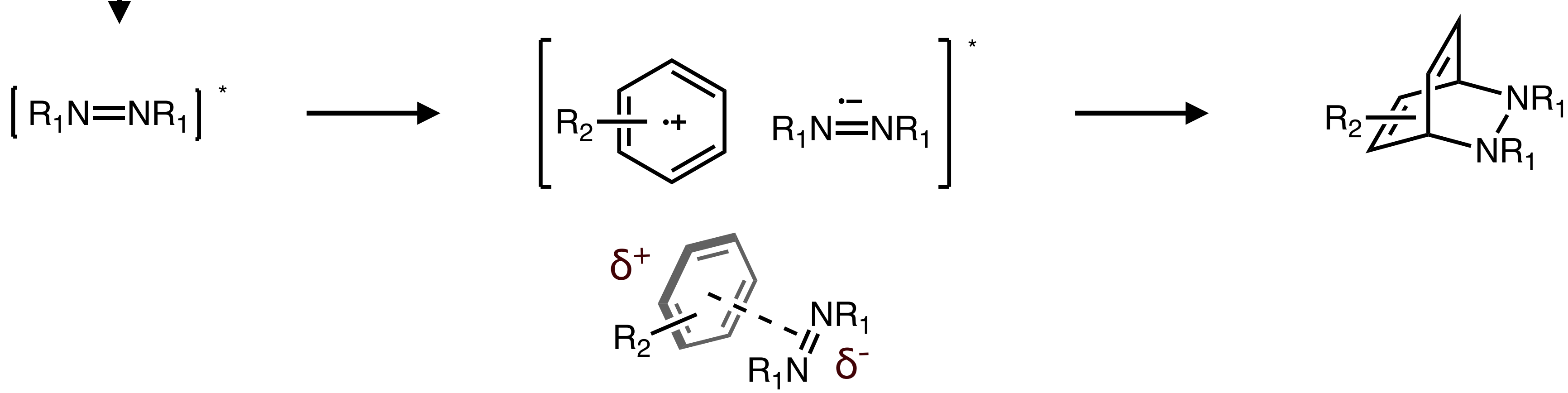

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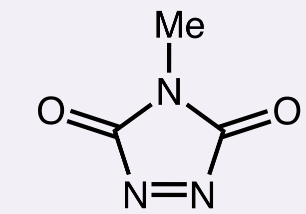
Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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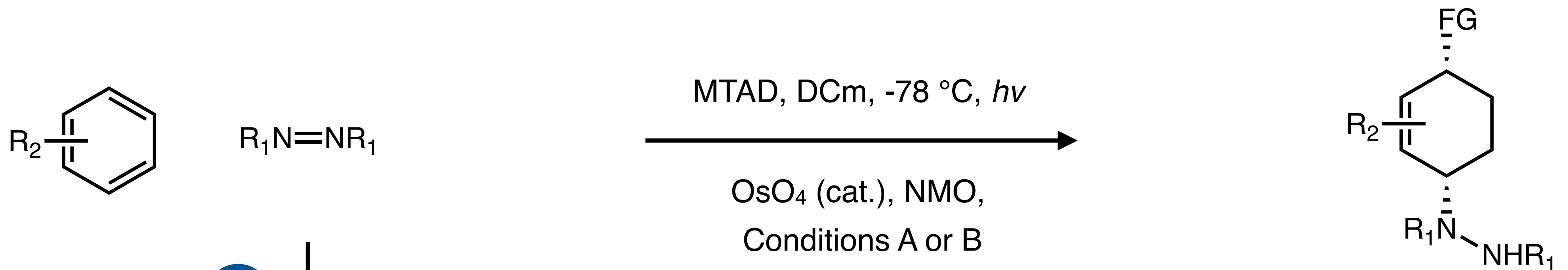

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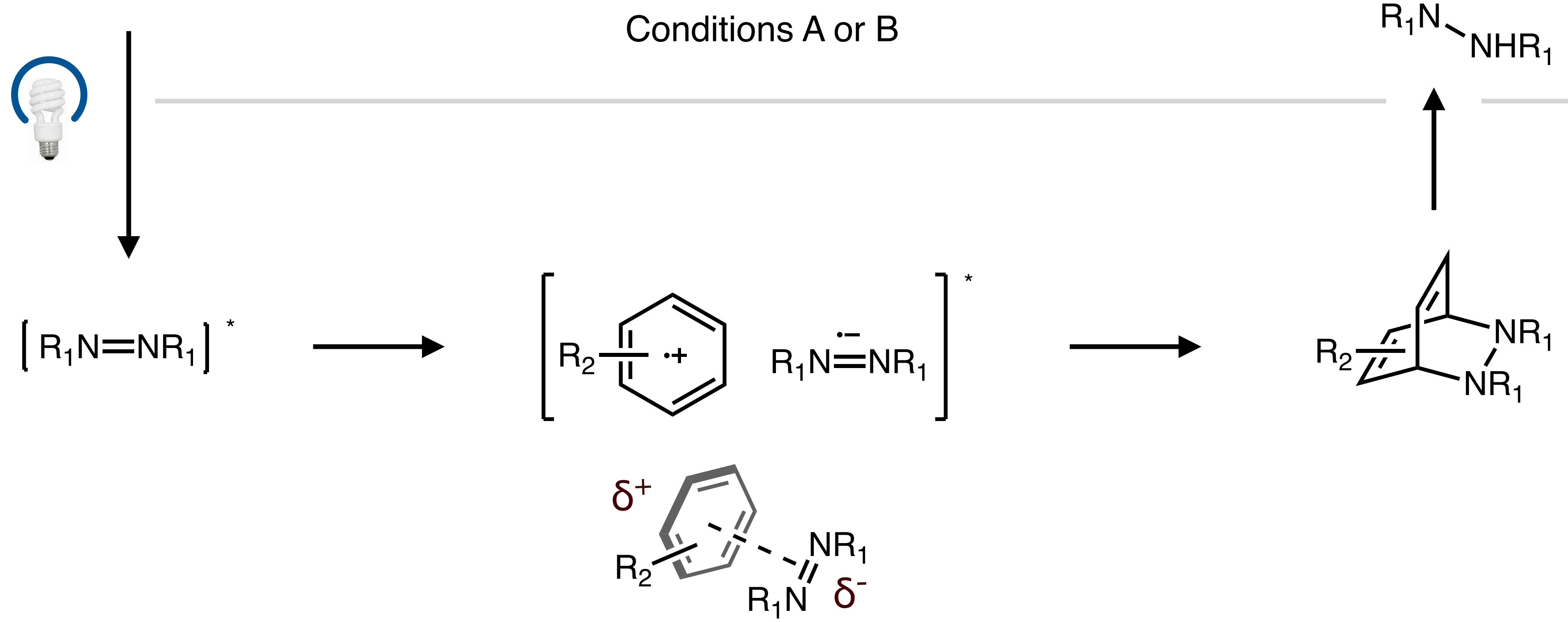

- Versatile functionalization

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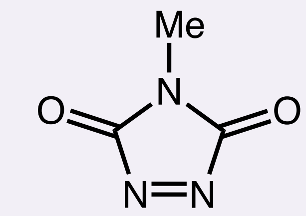
Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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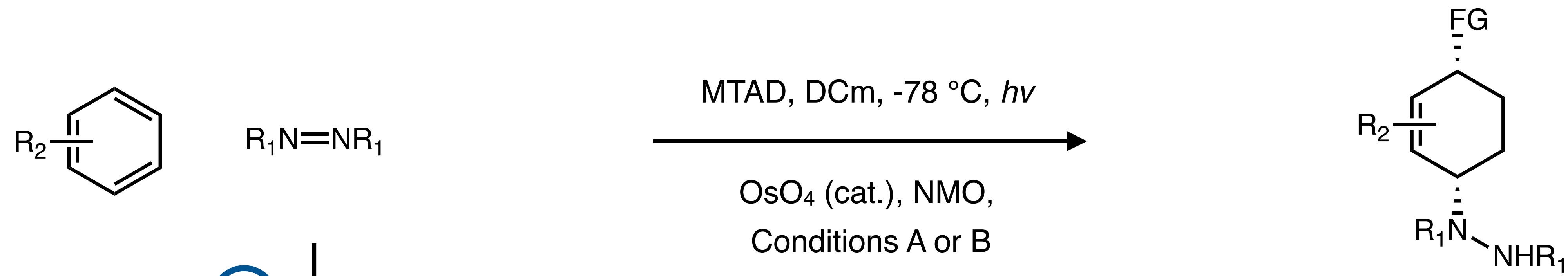

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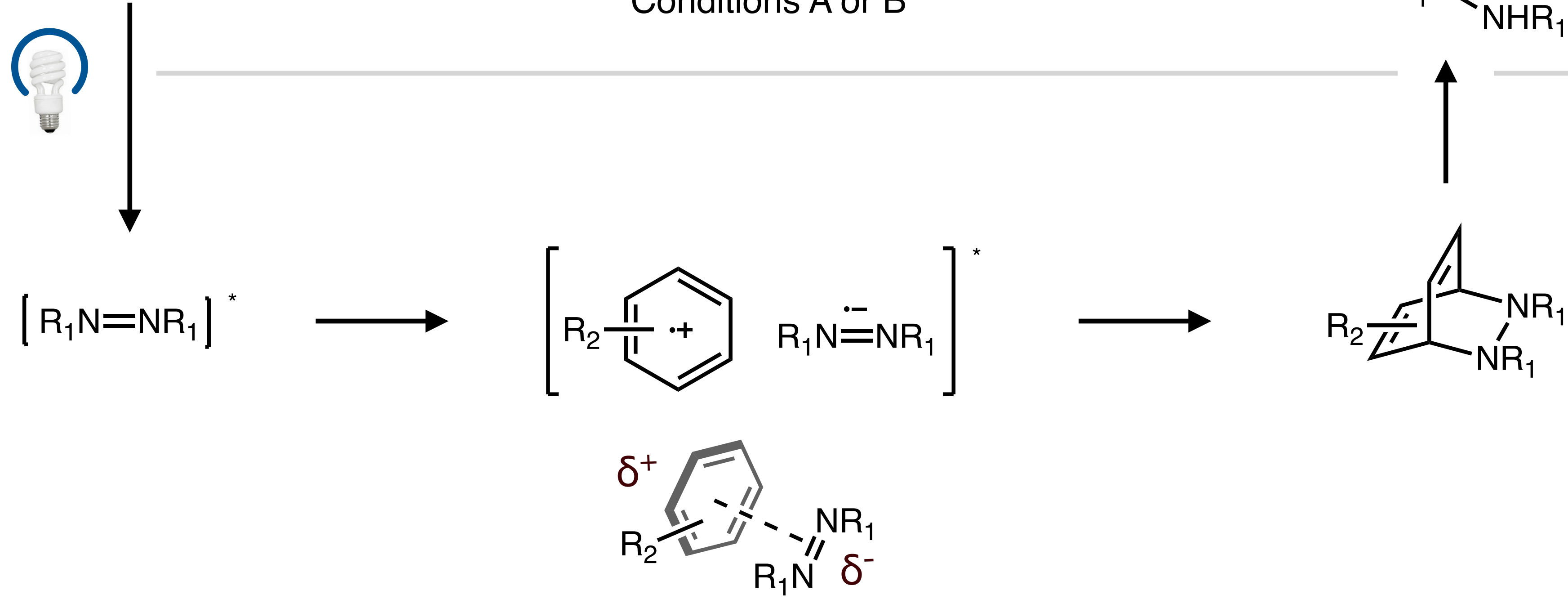
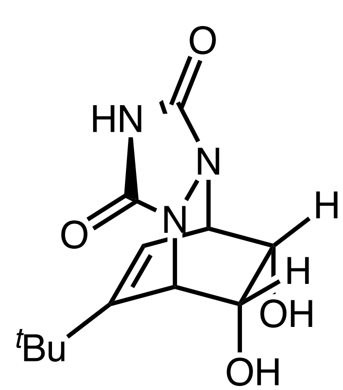


■ Versatile functionalization

Conditions A

p-TsNH$_2$, H$_2$O,

acetone, -78 °C to rt

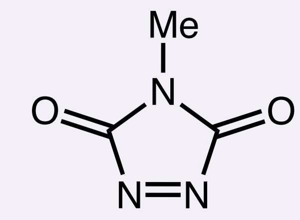


70% yield

Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. *Nat Chem* **2016**, *8* (10), 922-928.

Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - direct excitation



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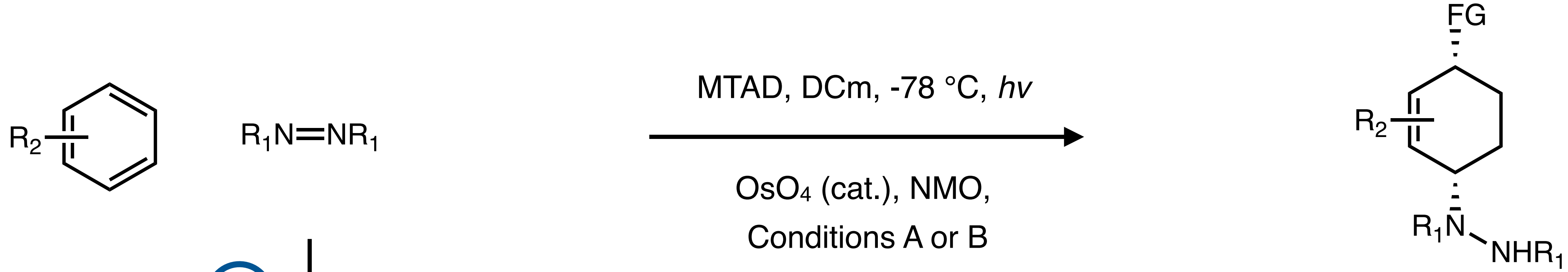
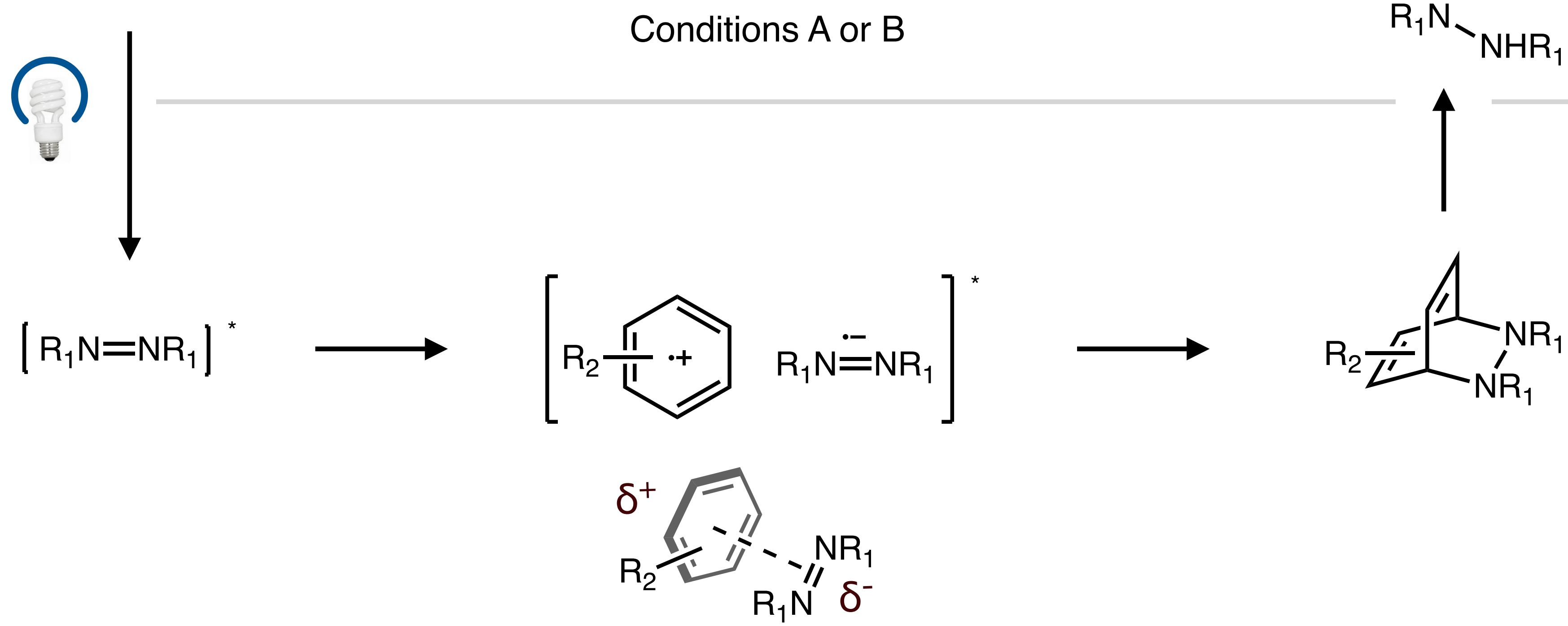


■ Mechanism



■ Versatile functionalization

Conditions A

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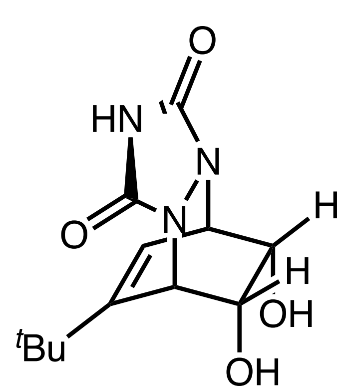
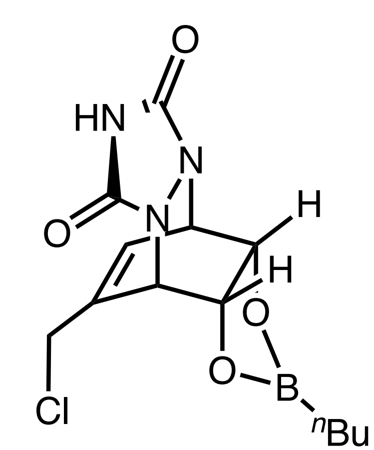


70% yield

Conditions B

^{n}BuB(OH)$_2$, DCM

-78 °C to rt



64% yield

Southgate, E. H.; Pospech, J.; Fu, J.; Holycross, D. R.; Sarlah, D. *Nat Chem* **2016**, *8* (10), 922-928.

Outline

Radical approach

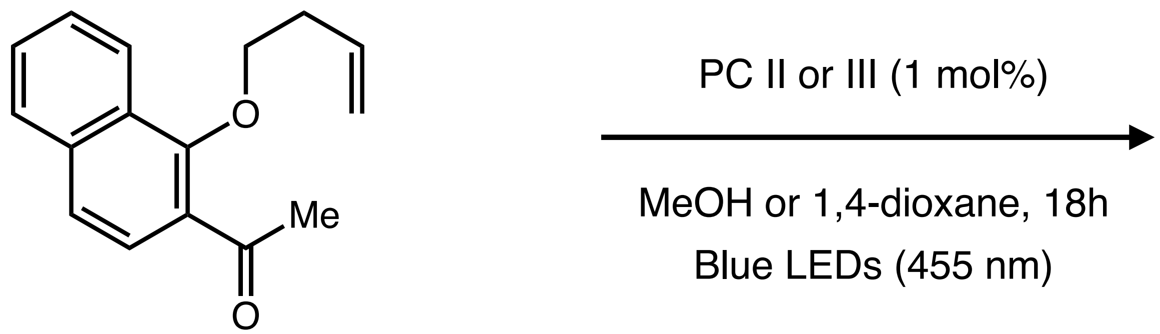
- **Traditional radical generation** — Birch & SmI_2
- **Photochemical**
  - **Single electron transfer**
    - Radical addition
    - Oxidation
    - Reduction
  - **Energy transfer**
    - Direct excitation
    - Sensitization

Transition-metal

- **Mediated**
  - η^2
  - η^6
- **Catalyzed** — *Pd*

Radical Approach to Dearomatization

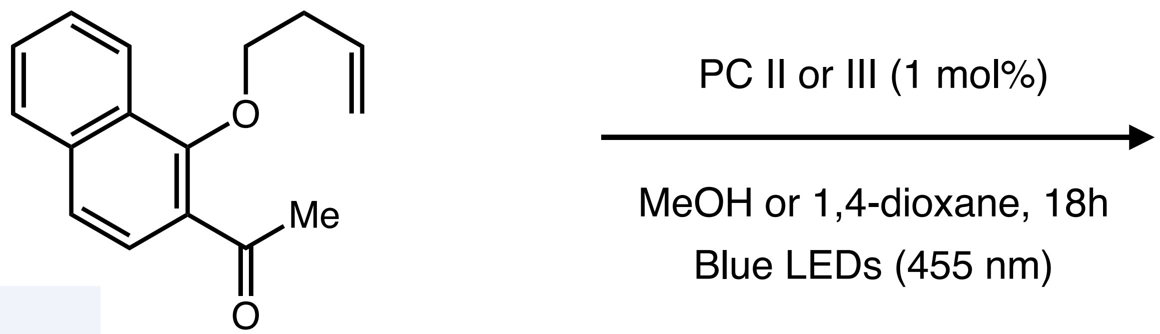
Photochemistry via visible light - energy transfer - sensitization

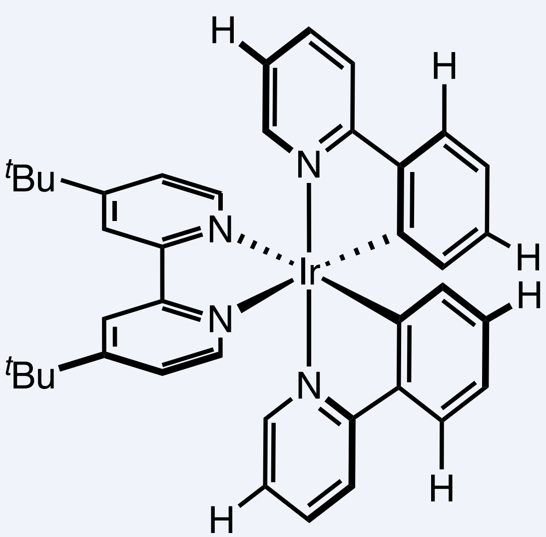


James, M. J.; Schwarz, J. L.; Strieth-Kalthoff, F.; Wibbeling, B.; Glorius, F. *J Am Chem Soc* **2018**, *140* (28), 8624-8628.

Radical Approach to Dearomatization

Photochemistry via visible light - energy transfer - sensitization





PC II (E_T 49.2 kcal/mol)

James, M. J.; Schwarz, J. L.; Strieth-Kalthoff, F.; Wibbeling, B.; Glorius, F. *J Am Chem Soc* **2018**, *140* (28), 8624-8628.

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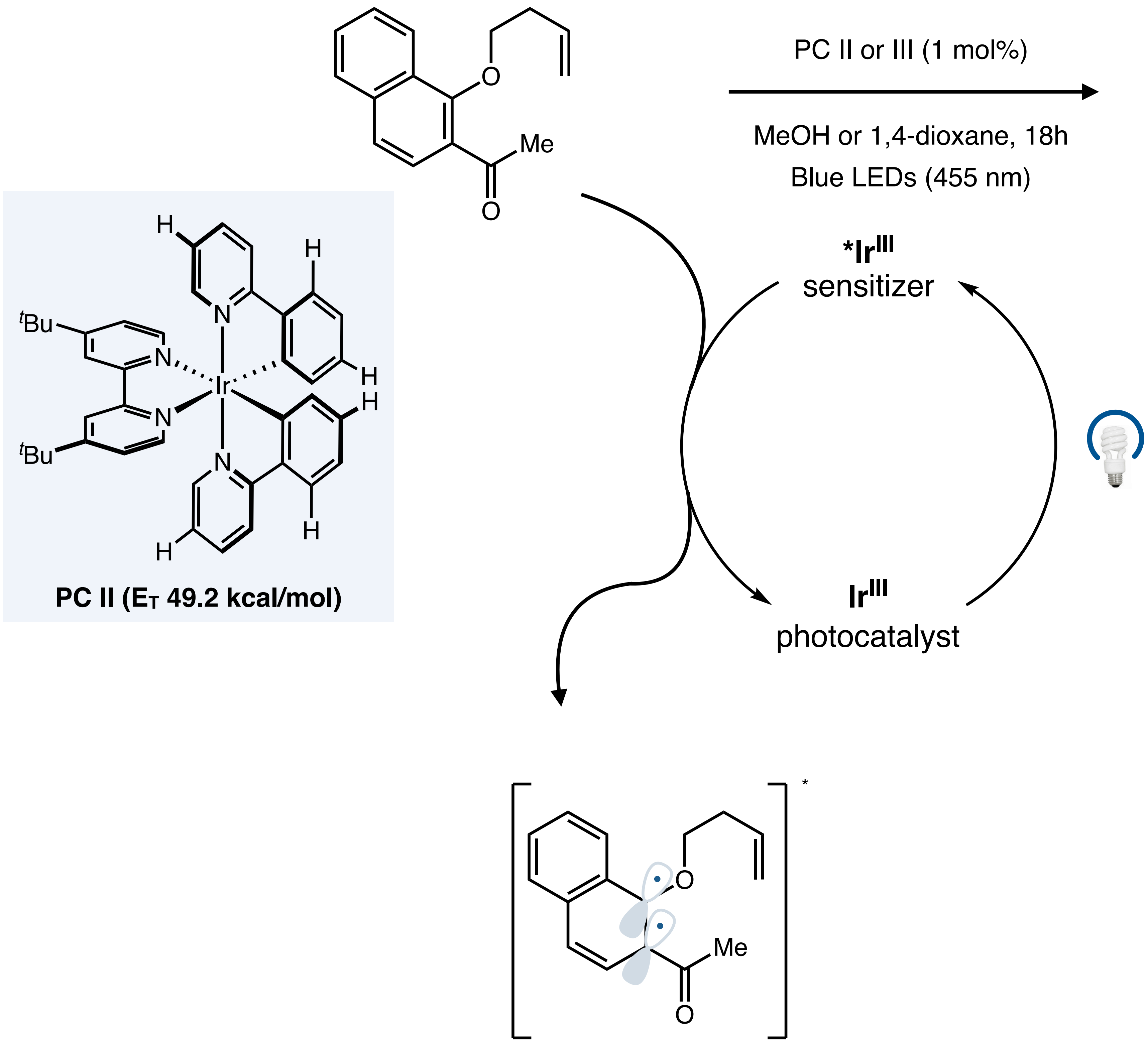

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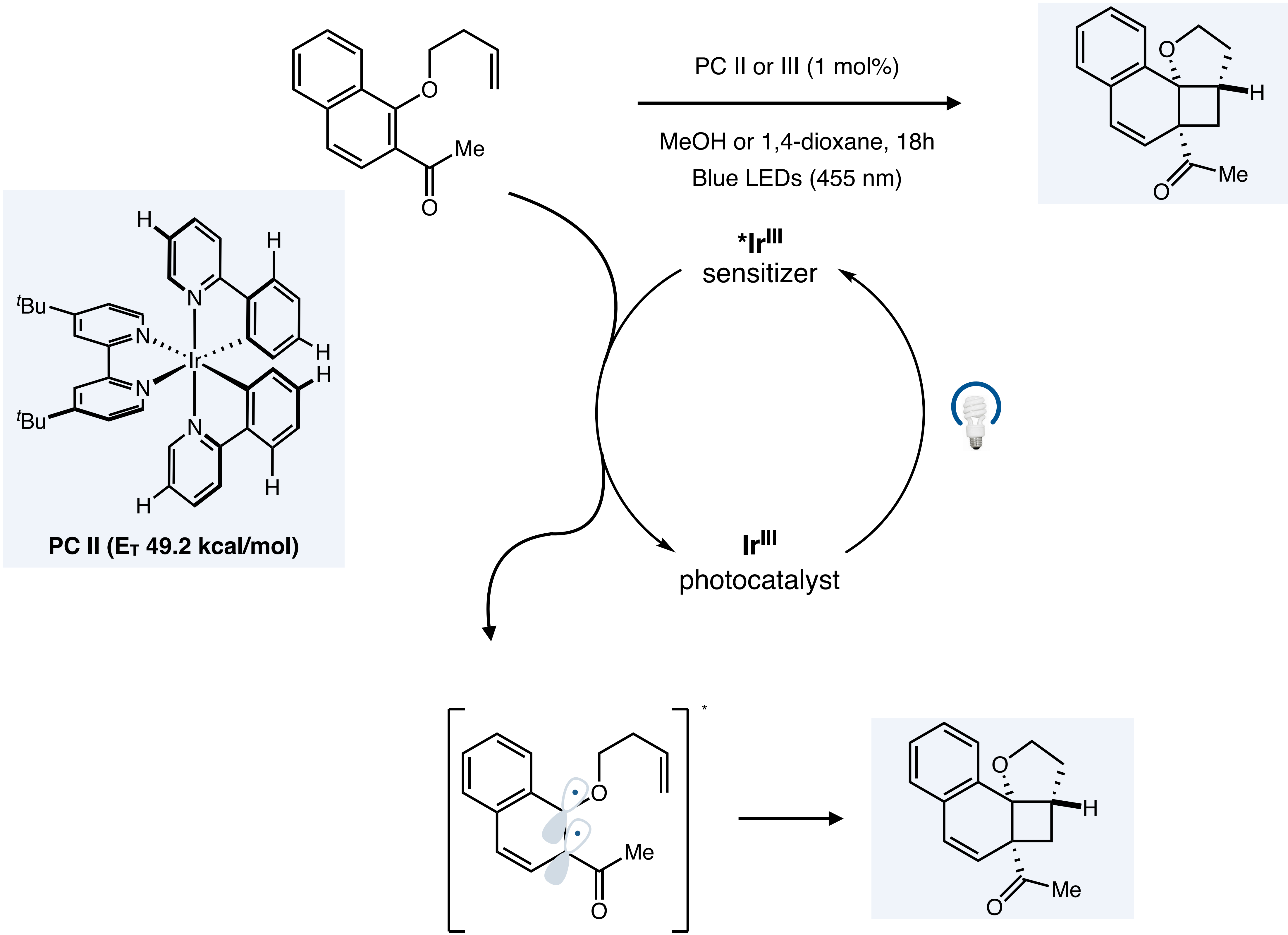

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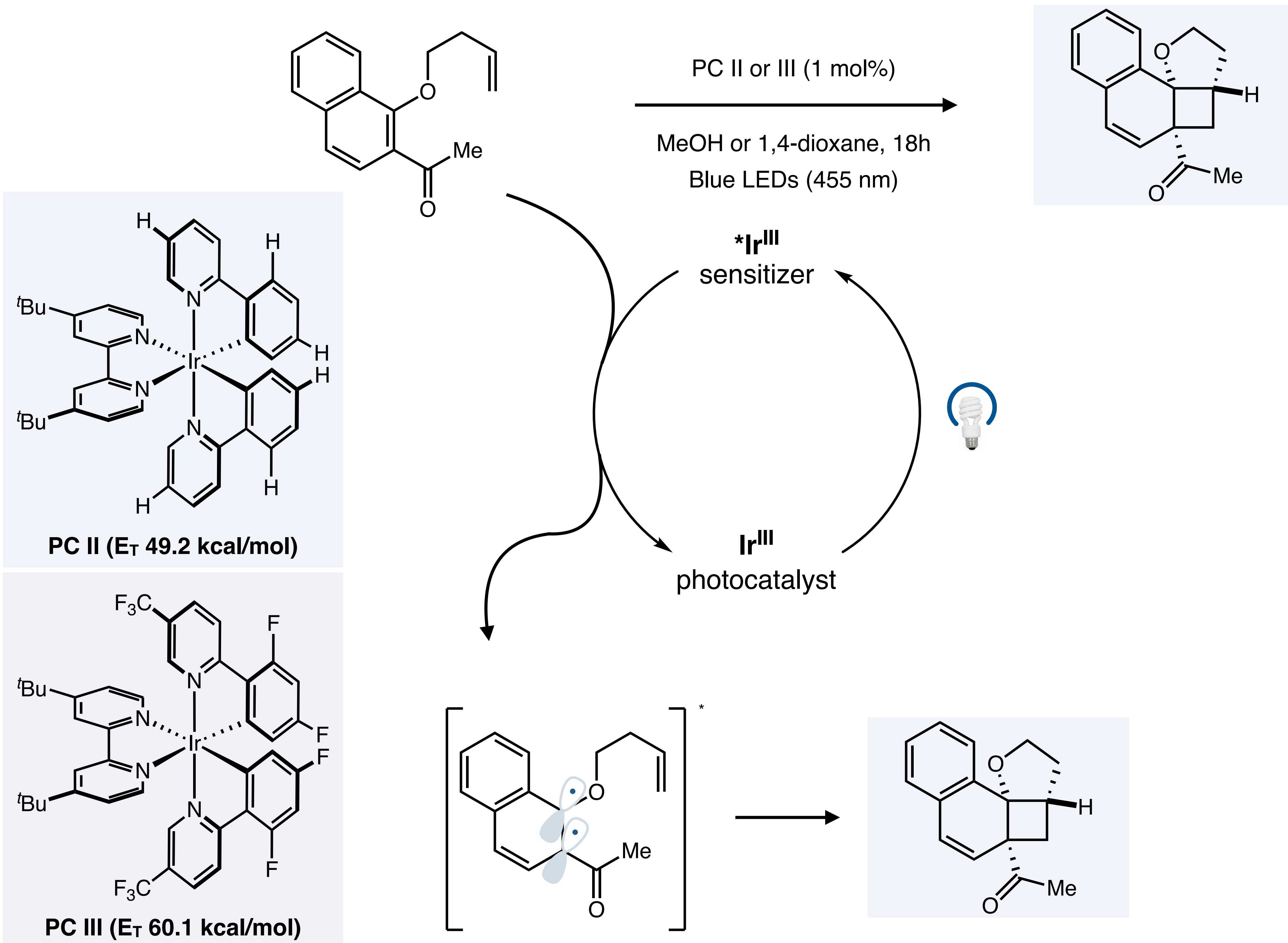

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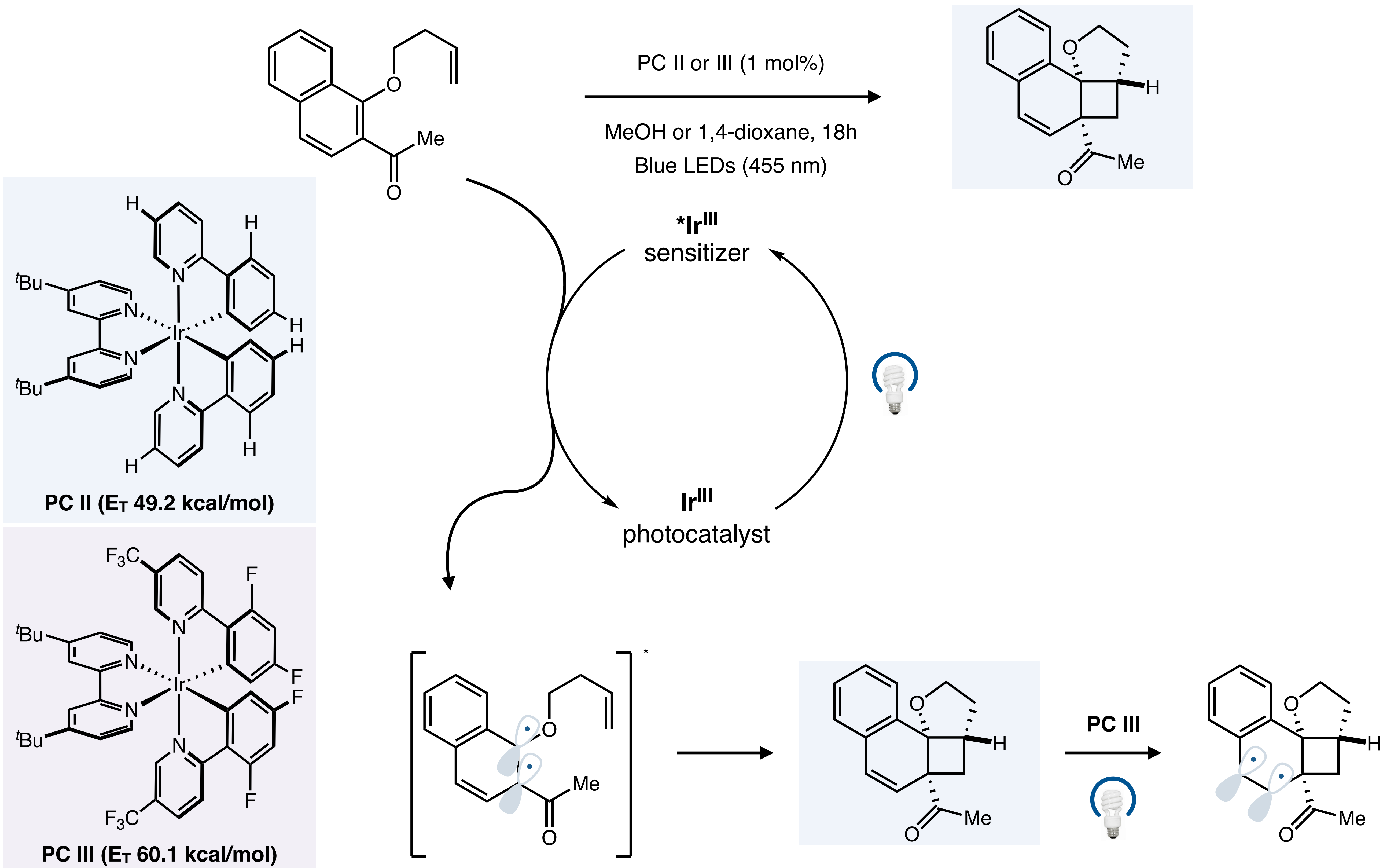

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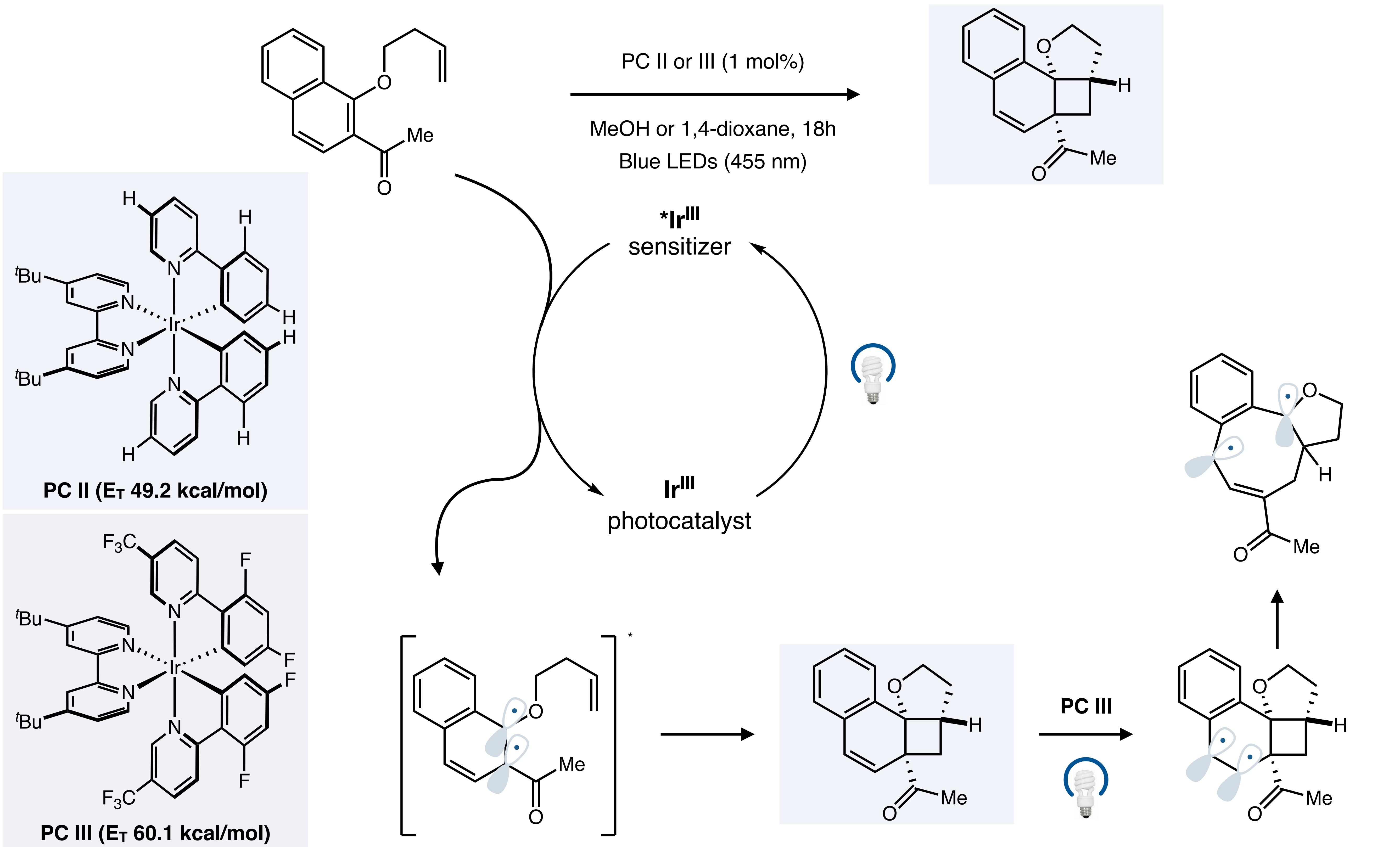

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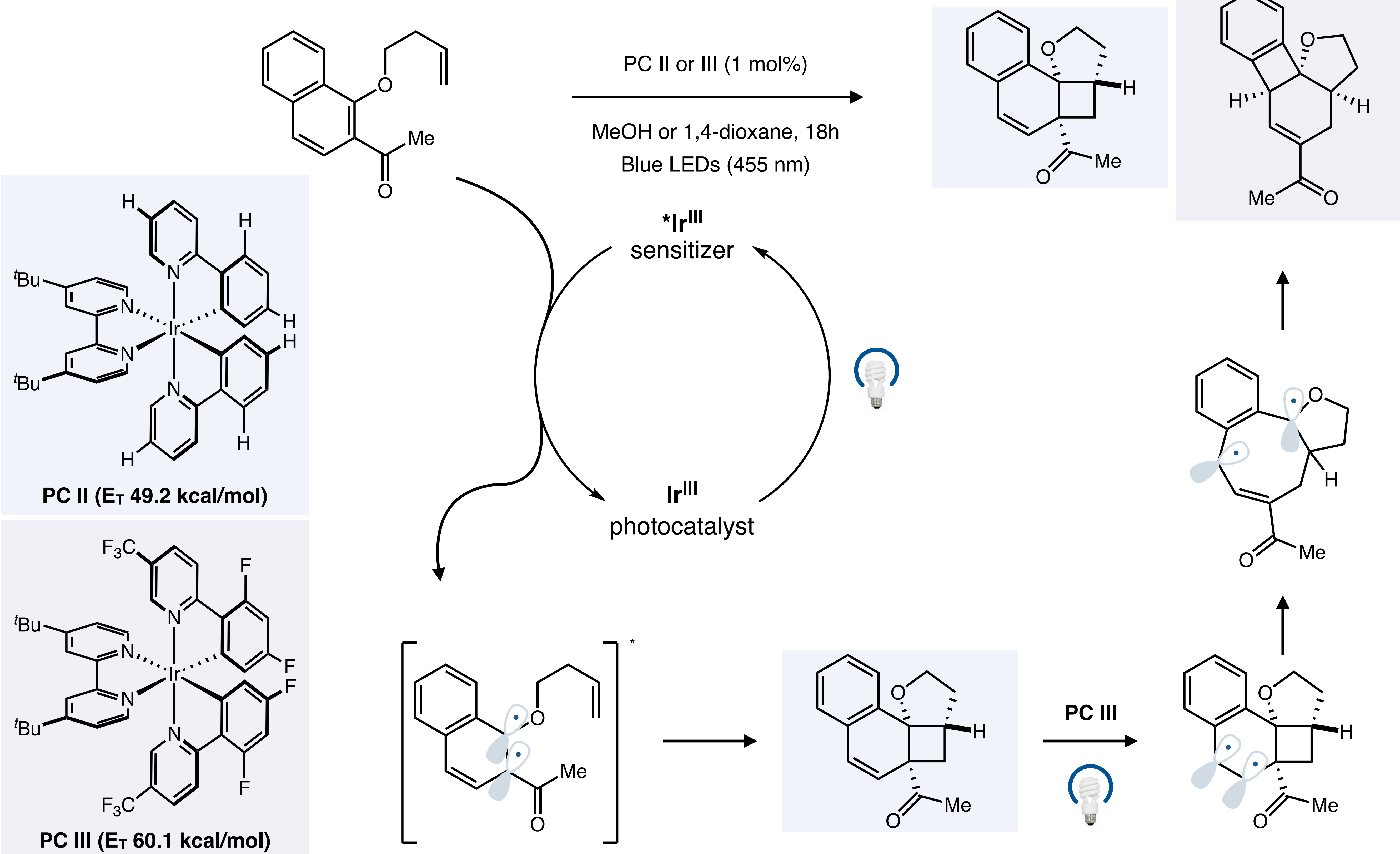

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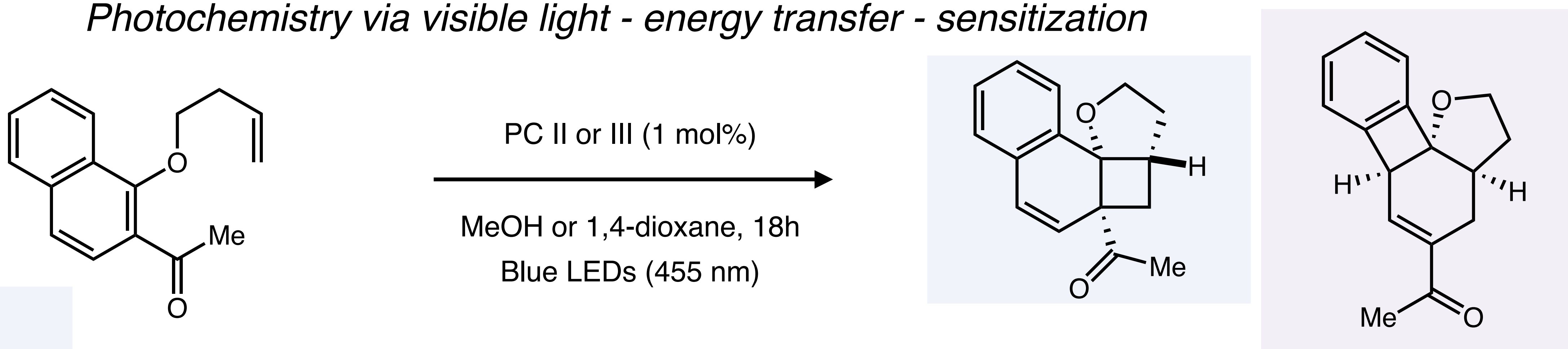
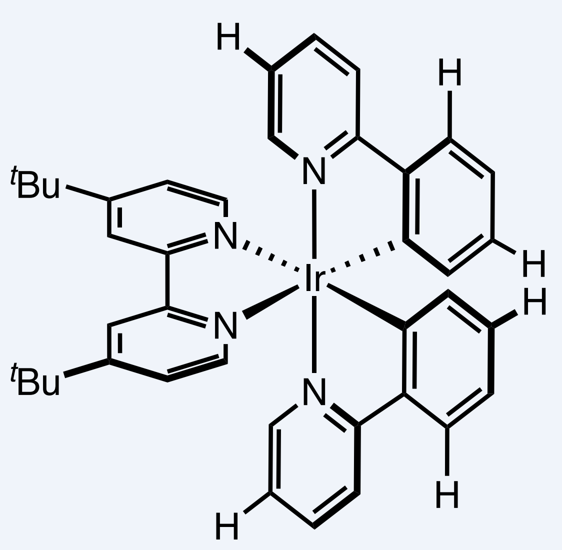


1a **2a**



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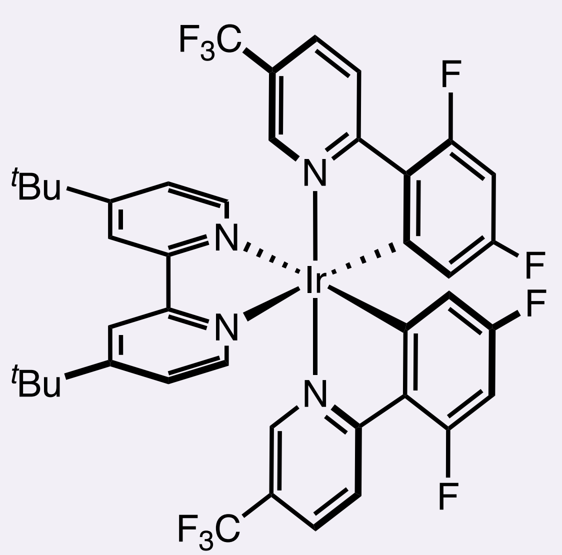

PC III (E_T 60.1 kcal/mol)

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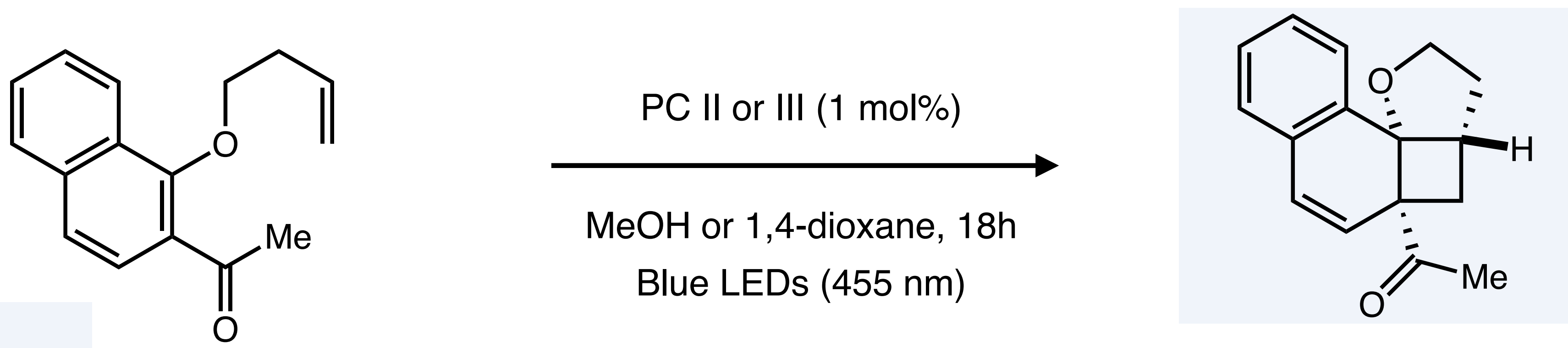
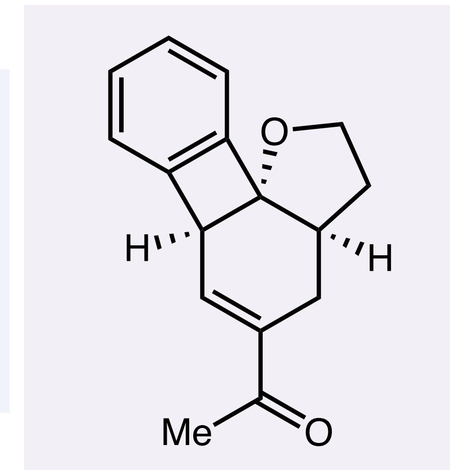
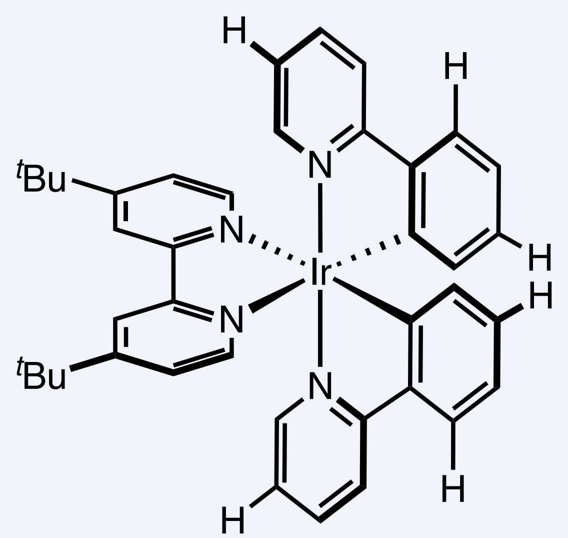


1a **2a**





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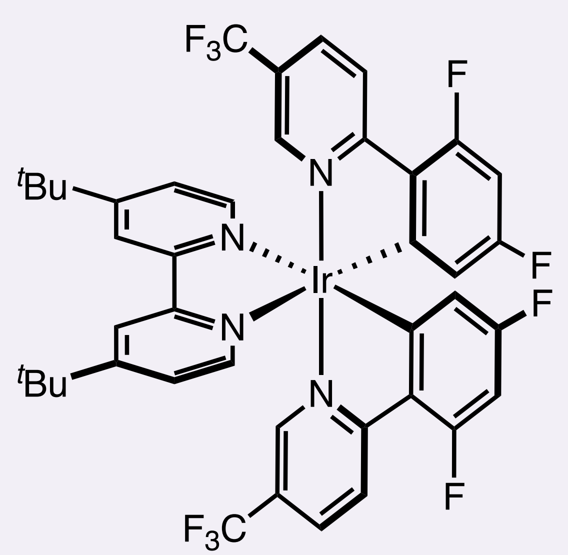

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Stern-Volmer Quenching Studies

James, M. J.; Schwarz, J. L.; Strieth-Kalthoff, F.; Wibbeling, B.; Glorius, F. *J Am Chem Soc* **2018**, *140* (28), 8624-8628.

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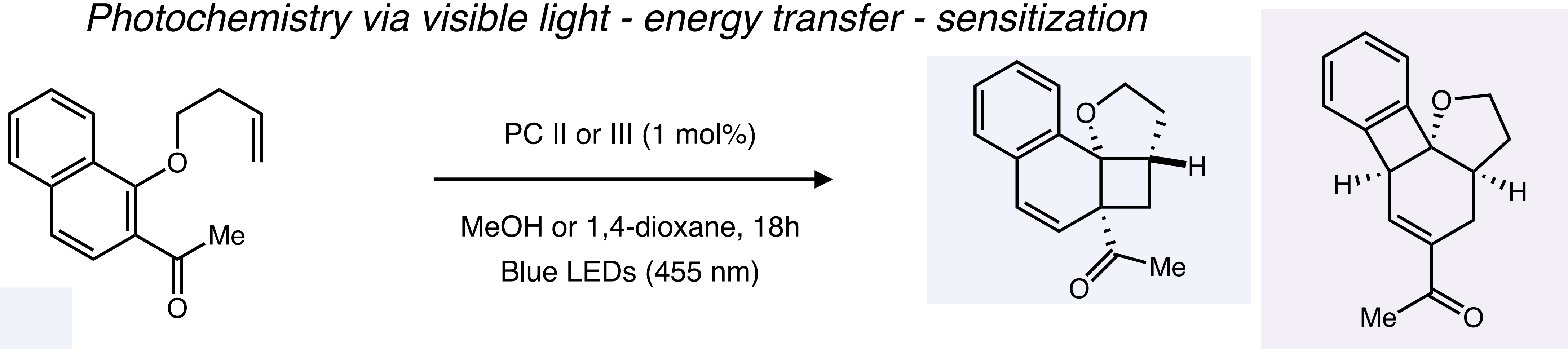

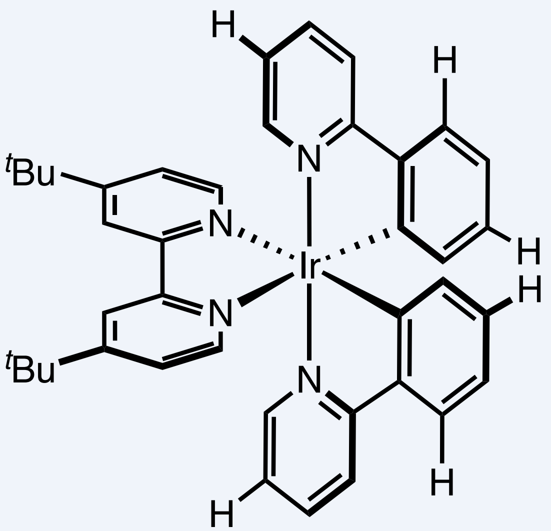

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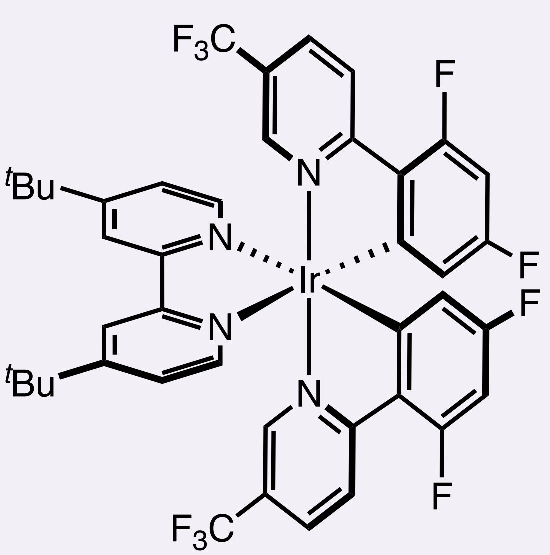

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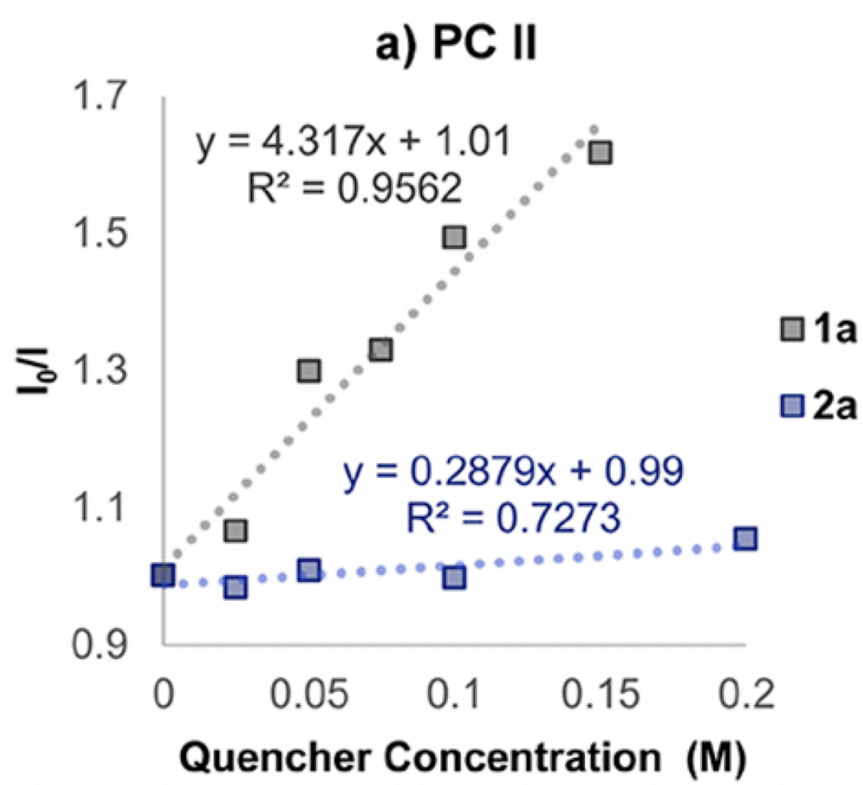

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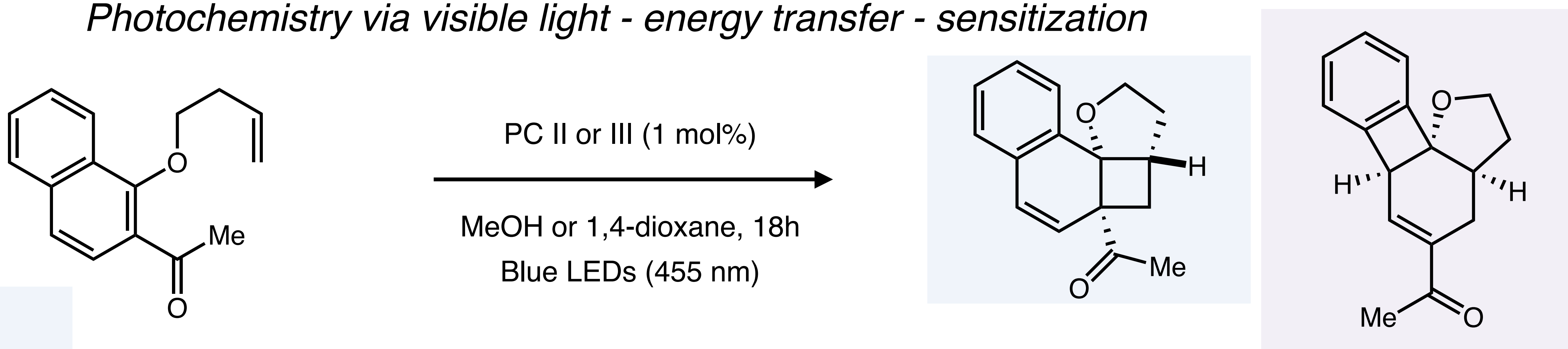
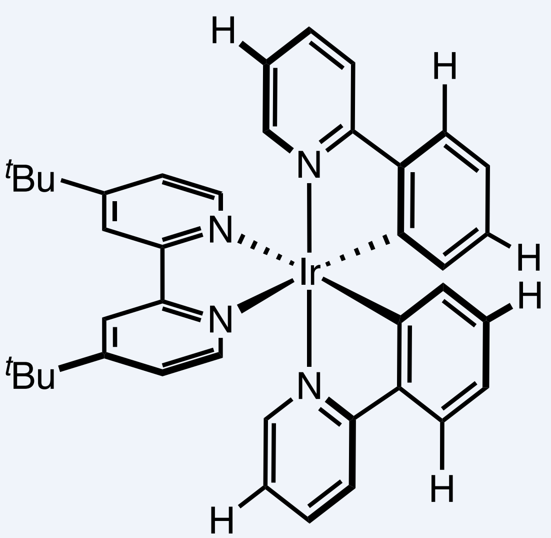


1a **2a**



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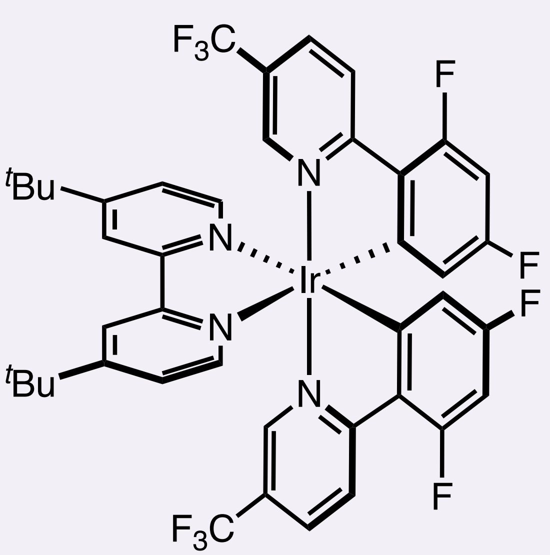

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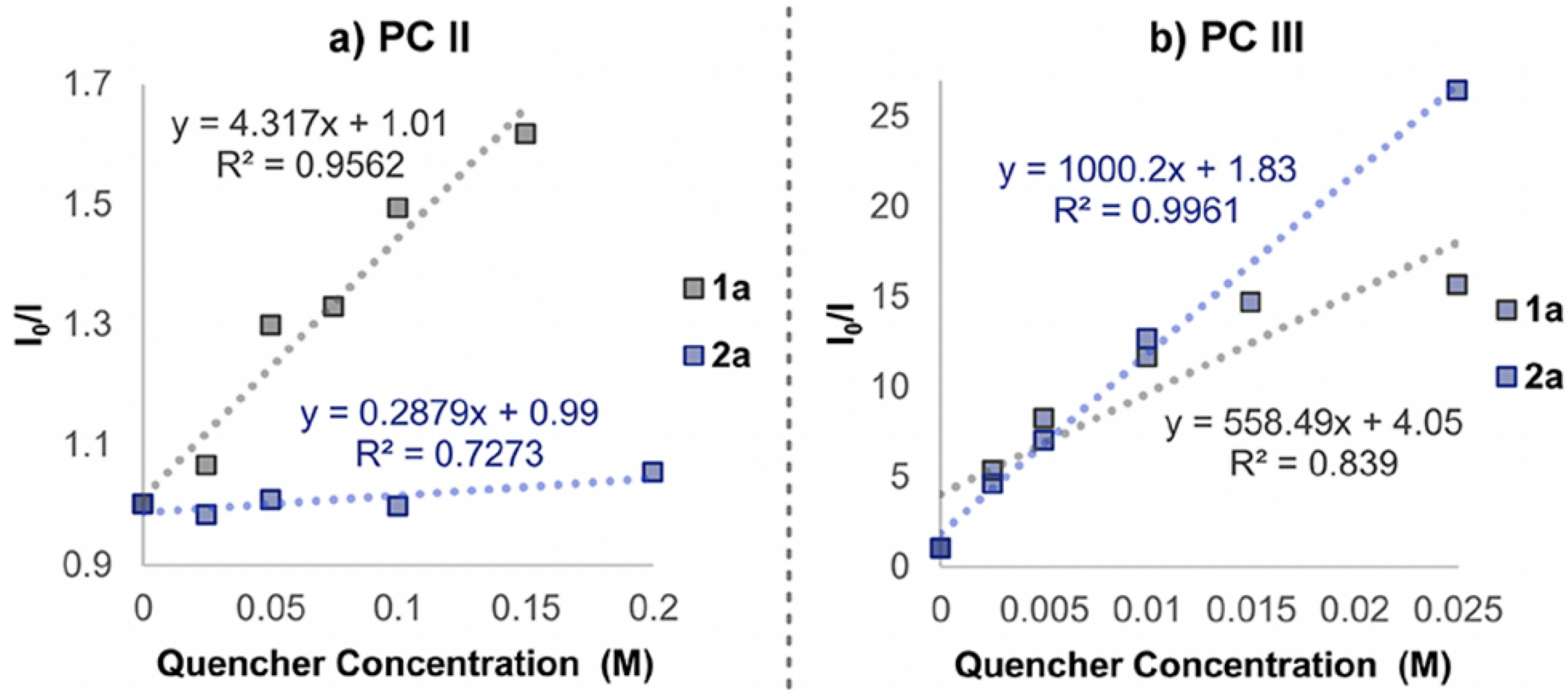

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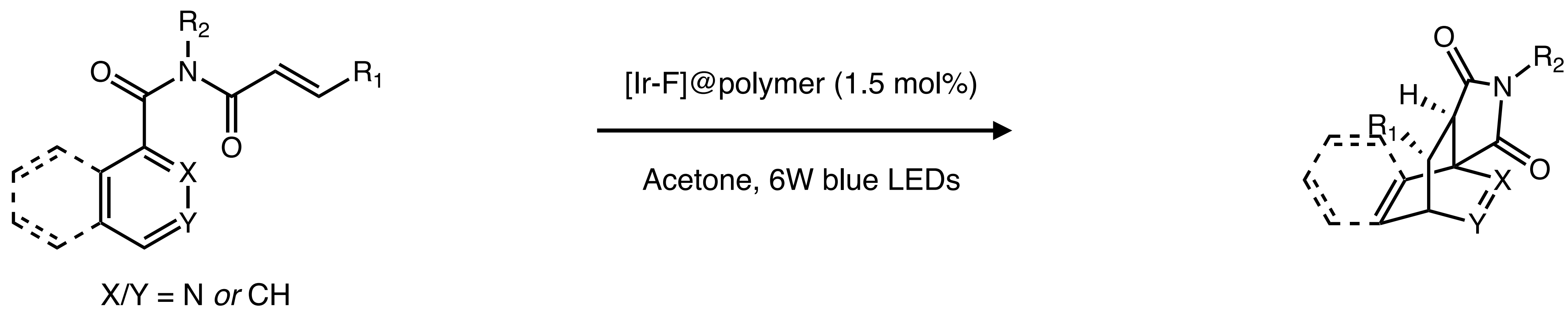

Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. *Chem* **2019**, *5* (11), 2854-2864.

Radical Approach to Dearomatization

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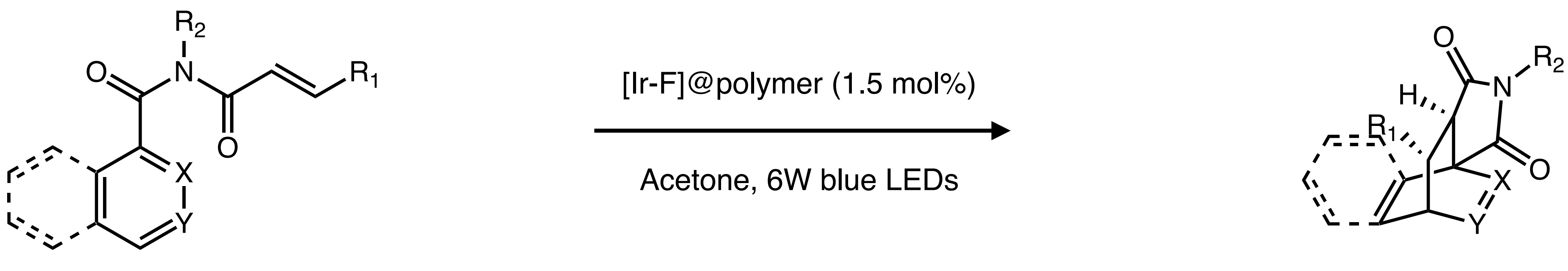
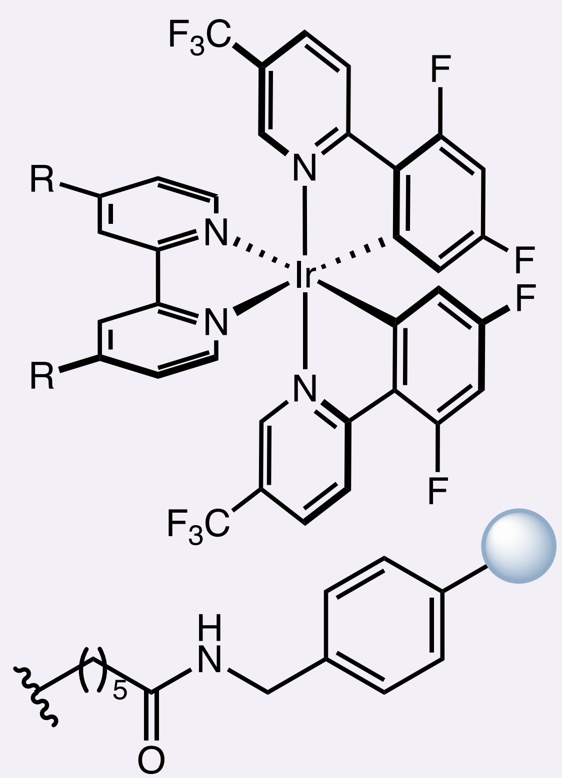


X/Y = N *or* CH



[Ir-F]@polymer

Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. *Chem* **2019**, *5* (11), 2854-2864.

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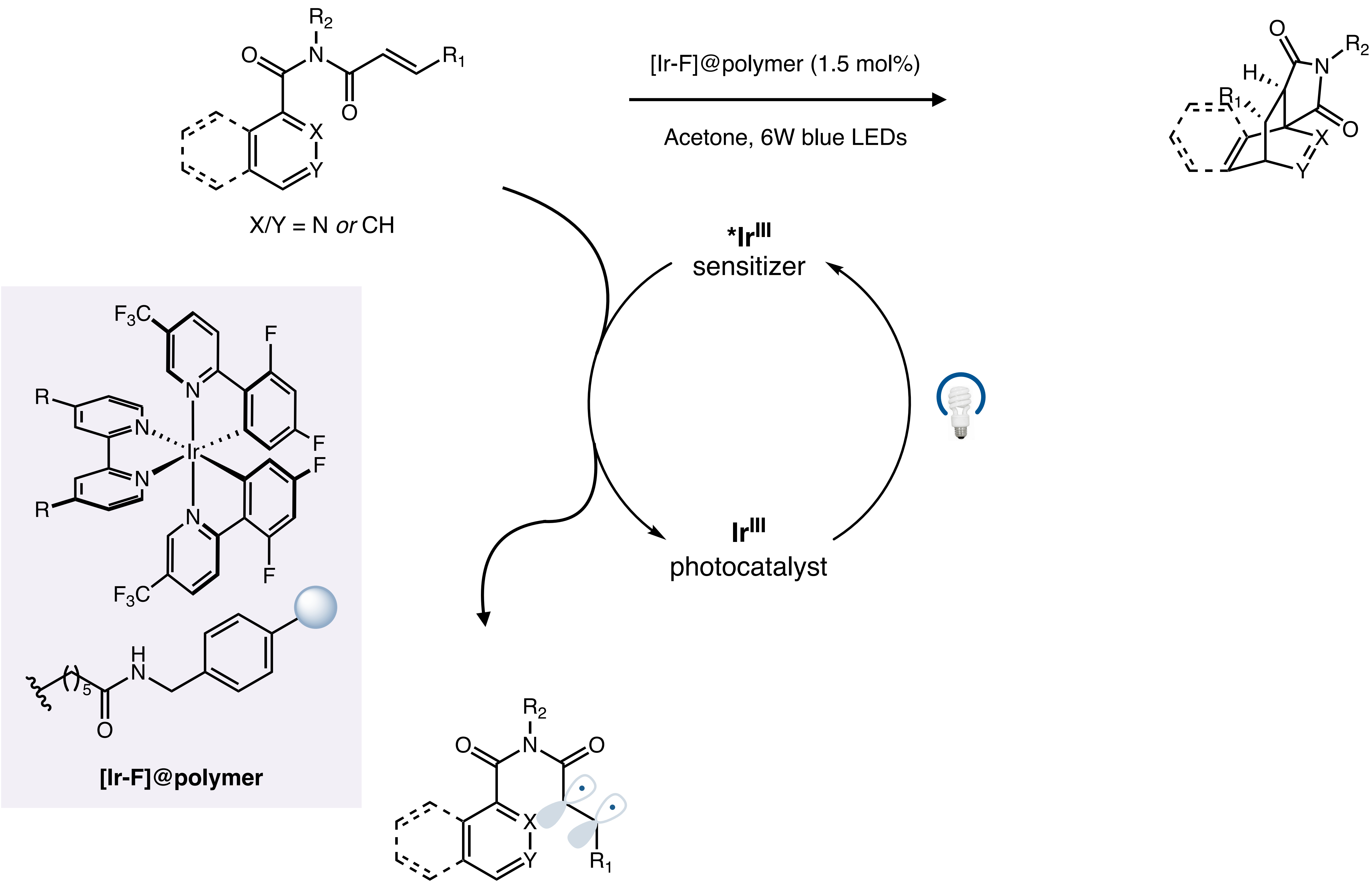

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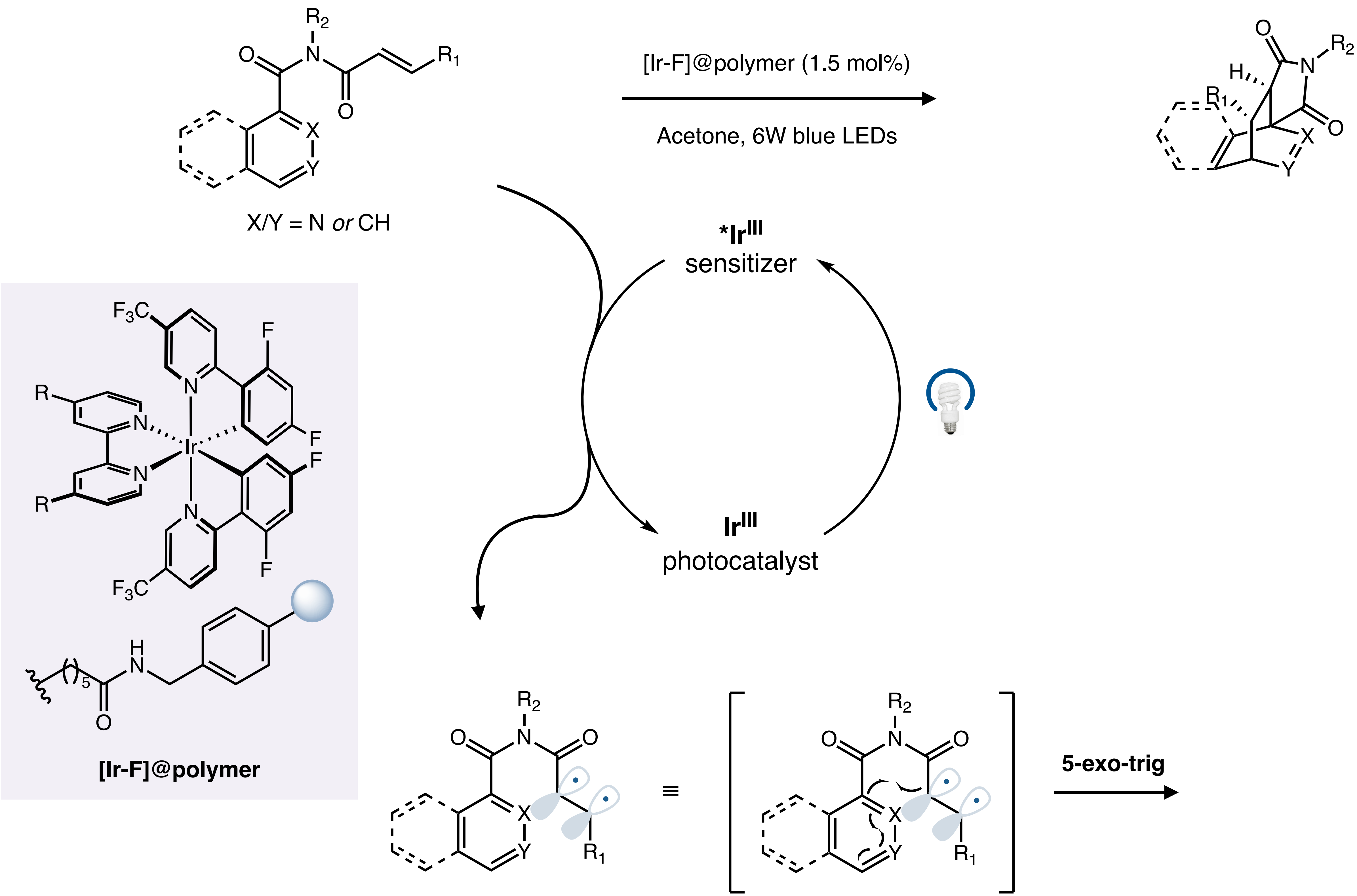

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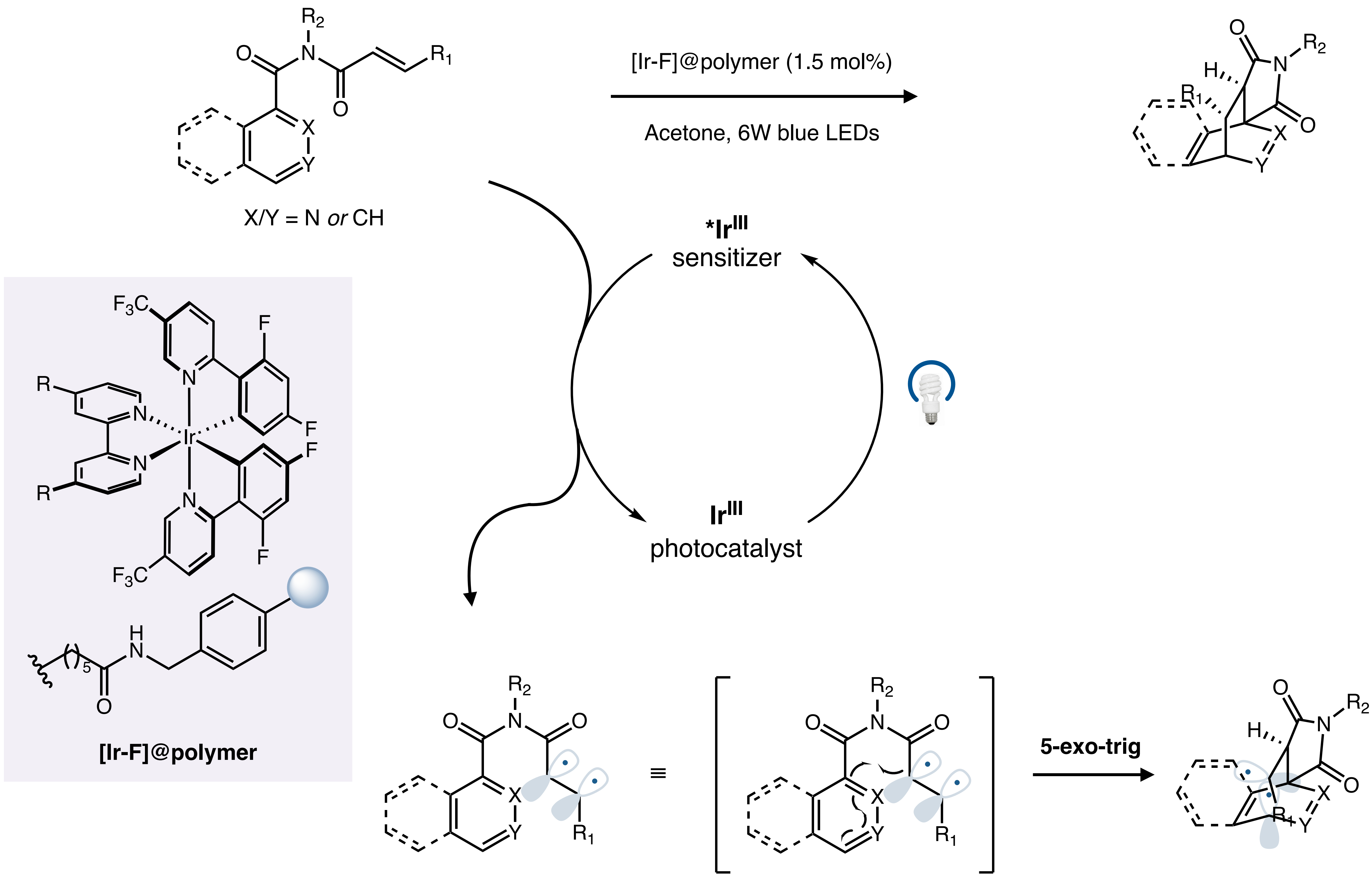

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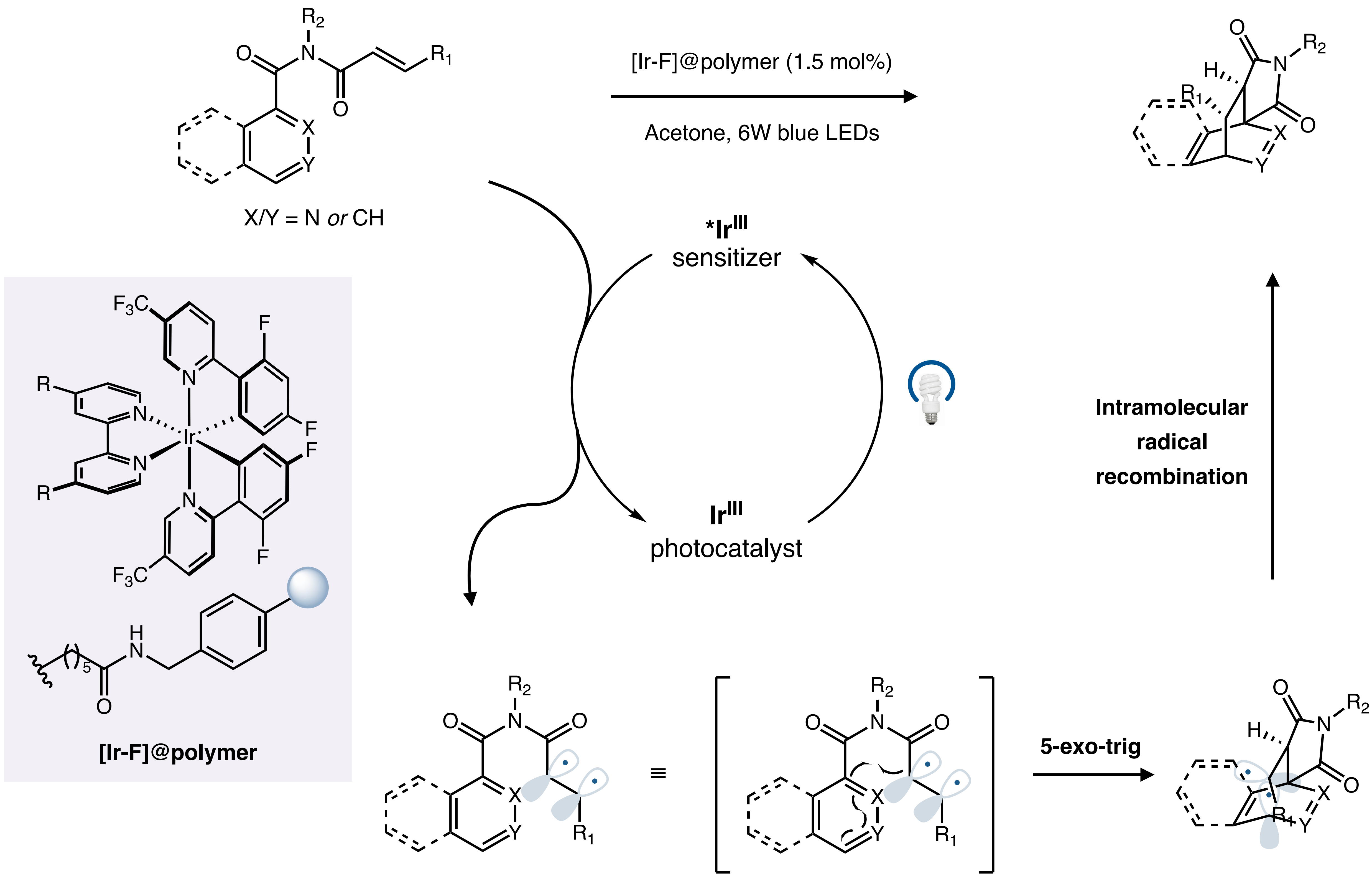

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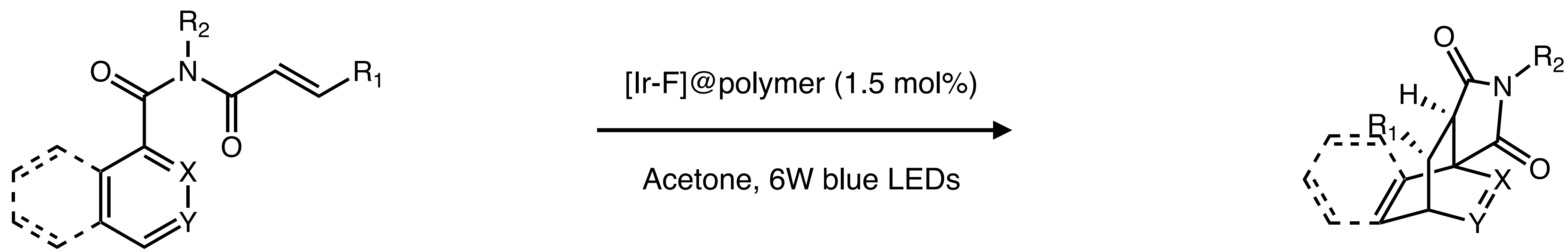

- Reaction scope

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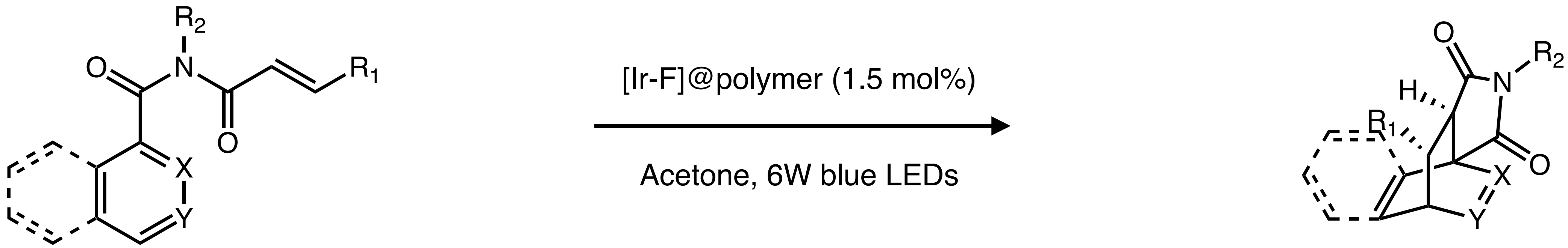
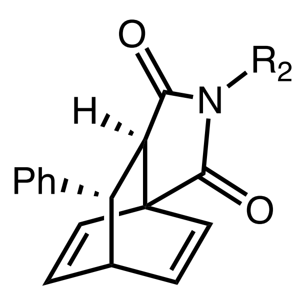
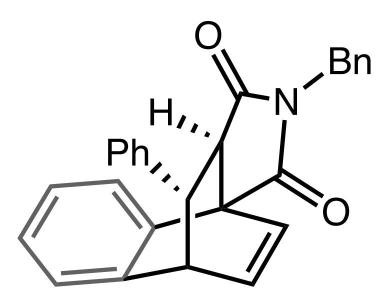


■ Reaction scope



92% yield, >20:1 dr



92% yield, >7:1 dr

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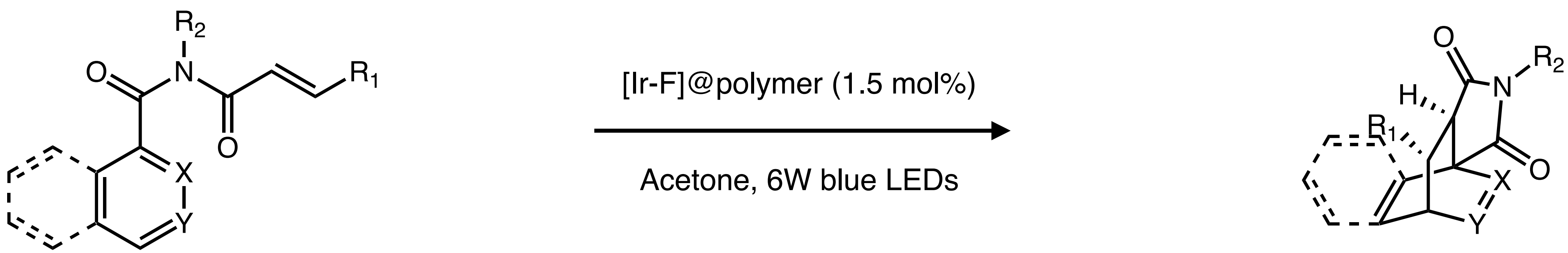

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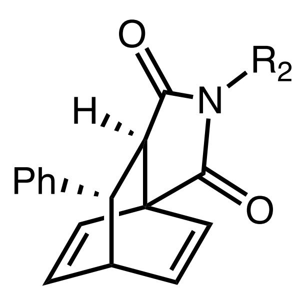

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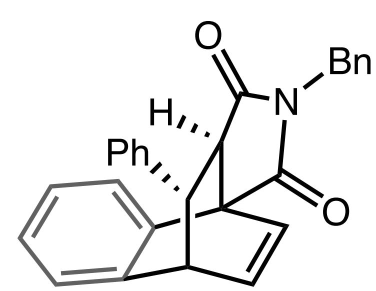
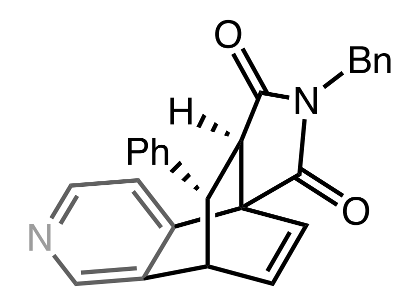


92% yield, >7:1 dr



95% yield, >10:1 dr

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Outline

Radical approach

Traditional radical generation — Birch & SmI_2

Photochemical

- **Single electron transfer**
  - Radical addition
  - Oxidation
  - Reduction
- **Energy transfer**
  - Direct excitation
  - Sensitization

Transition-metal

Mediated
- *η^2*
- *η^6*

Catalyzed — *Pd*

Transition Metal Approach to Dearomatization

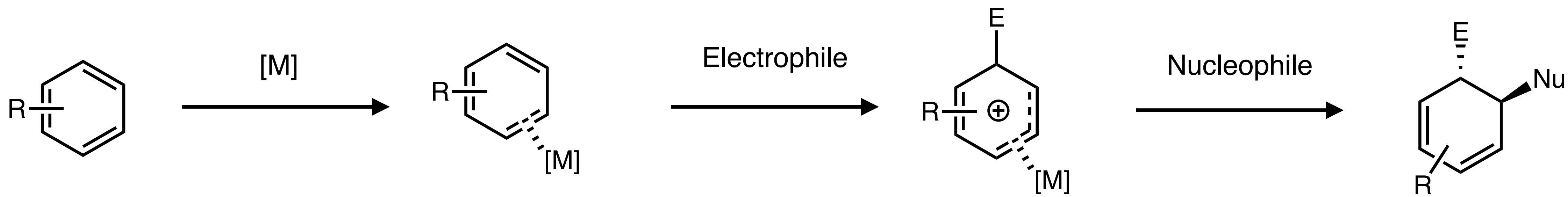
*Transition metal **mediated** dearomatization - η^2 & η^6*

Wertjes, W. C.; Southgate, E. H.; Sarlah, D. *Chem Soc Rev* **2018**, *47* (21), 7996-8017.
A. R. Pape, K. P. Kaliappan and E. P. Kundig, *Chem. Rev.*, **2000**, *100*, 2917–2940.

Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η² & η⁶*

η² reactivity



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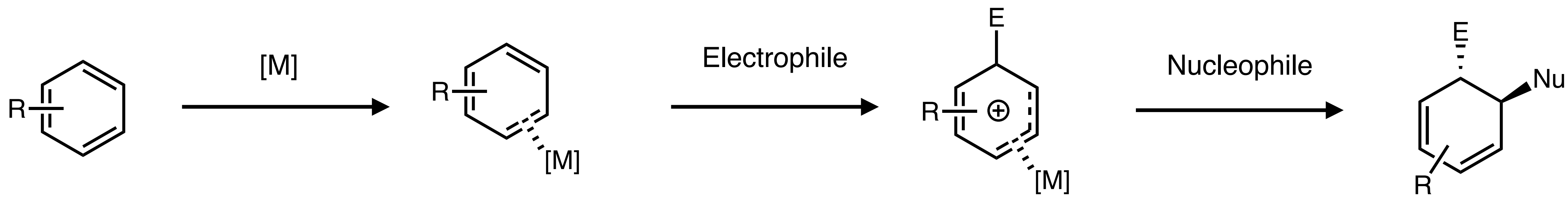
η² reactivity



[M] = Mo, W, Re, $Os(NH_3)_5^{2+}$

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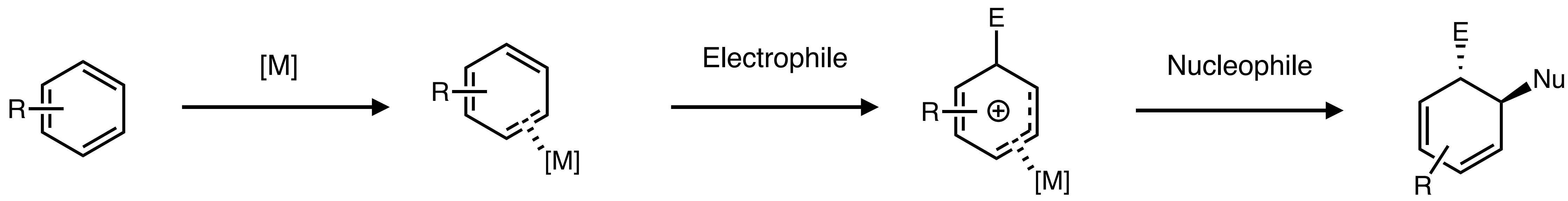
η² reactivity



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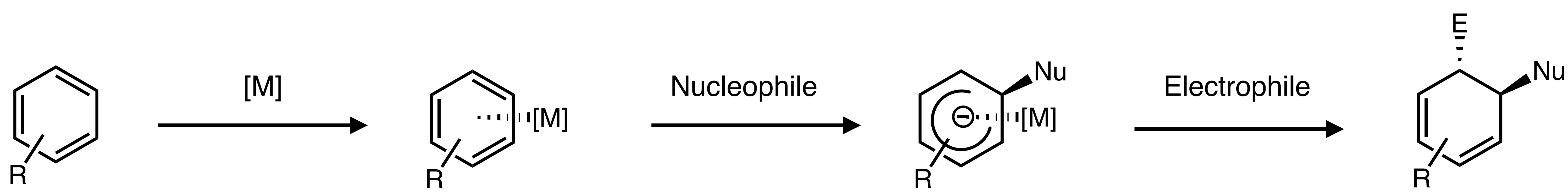
η⁶ reactivity



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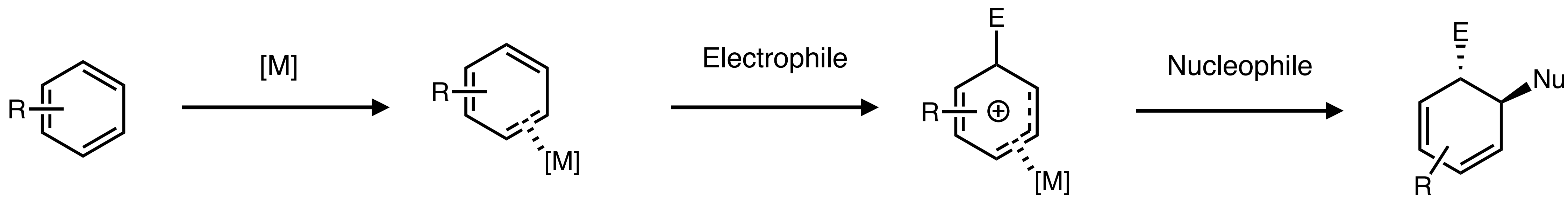
A. R. Pape, K. P. Kaliappan and E. P. Kundig, *Chem. Rev.*, **2000**, *100*, 2917–2940.

Transition Metal Approach to Dearomatization

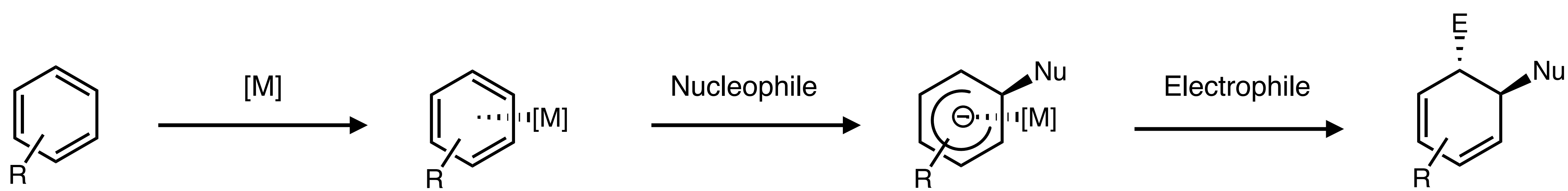
*Transition metal **mediated** dearomatization - η^2 & η^6*

η^2 reactivity



[M] = Mo, W, Re, $Os(NH_3)_5^{2+}$

η^6 reactivity



[M] = $Cr(CO)_3$, $Mn(CO)_3^+$, $FeCp^+$

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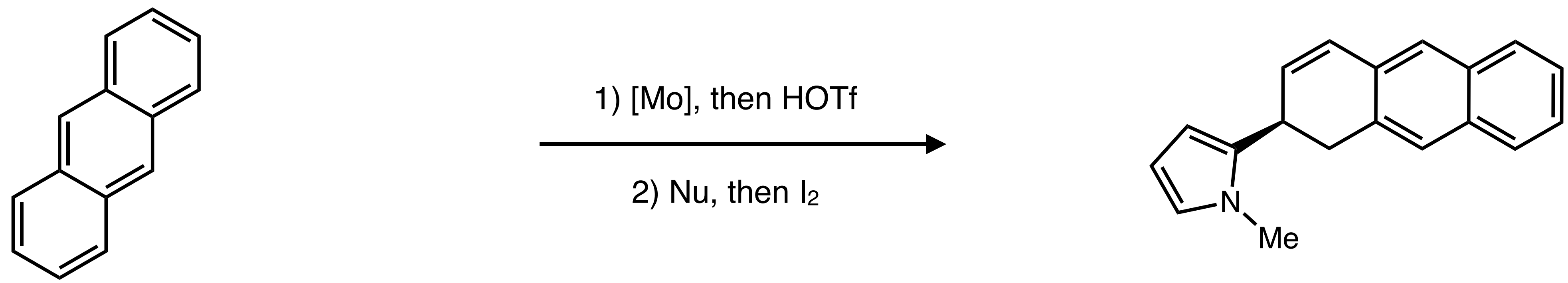
A. R. Pape, K. P. Kaliappan and E. P. Kundig, *Chem. Rev.*, **2000**, *100*, 2917–2940.

Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^2*



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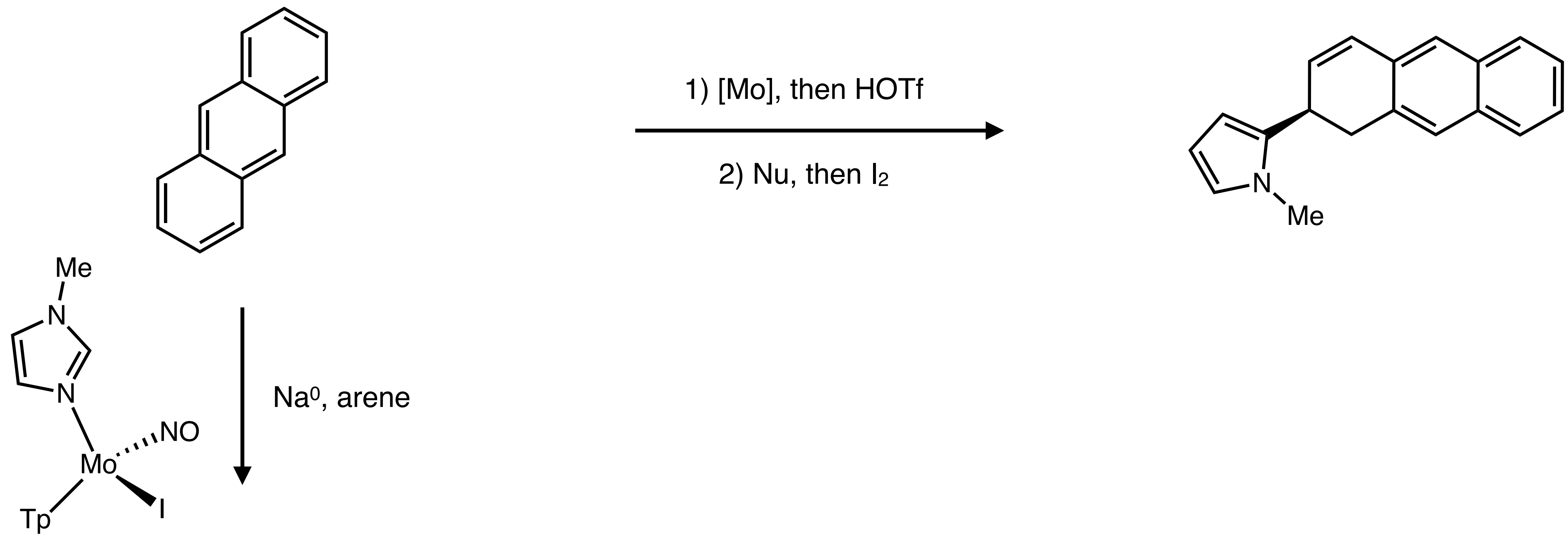
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η²*



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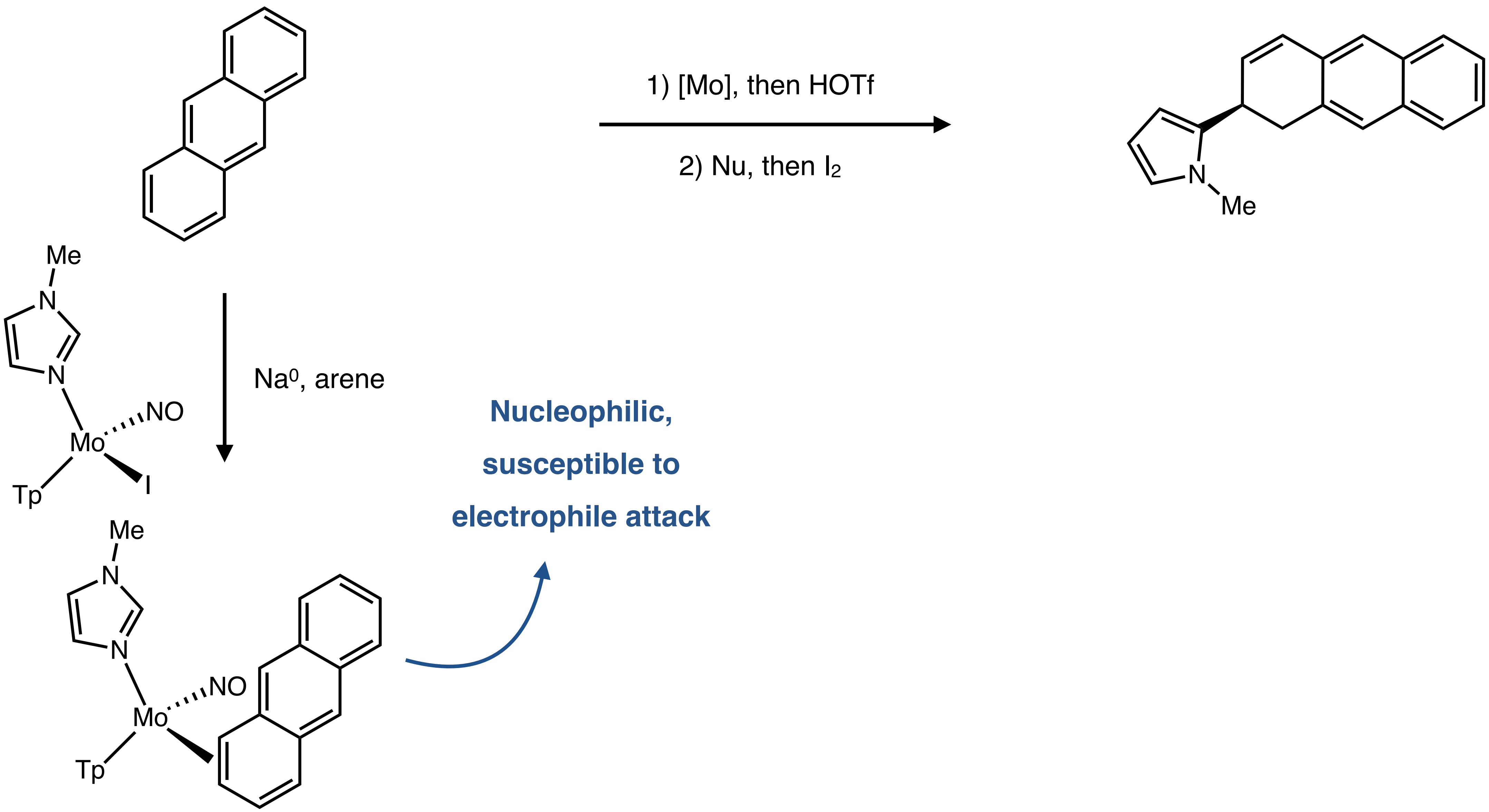

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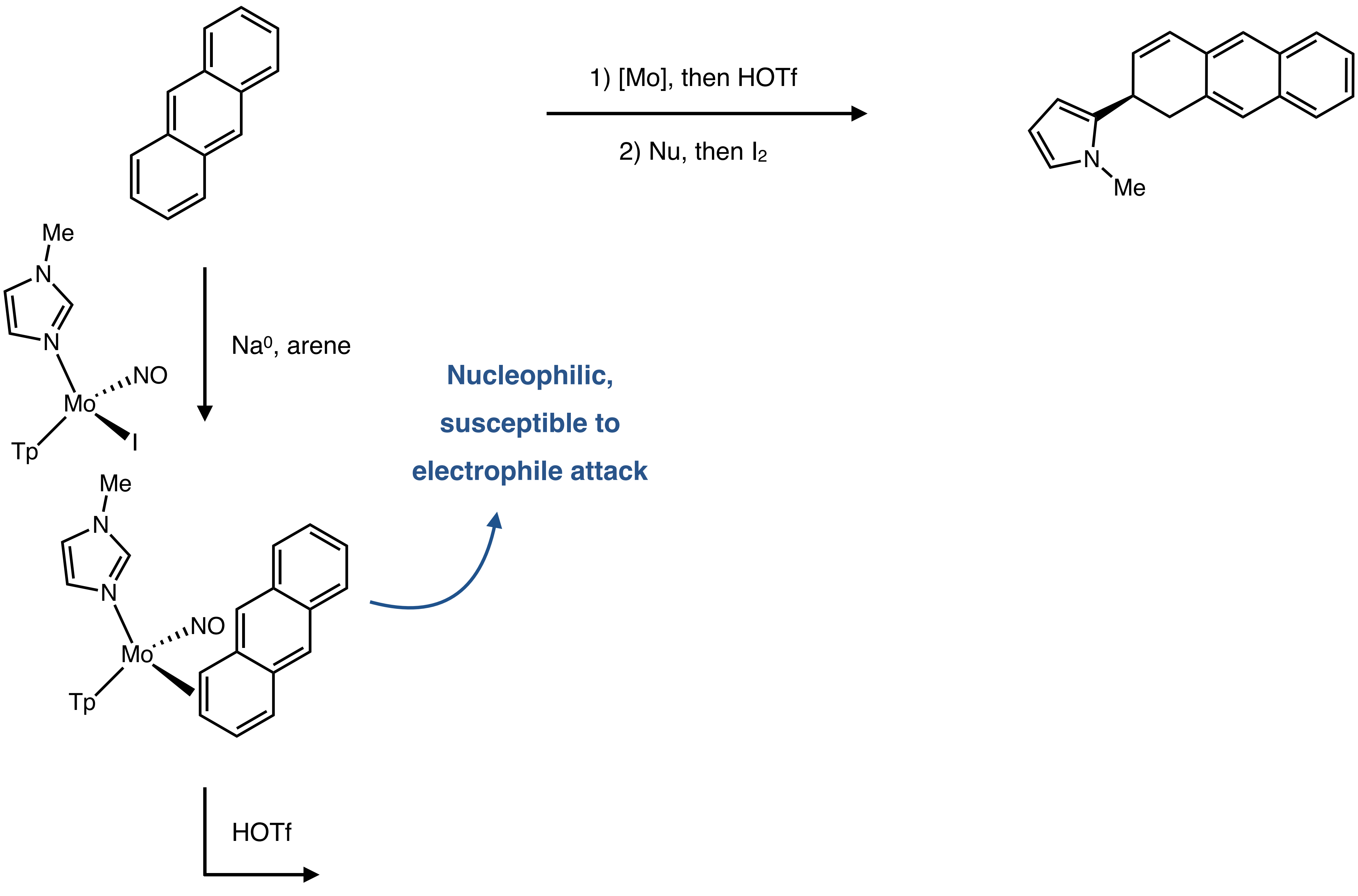

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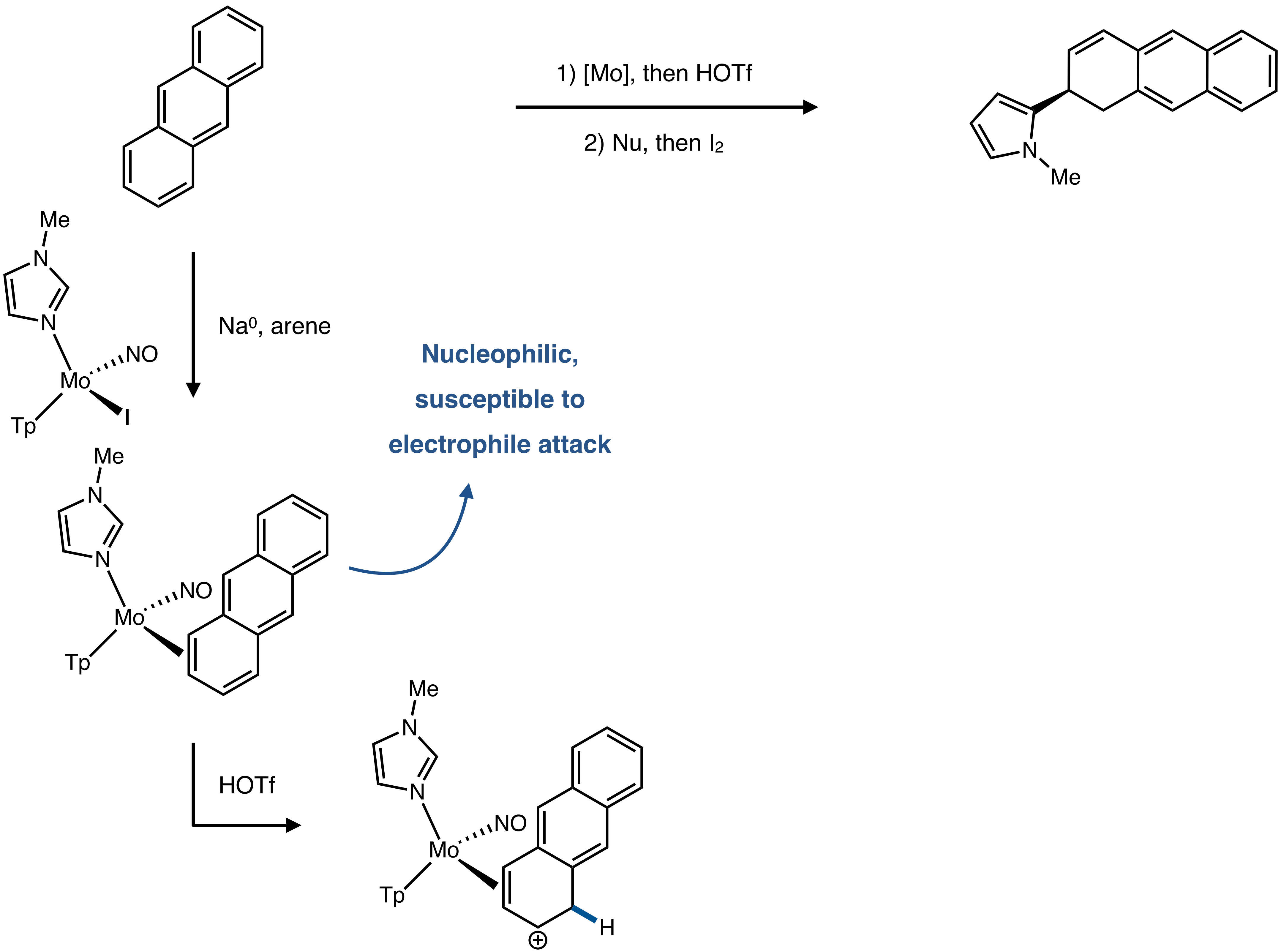
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η²*



Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. *Chem* **2019**, *5* (11), 2854-2864.

Transition Metal Approach to Dearomatization

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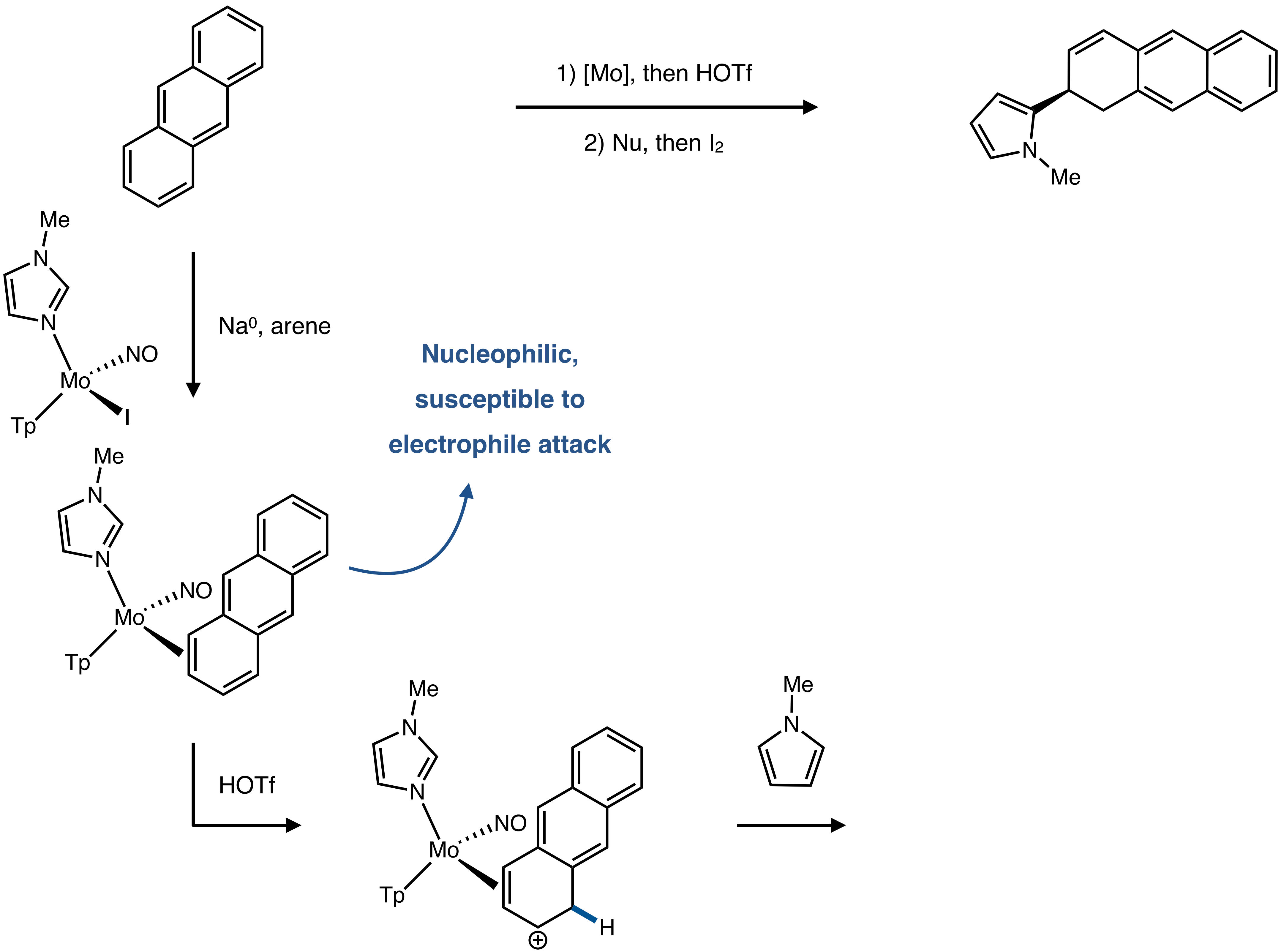

Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. *Chem* **2019**, *5* (11), 2854-2864.

Transition Metal Approach to Dearomatization

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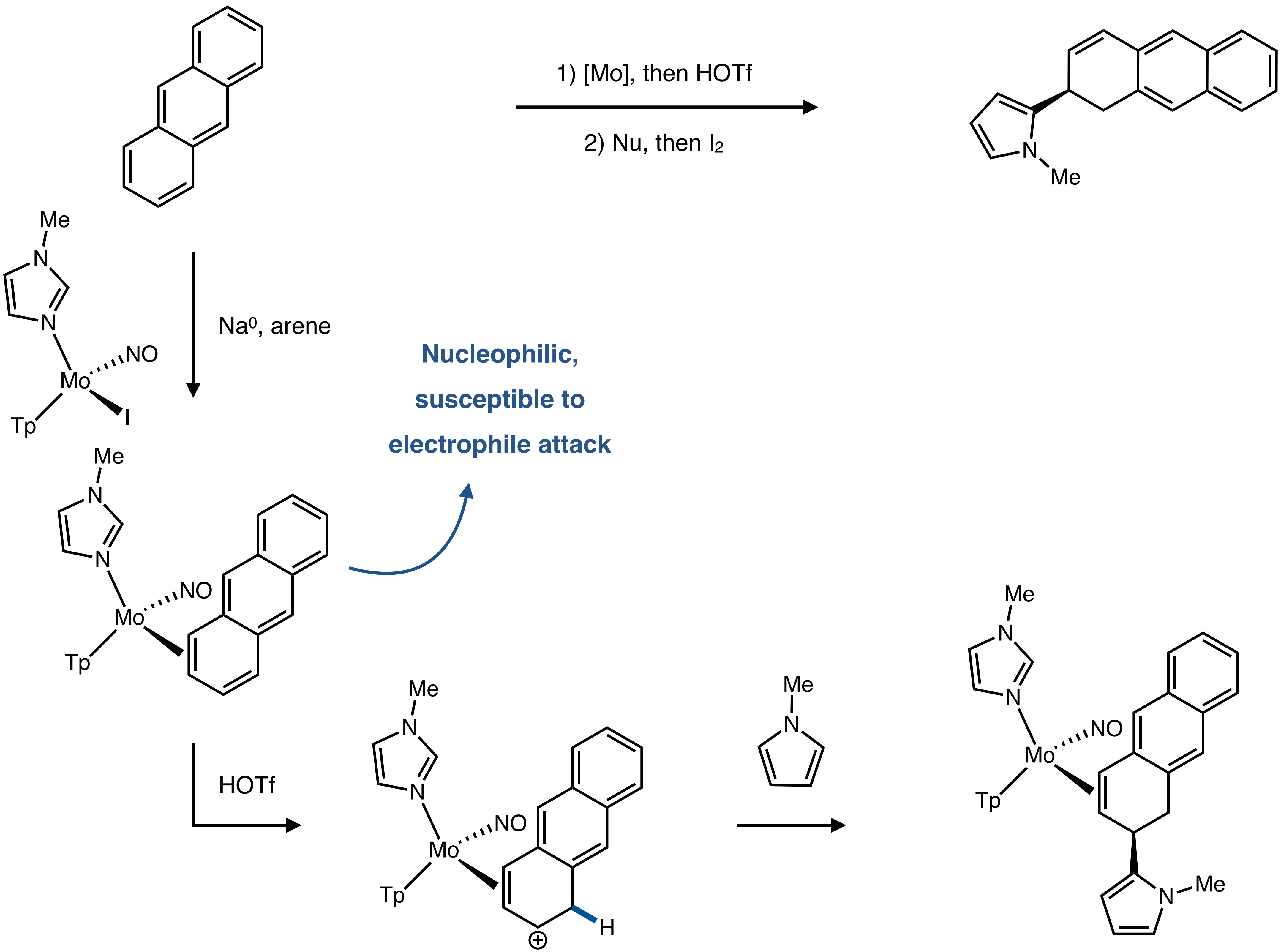

Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. *Chem* **2019**, *5* (11), 2854-2864.

Transition Metal Approach to Dearomatization

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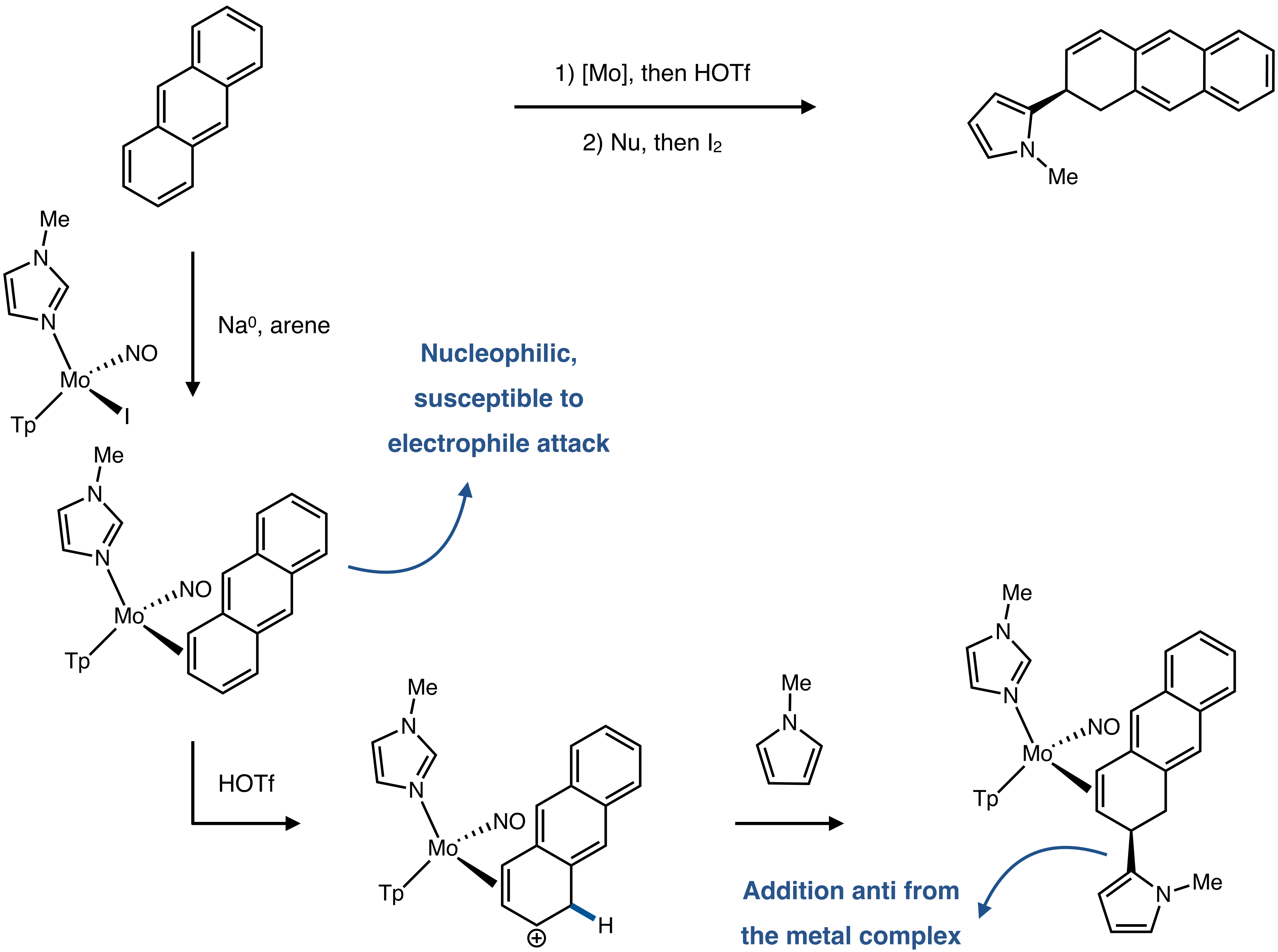

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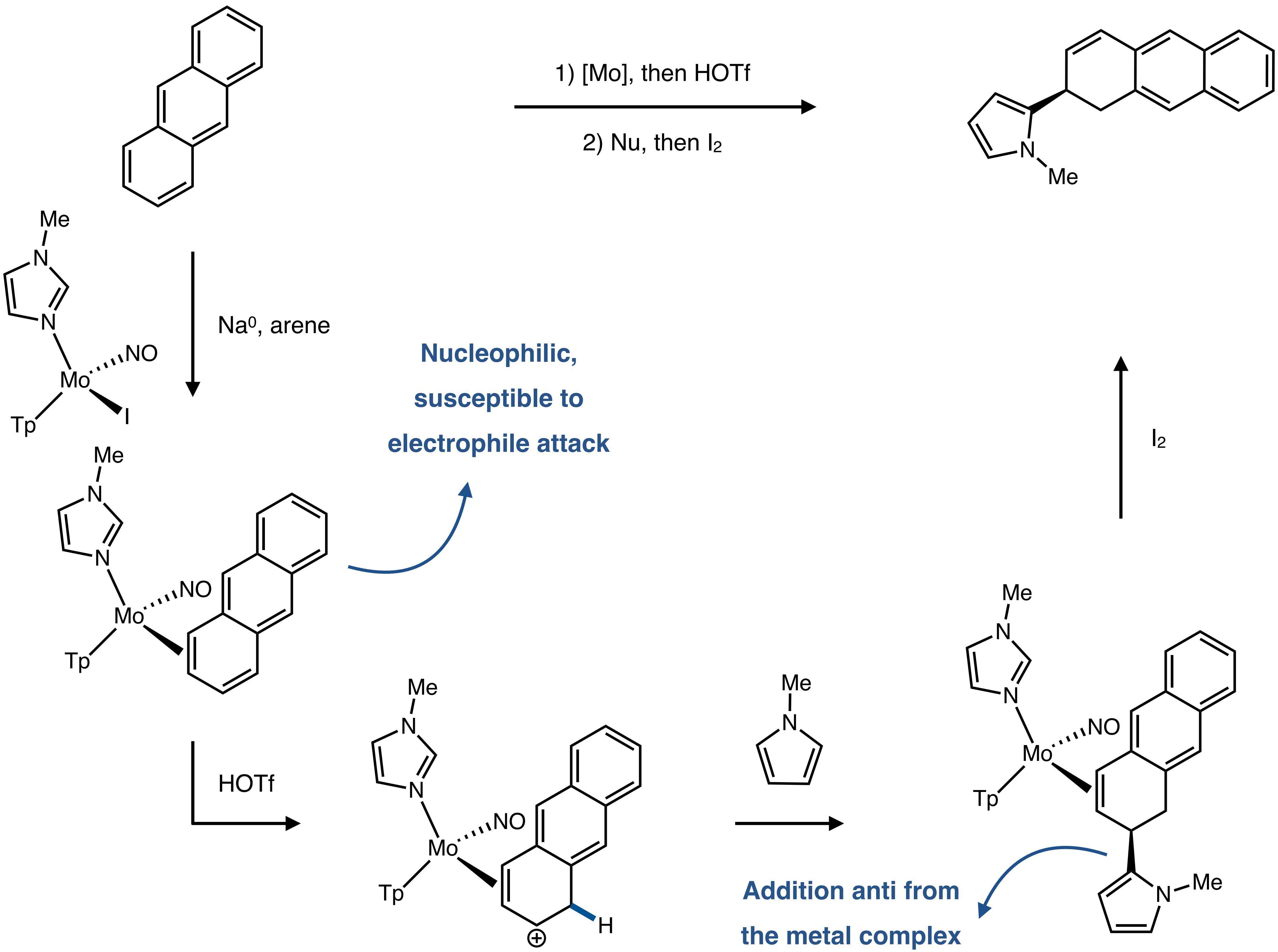
Transition Metal Approach to Dearomatization

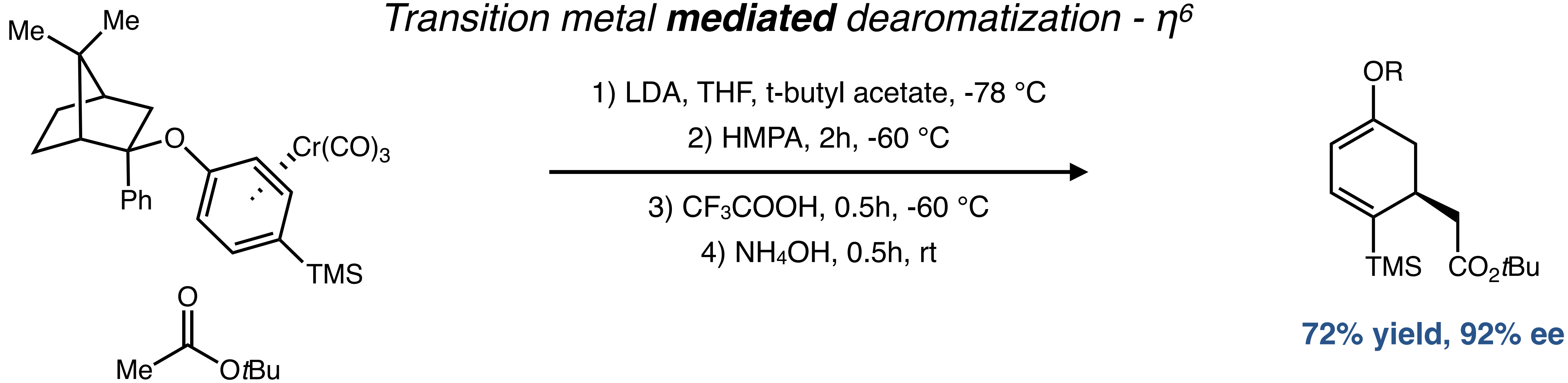
*Transition metal **mediated** dearomatization - η²*



Ma, J.; Strieth-Kalthoff, F.; Dalton, T.; Freitag, M.; Schwarz, J. L.; Bergander, K.; Daniliuc, C.; Glorius, F. *Chem* **2019**, *5* (11), 2854-2864.

Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η⁶*

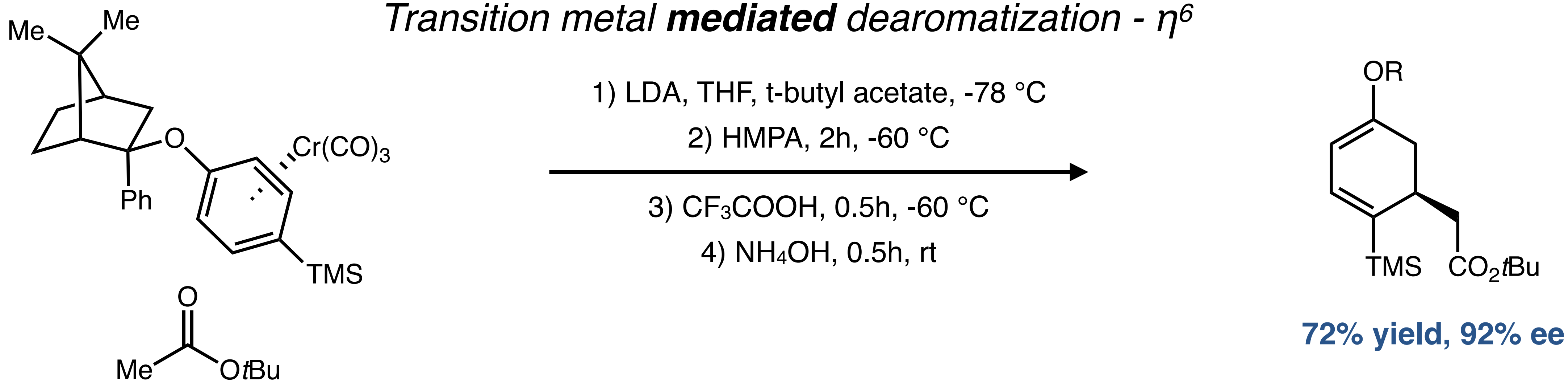


72% yield, 92% ee

H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

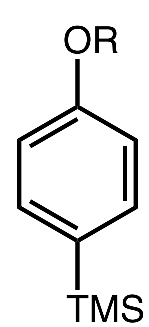
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^6*



72% yield, 92% ee

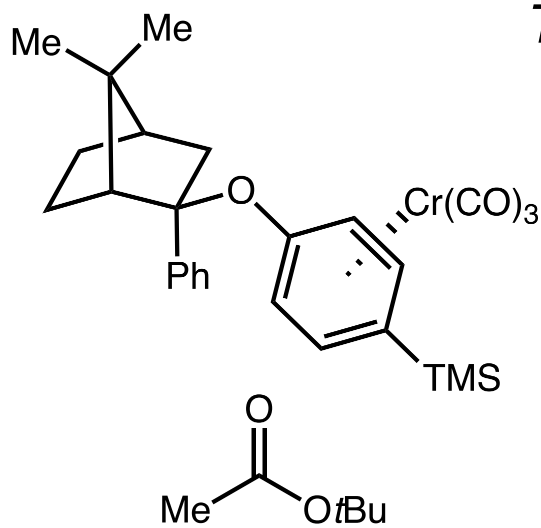
- Regioselectivity

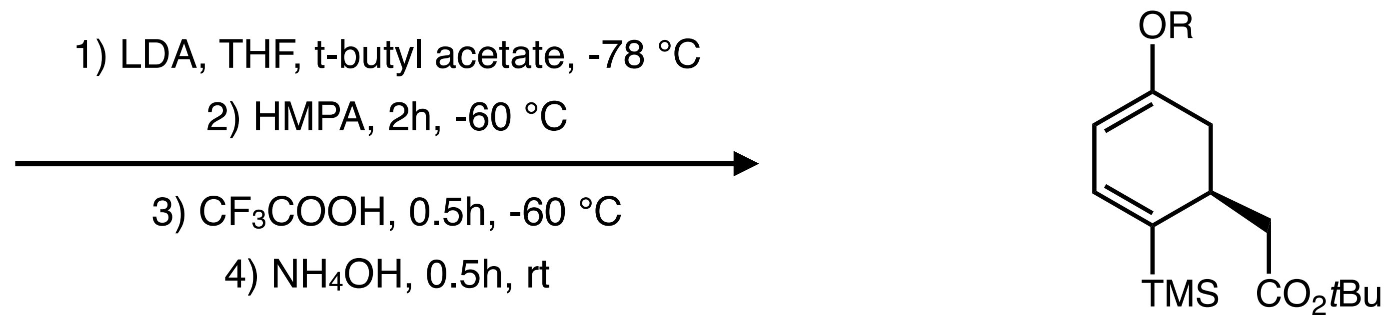


H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^6*

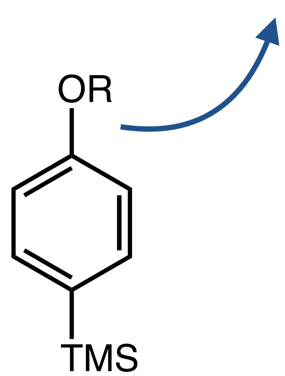




72% yield, 92% ee

- Regioselectivity

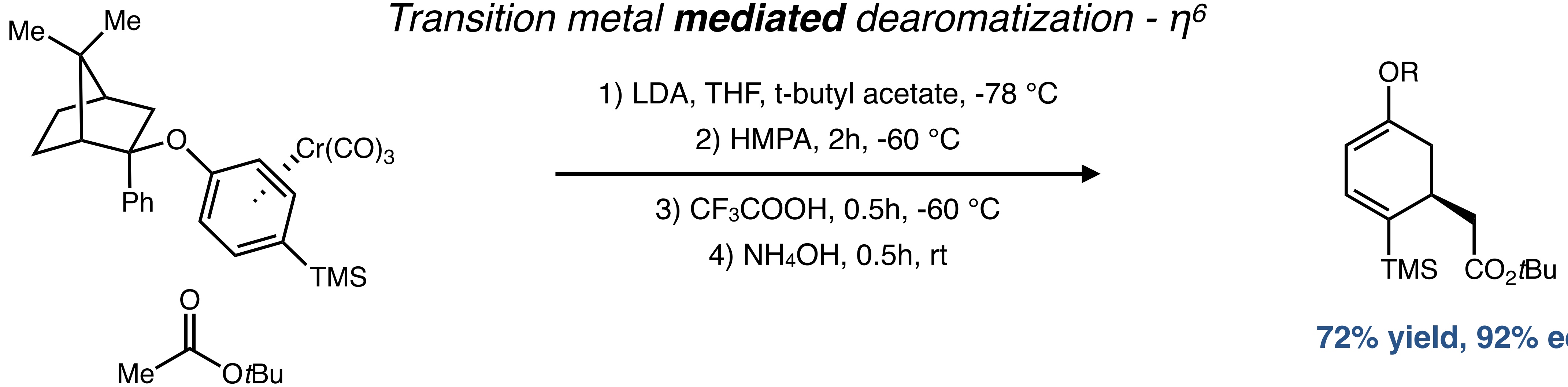
Prefer nucleophilic addition at meta



H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

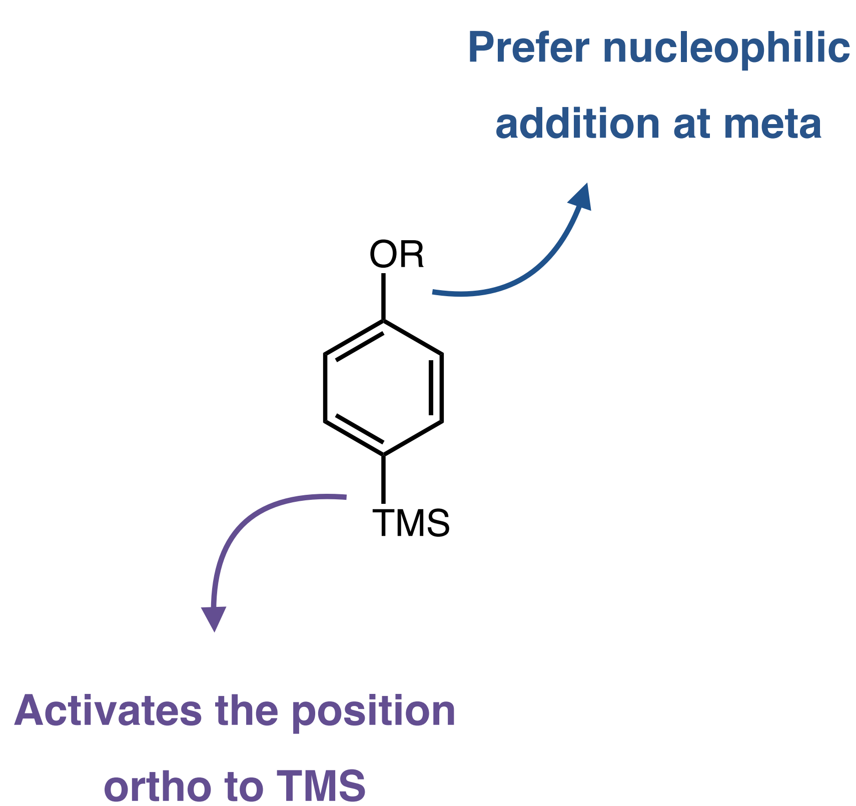
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η[6]*



72% yield, 92% ee

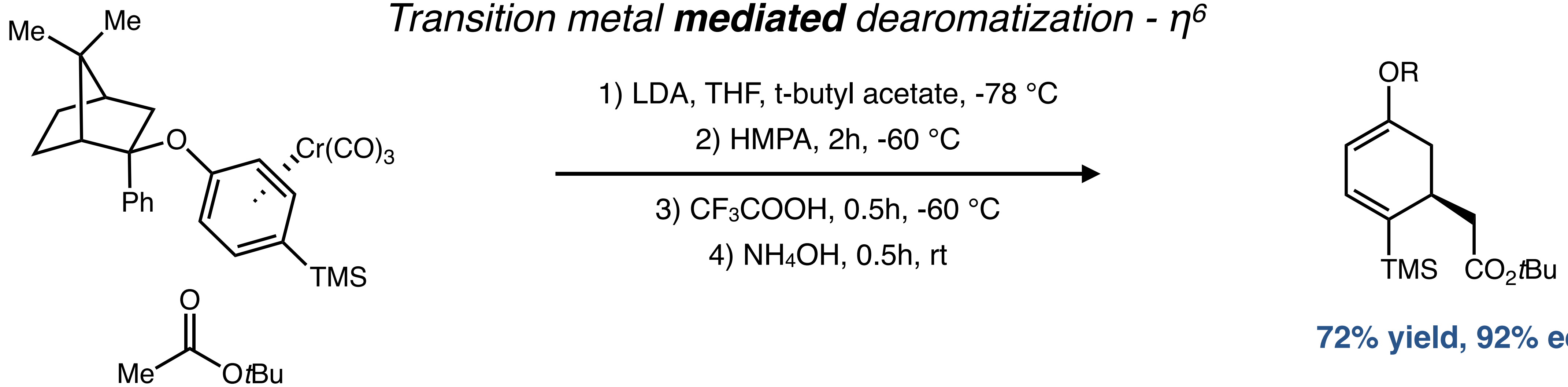
- Regioselectivity



H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

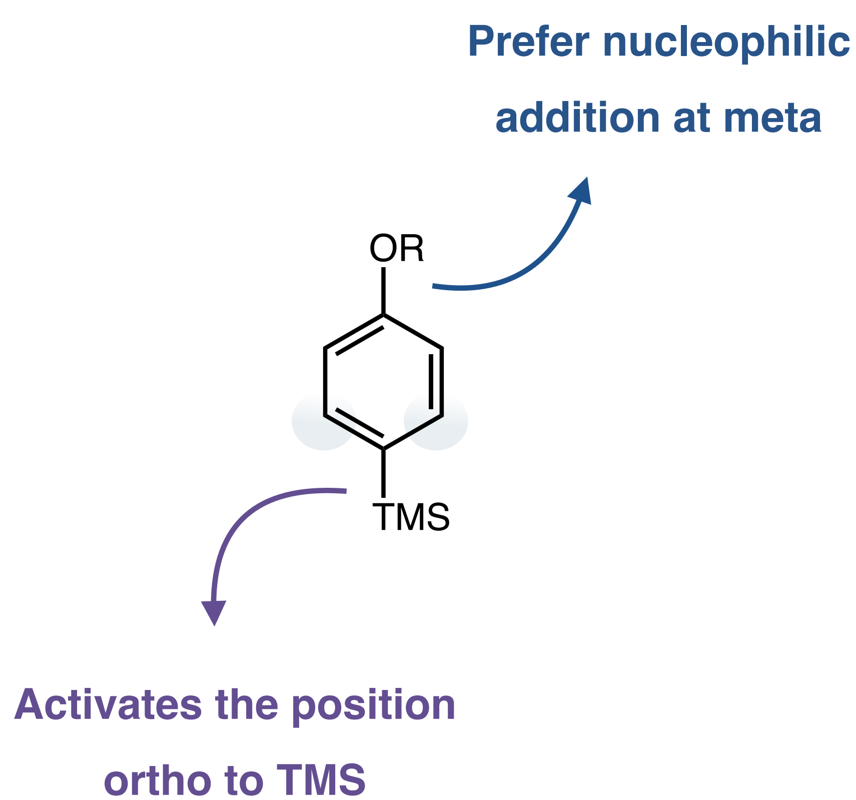
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^6*



72% yield, 92% ee

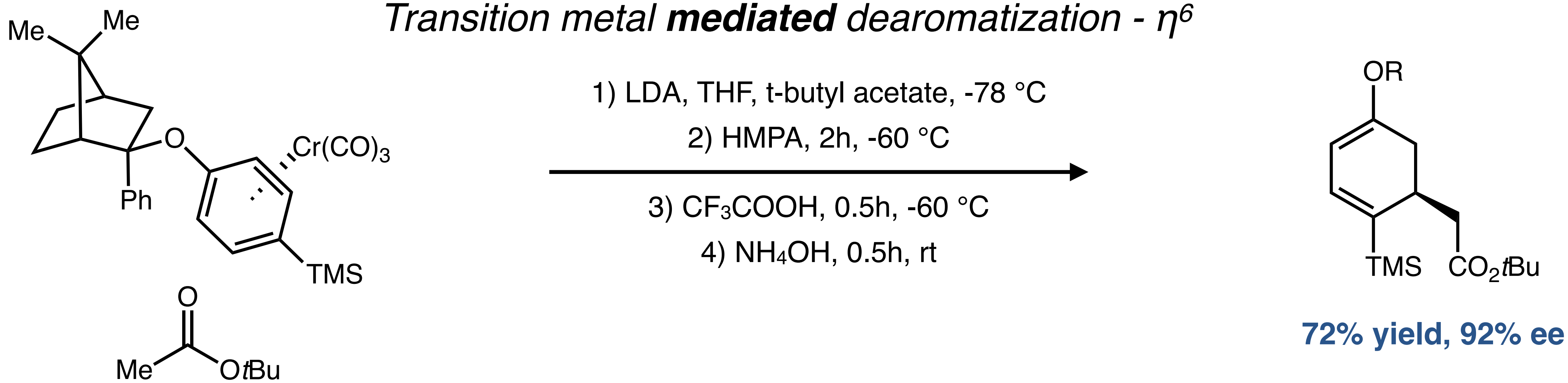
- Regioselectivity



H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

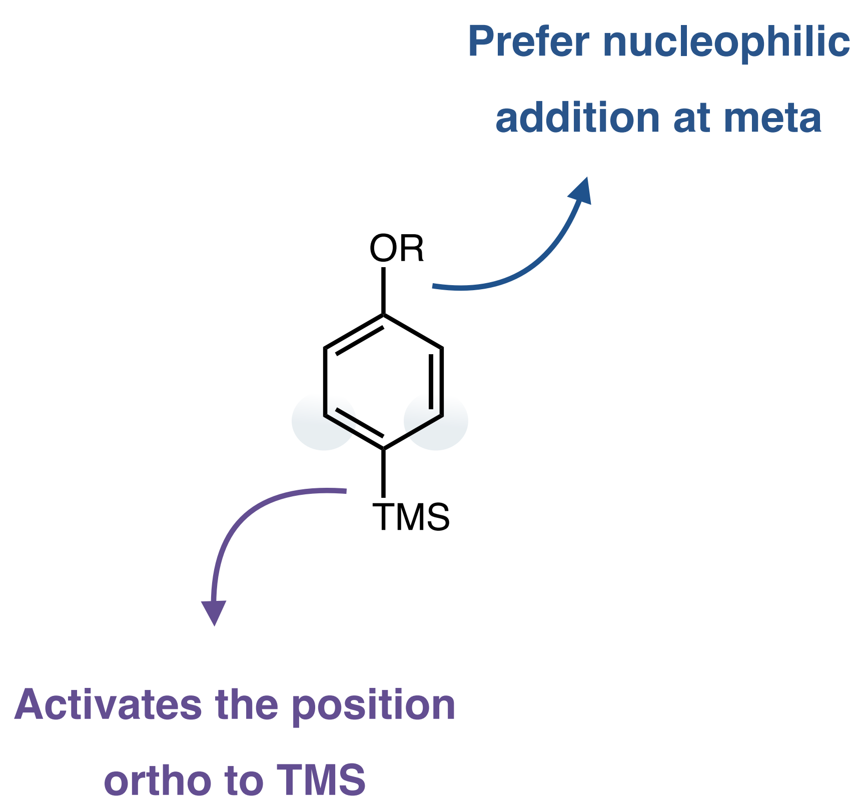
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η⁶*



72% yield, 92% ee

■ Regioselectivity

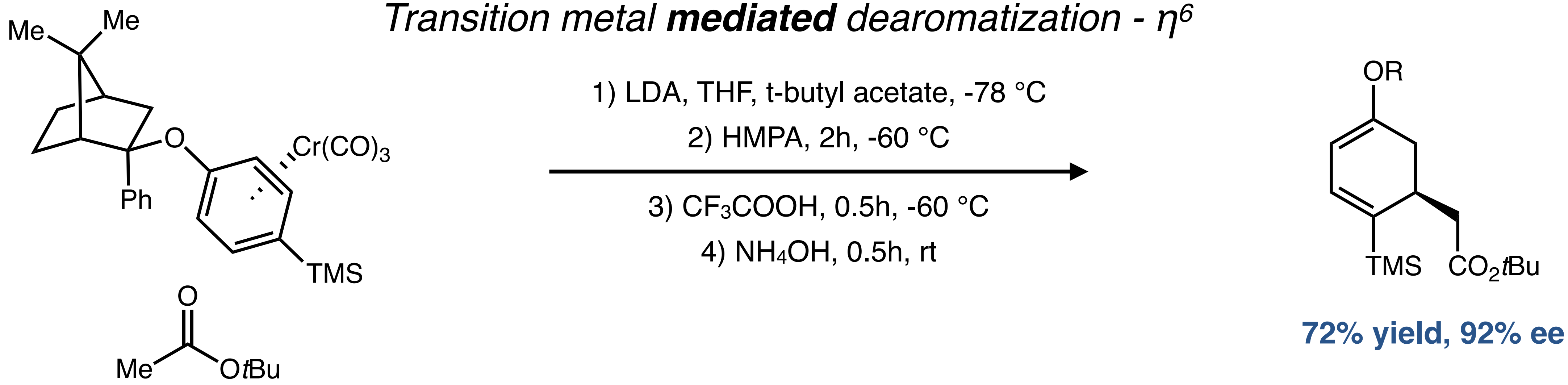


■ Stereoselectivity

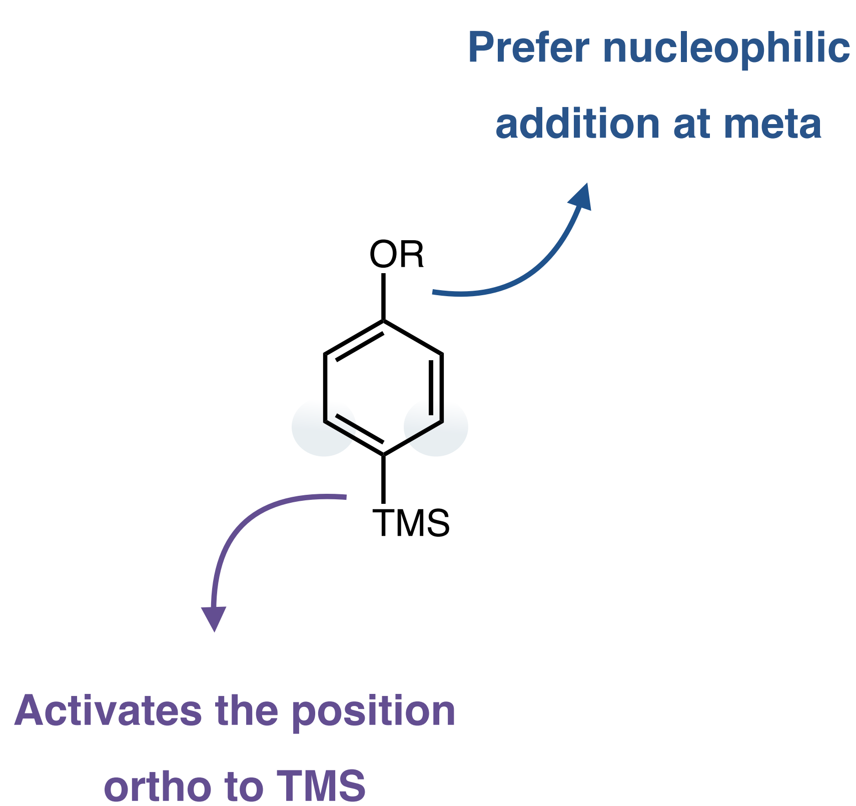
H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

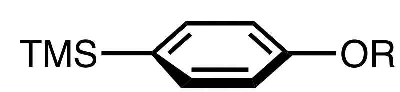
*Transition metal **mediated** dearomatization - η⁶*



- Regioselectivity



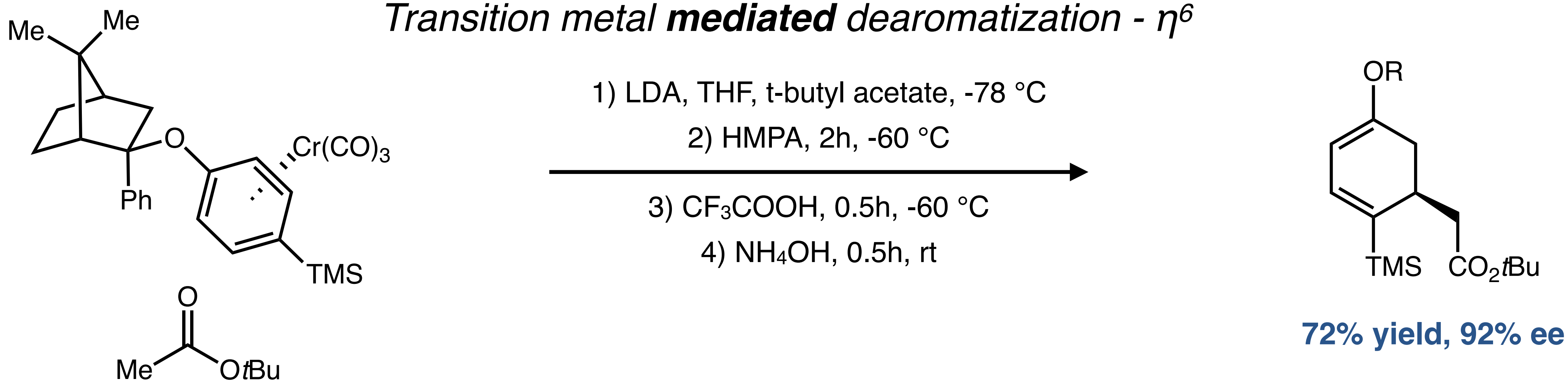
- Stereoselectivity



H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

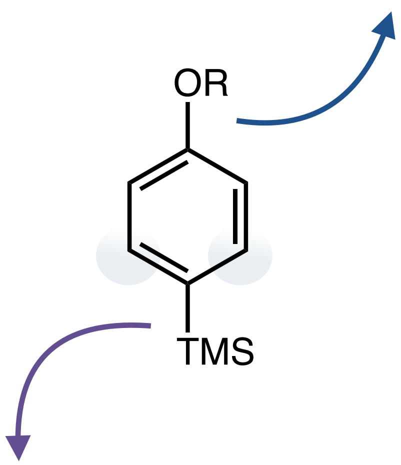
*Transition metal **mediated** dearomatization - η^6*



72% yield, 92% ee

- Regioselectivity

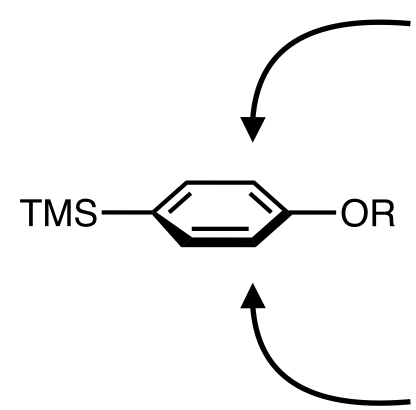
Prefer nucleophilic addition at meta



Activates the position ortho to TMS

- Stereoselectivity

Top face coordination

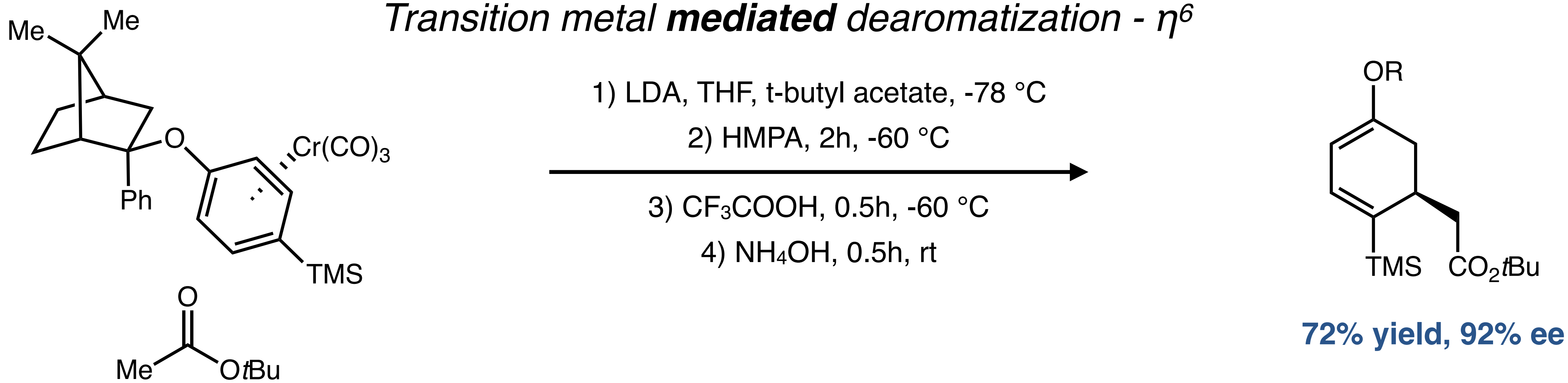


Bottom face coordination

H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

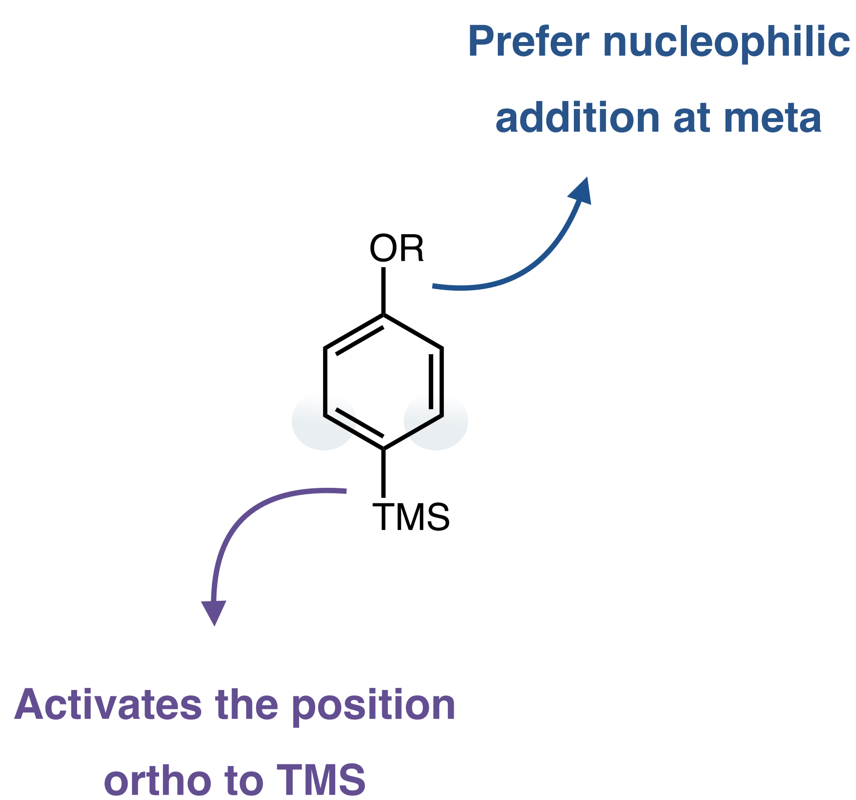
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^6*

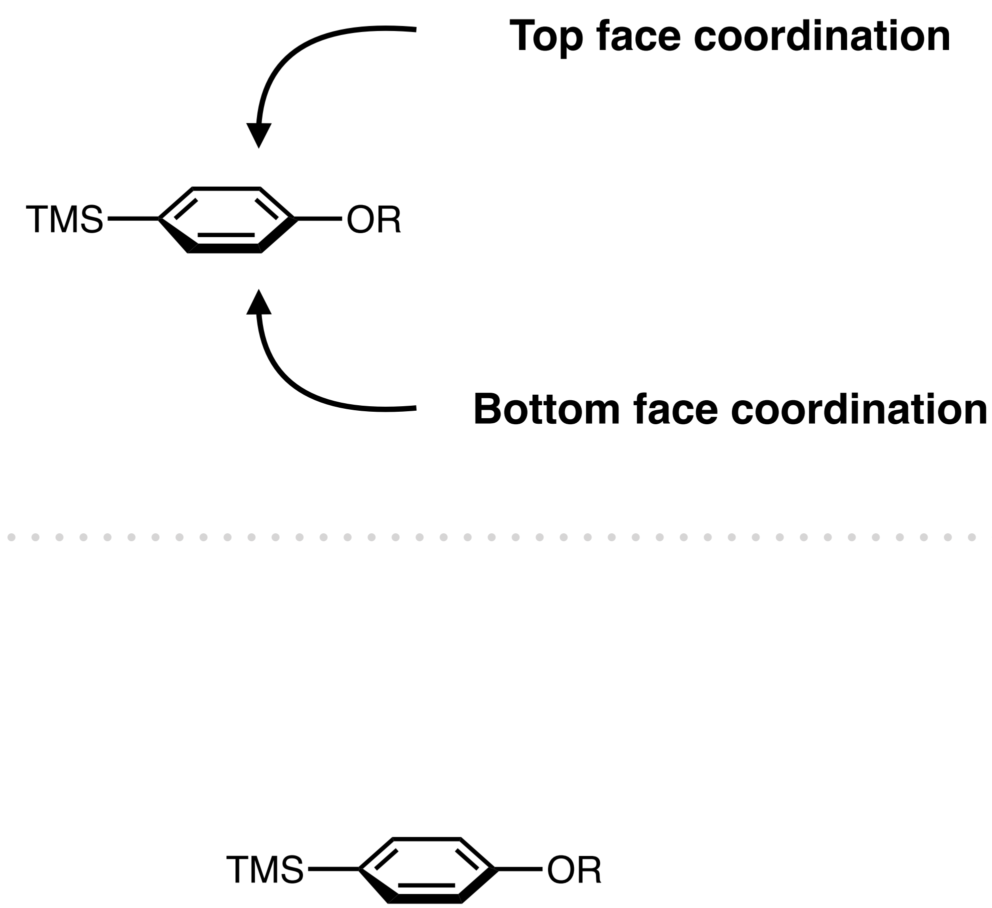


72% yield, 92% ee

- Regioselectivity



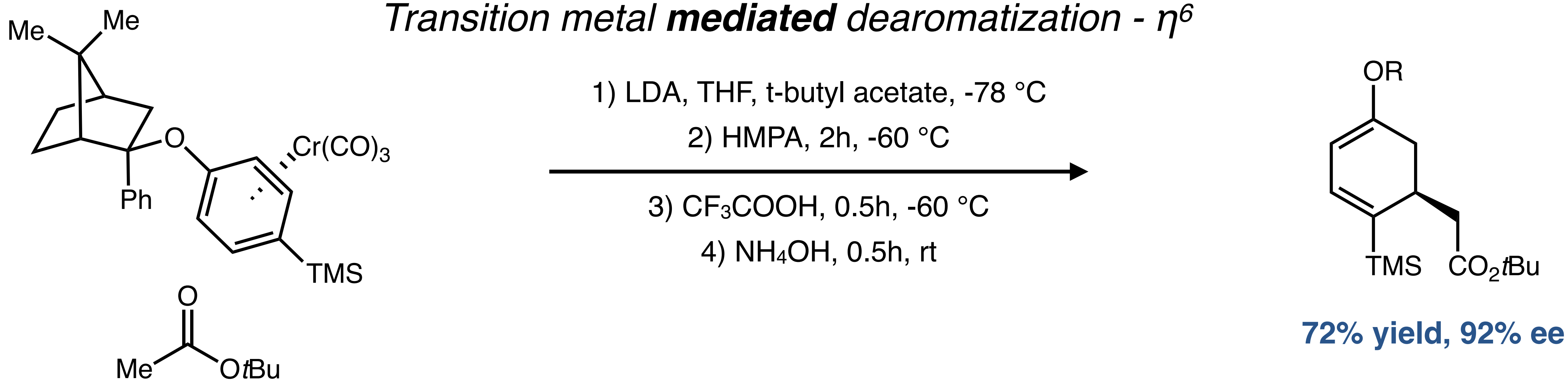
- Stereoselectivity



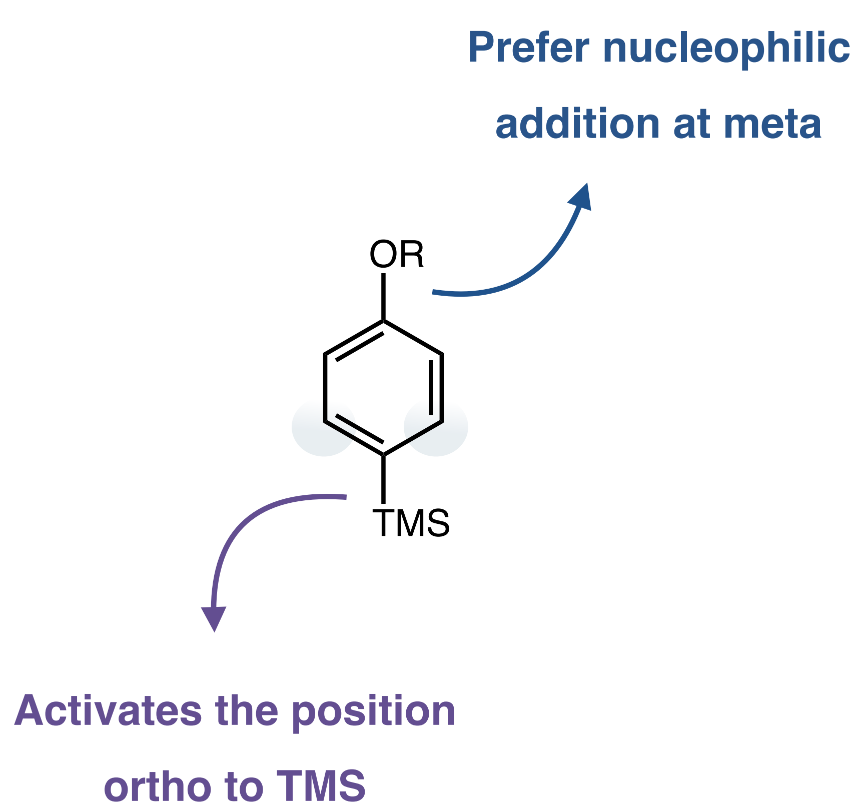
H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

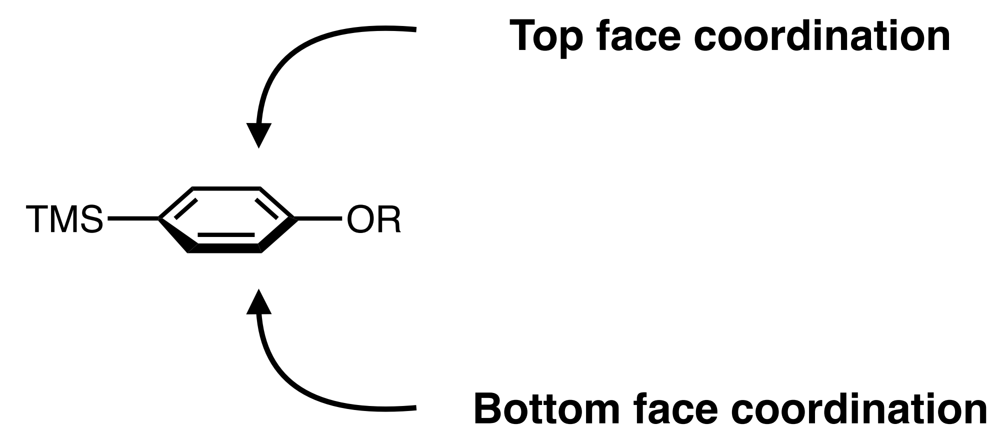
*Transition metal **mediated** dearomatization - η^6*

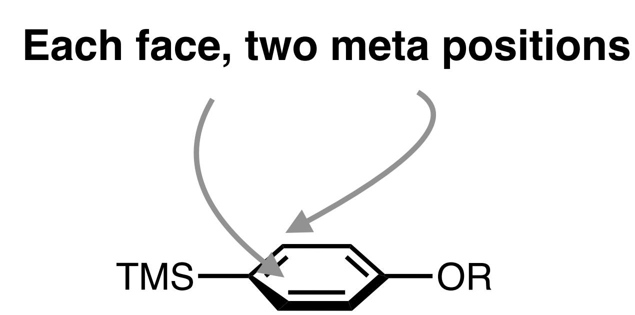


Regioselectivity



Stereoselectivity





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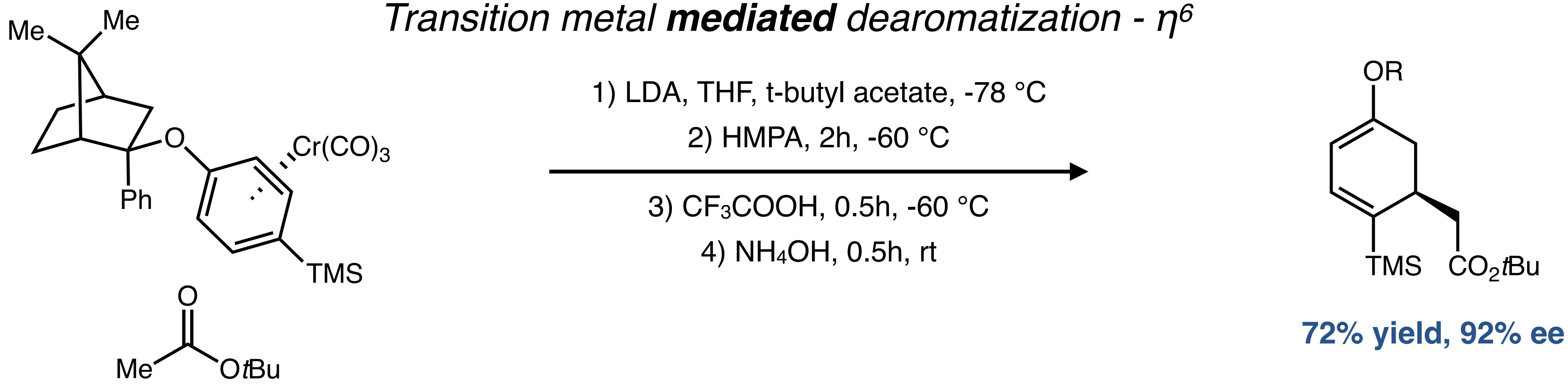
Transition Metal Approach to Dearomatization

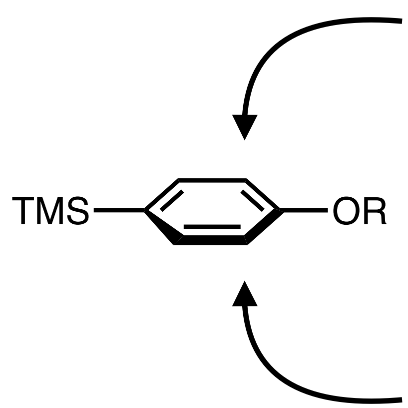
*Transition metal **mediated** dearomatization - η⁶*



72% yield, 92% ee

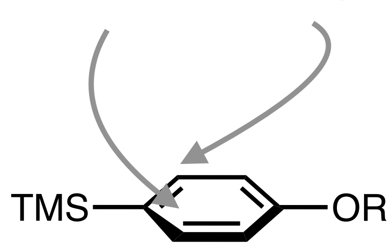
- Stereoselectivity

Top face coordination



Bottom face coordination

Each face, two meta positions



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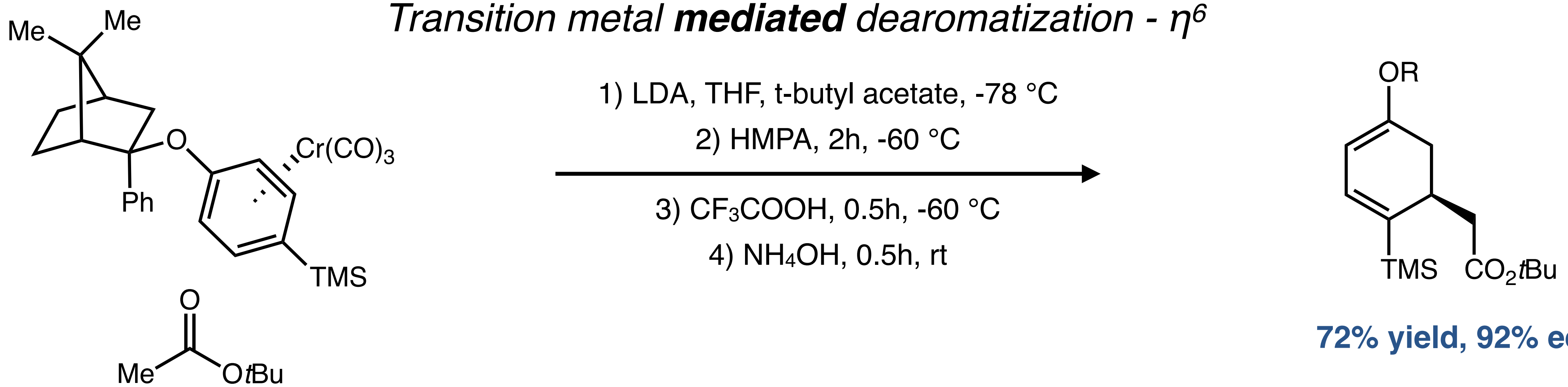
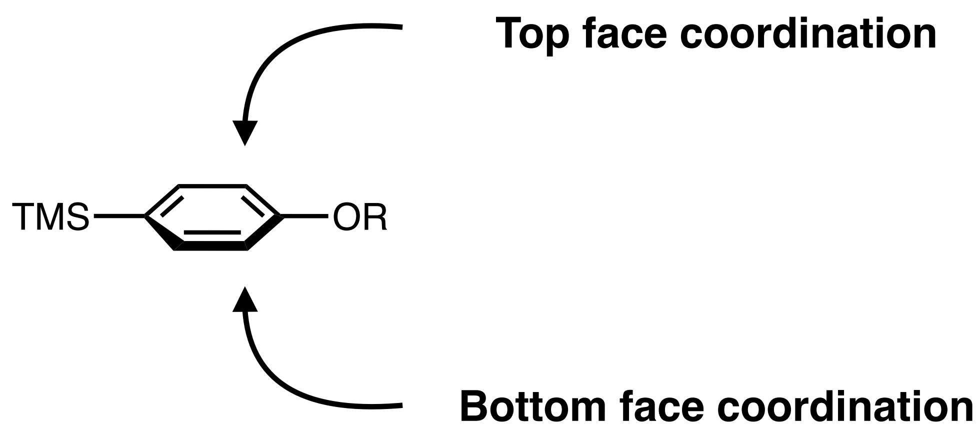
Transition Metal Approach to Dearomatization

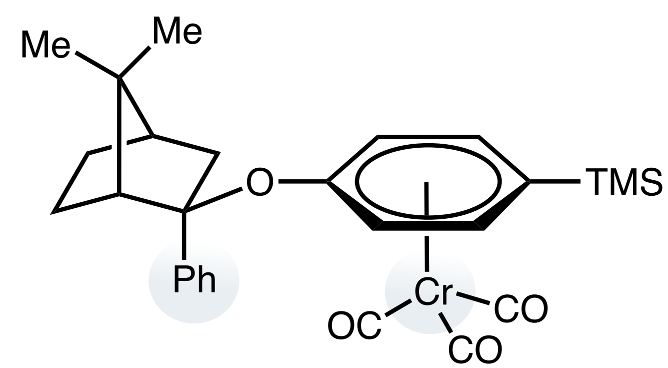
Transition metal ***mediated*** *dearomatization - η^6*



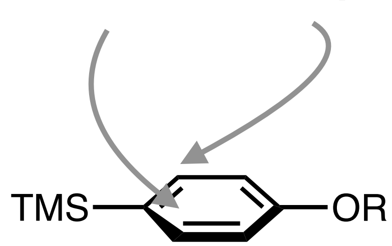
72% yield, 92% ee

- Stereoselectivity





Each face, two meta positions



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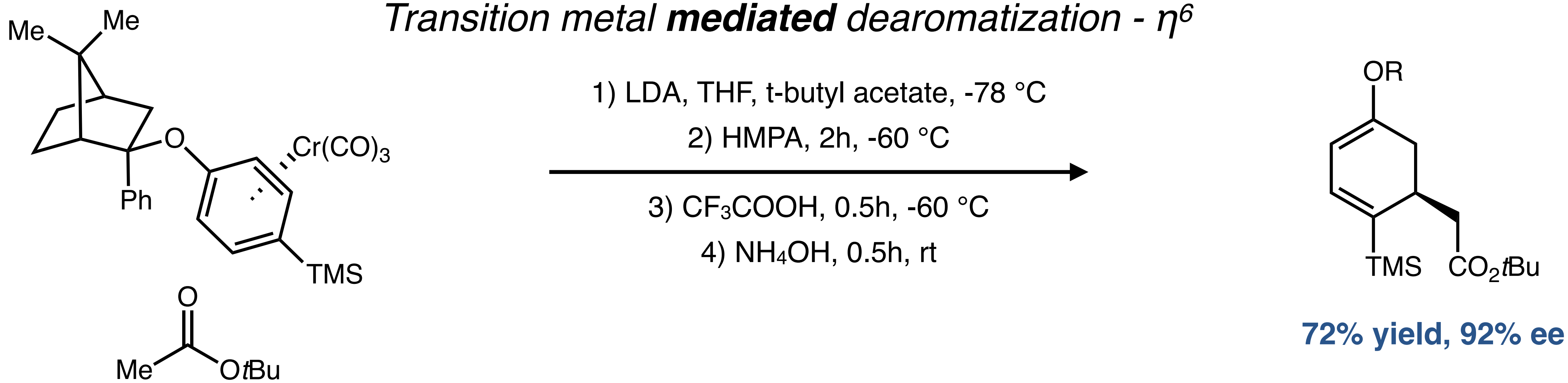
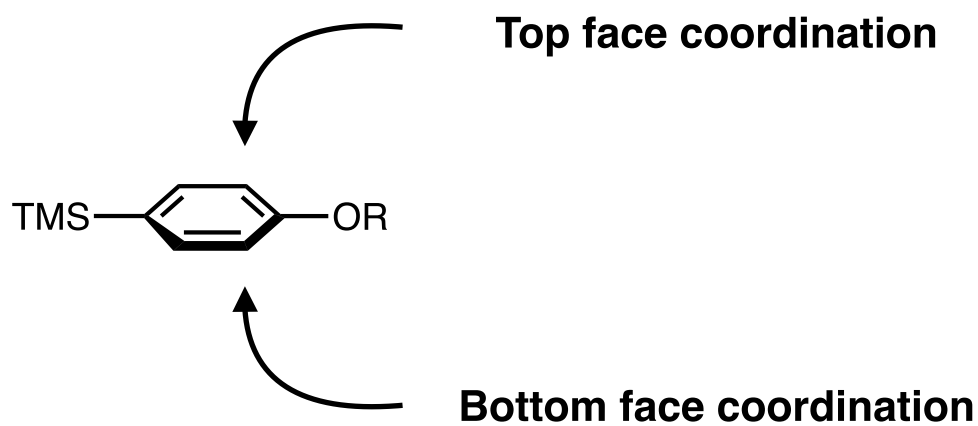
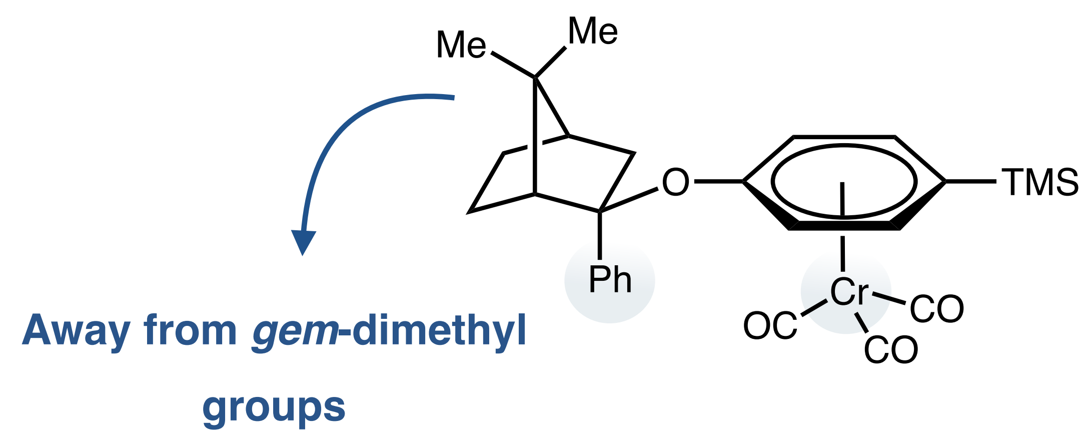
Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^6*

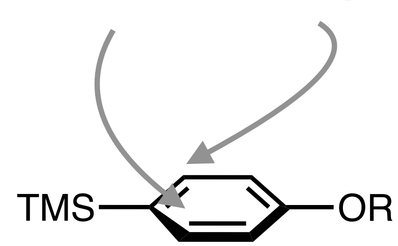


- Stereoselectivity





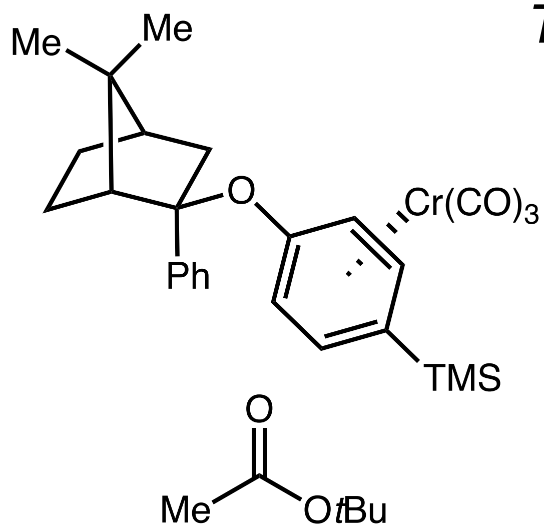
Each face, two meta positions

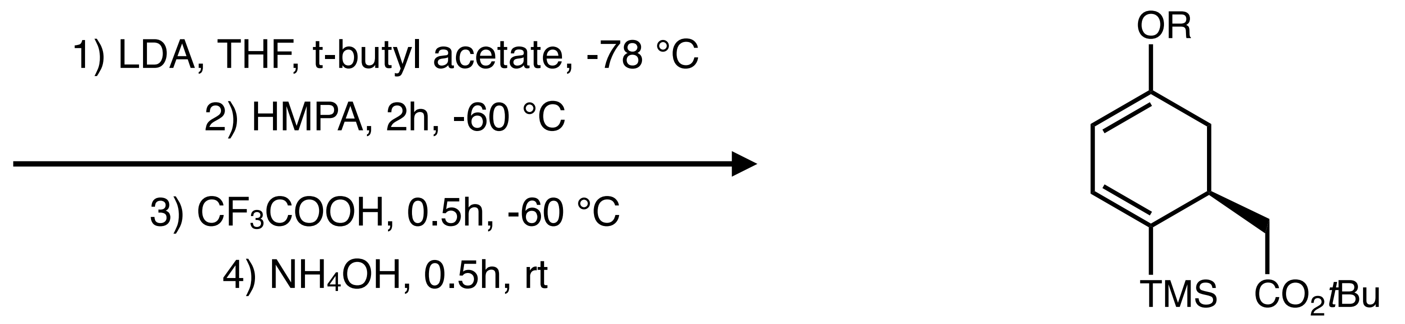


H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

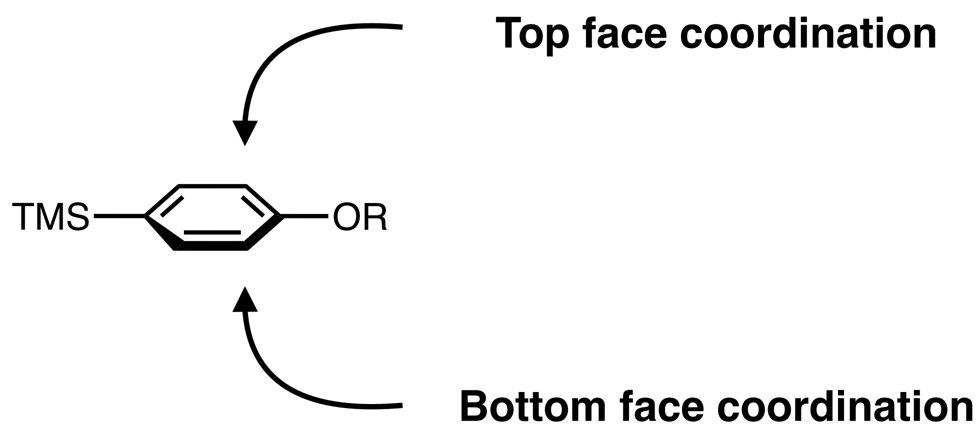
*Transition metal **mediated** dearomatization - η^6*

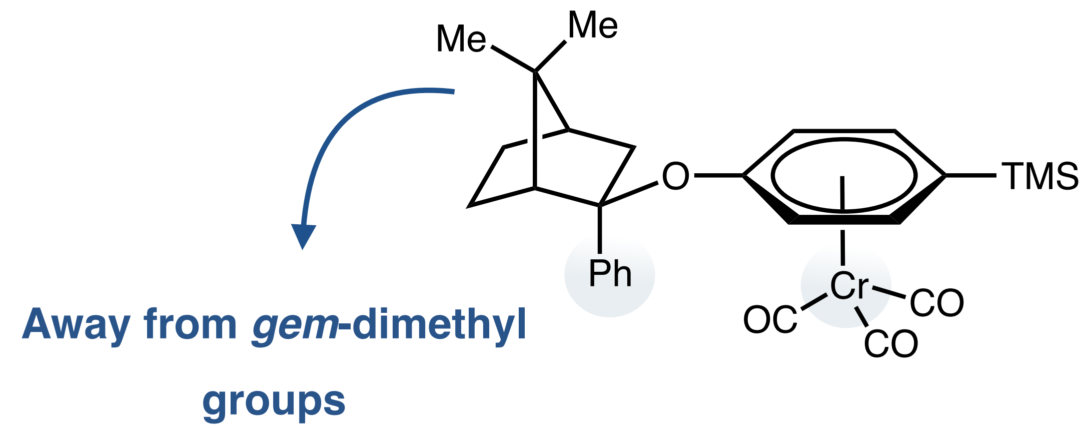




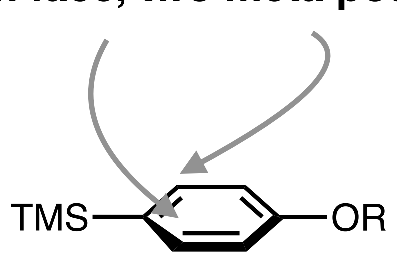
72% yield, 92% ee

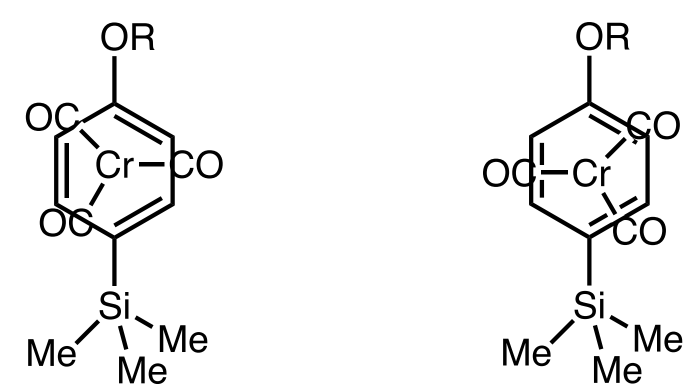
- Stereoselectivity





Each face, two meta positions



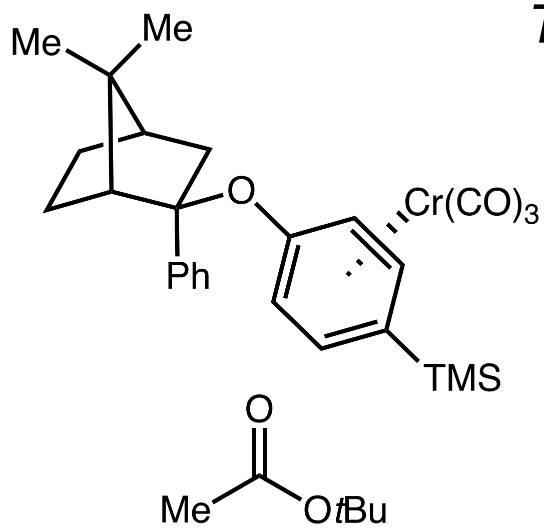


***I**$_l$* ***I**$_r$*

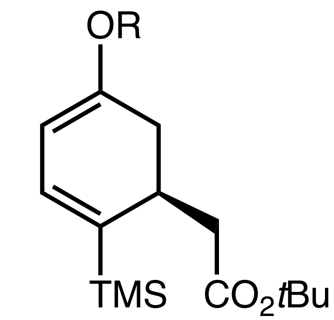
H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η^6*



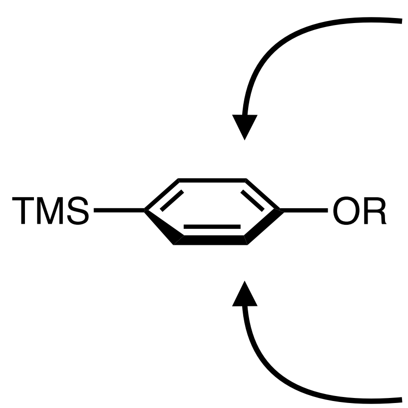
1) LDA, THF, t-butyl acetate, -78 °C
2) HMPA, 2h, -60 °C
3) CF_3COOH, 0.5h, -60 °C
4) NH_4OH, 0.5h, rt



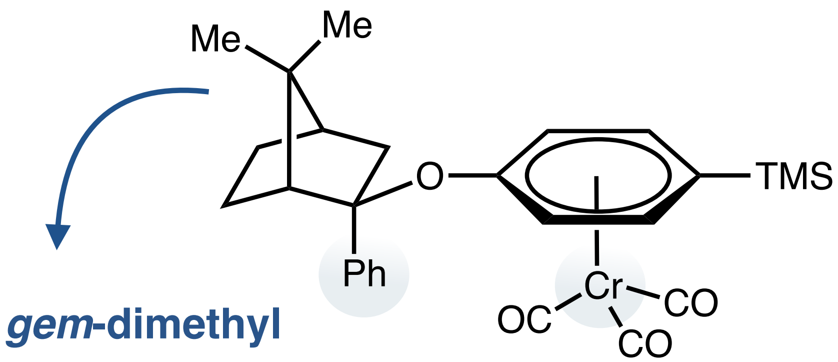
72% yield, 92% ee

- Stereoselectivity

Top face coordination

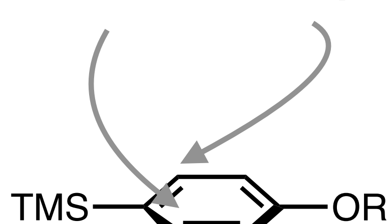


Bottom face coordination

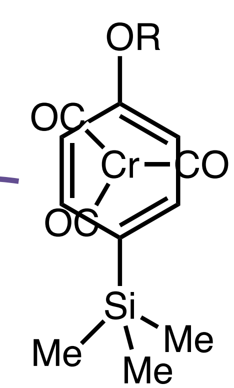


Away from *gem*-dimethyl groups

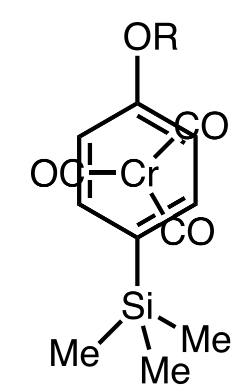
Each face, two meta positions



Chiral auxiliary controls tripod to favor I_l over I_r



I_l

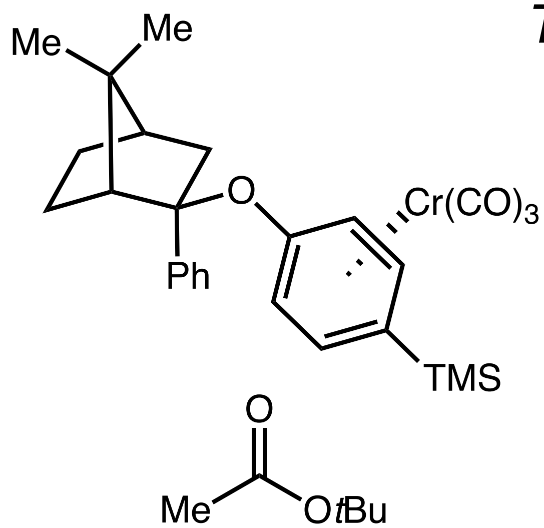


I_r

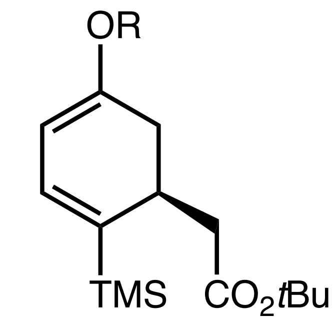
H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Transition Metal Approach to Dearomatization

*Transition metal **mediated** dearomatization - η⁶*

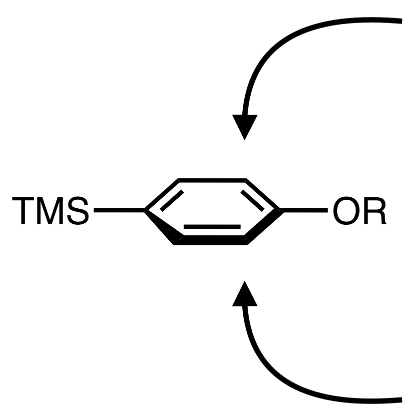


1) LDA, THF, t-butyl acetate, -78 °C
2) HMPA, 2h, -60 °C
3) CF_3COOH, 0.5h, -60 °C
4) NH_4OH, 0.5h, rt



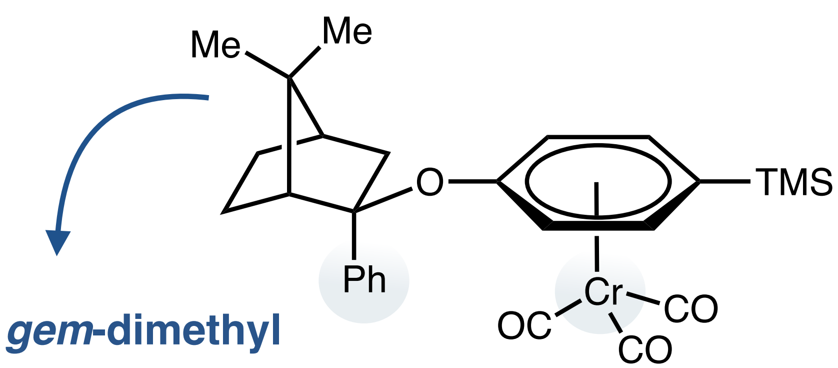
72% yield, 92% ee

- Stereoselectivity



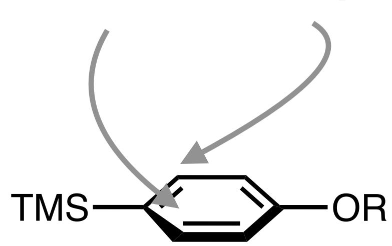
Top face coordination

Bottom face coordination

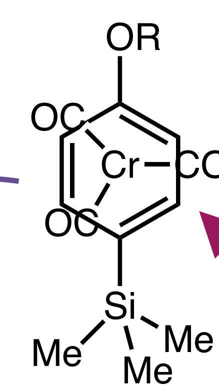


Away from *gem*-dimethyl groups

Each face, two meta positions

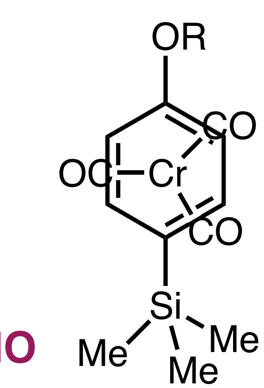


Chiral auxiliary controls tripod to favor I_l over I_r



I_l

Larger MO coefficient



I_r

H. Paramahamsan, A. J. Pearson, A. A. Pinkerton and E. A. Zhurova, *Organometallics*, **2008**, *27*, 900–907.

Outline

Radical approach

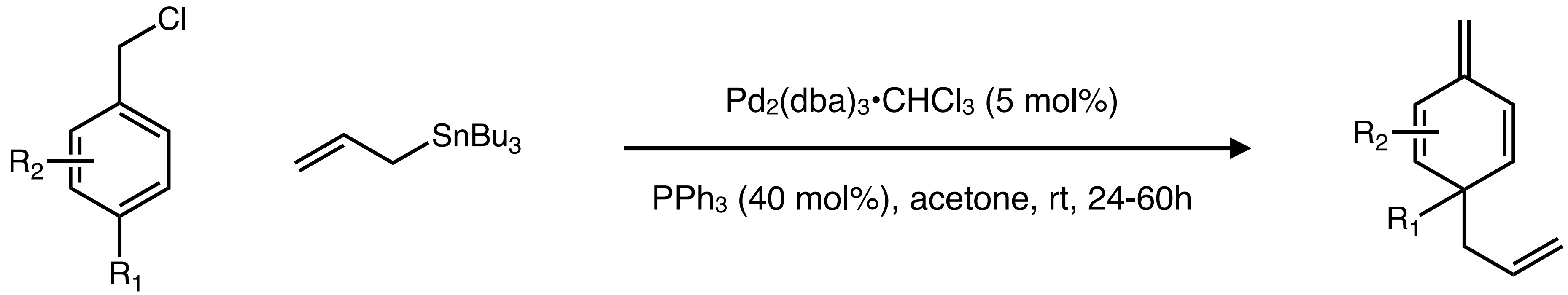
- **Traditional radical generation** — Birch & SmI_2
- **Photochemical**
  - **Single electron transfer**
    - Radical addition
    - Oxidation
    - Reduction
  - **Energy transfer**
    - Direct excitation
    - Sensitization

Transition-metal

- **Mediated**
  - η^2
  - η^6
- **Catalyzed** — *Pd*

Transition Metal Approach to Dearomatization

*Transition metal **catalyzed** dearomatization*



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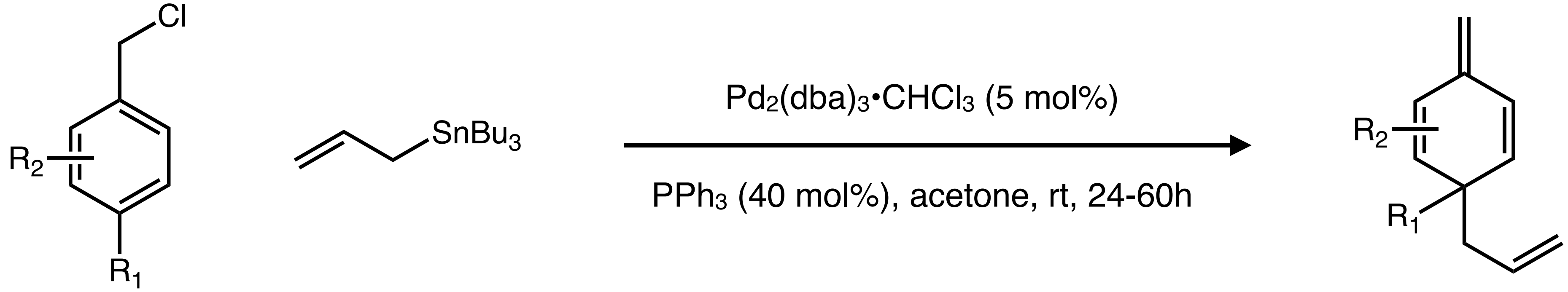

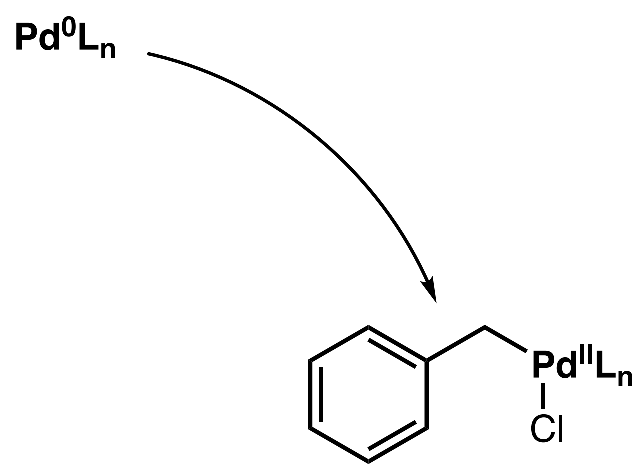

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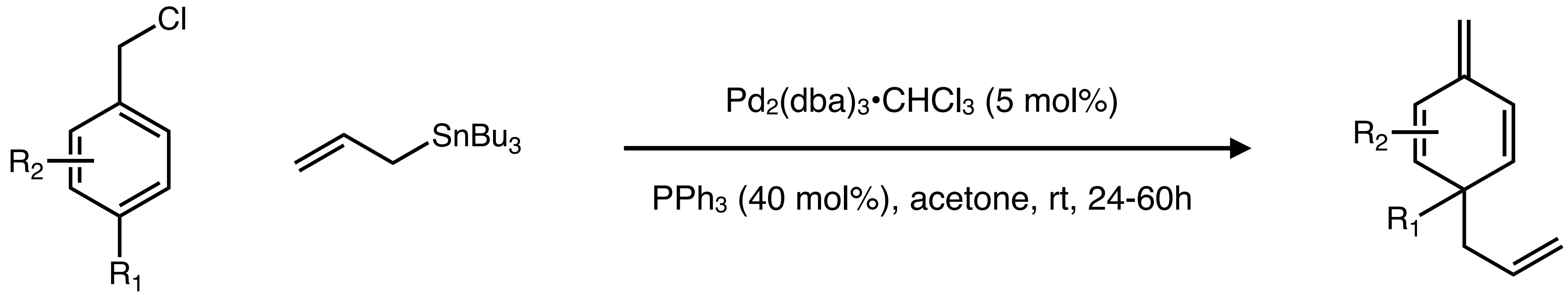

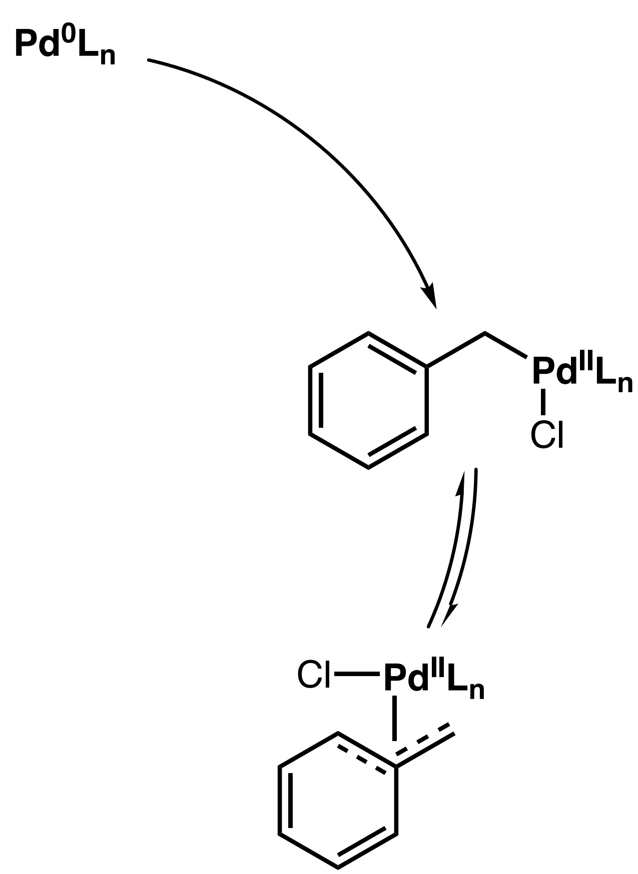

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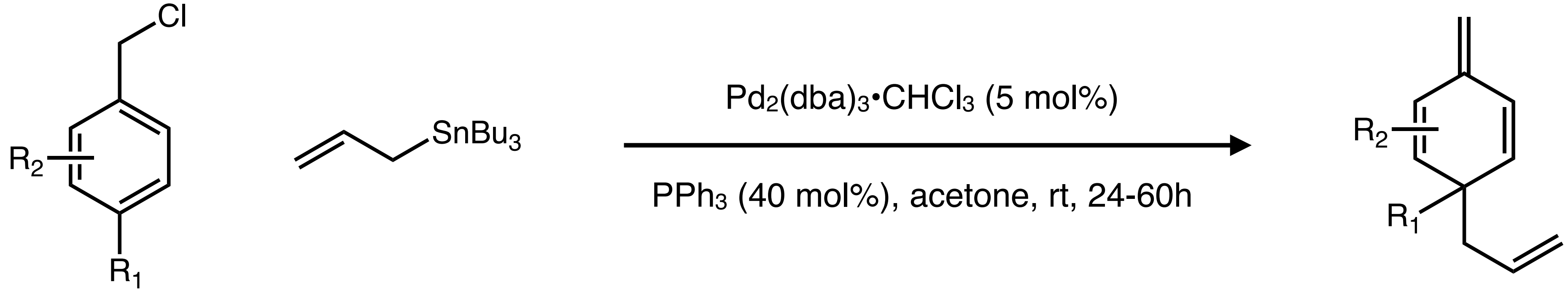

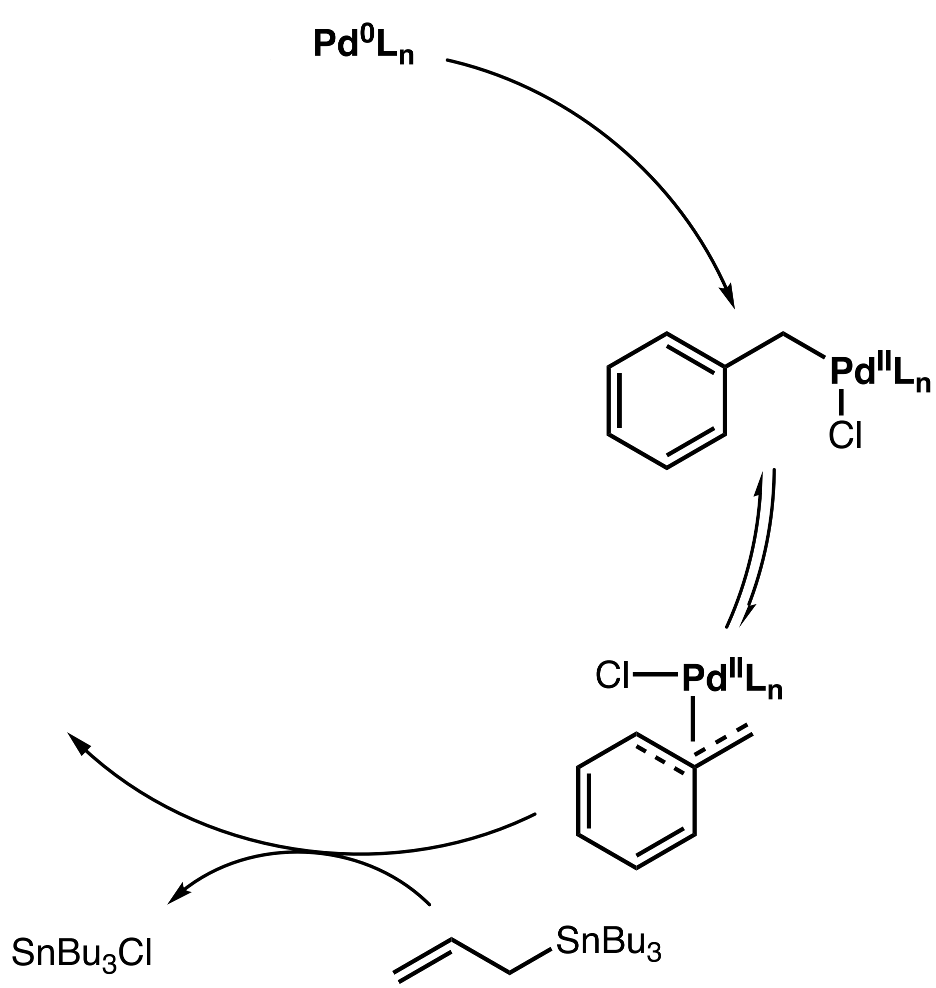

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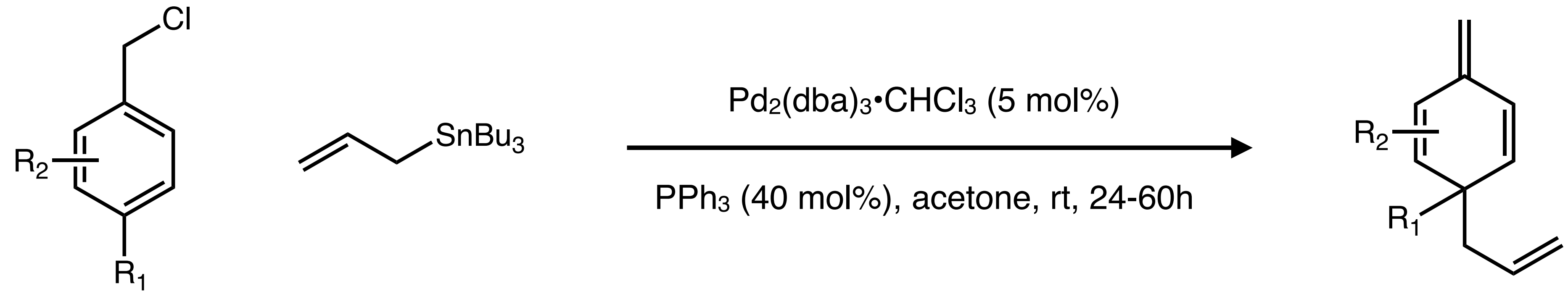

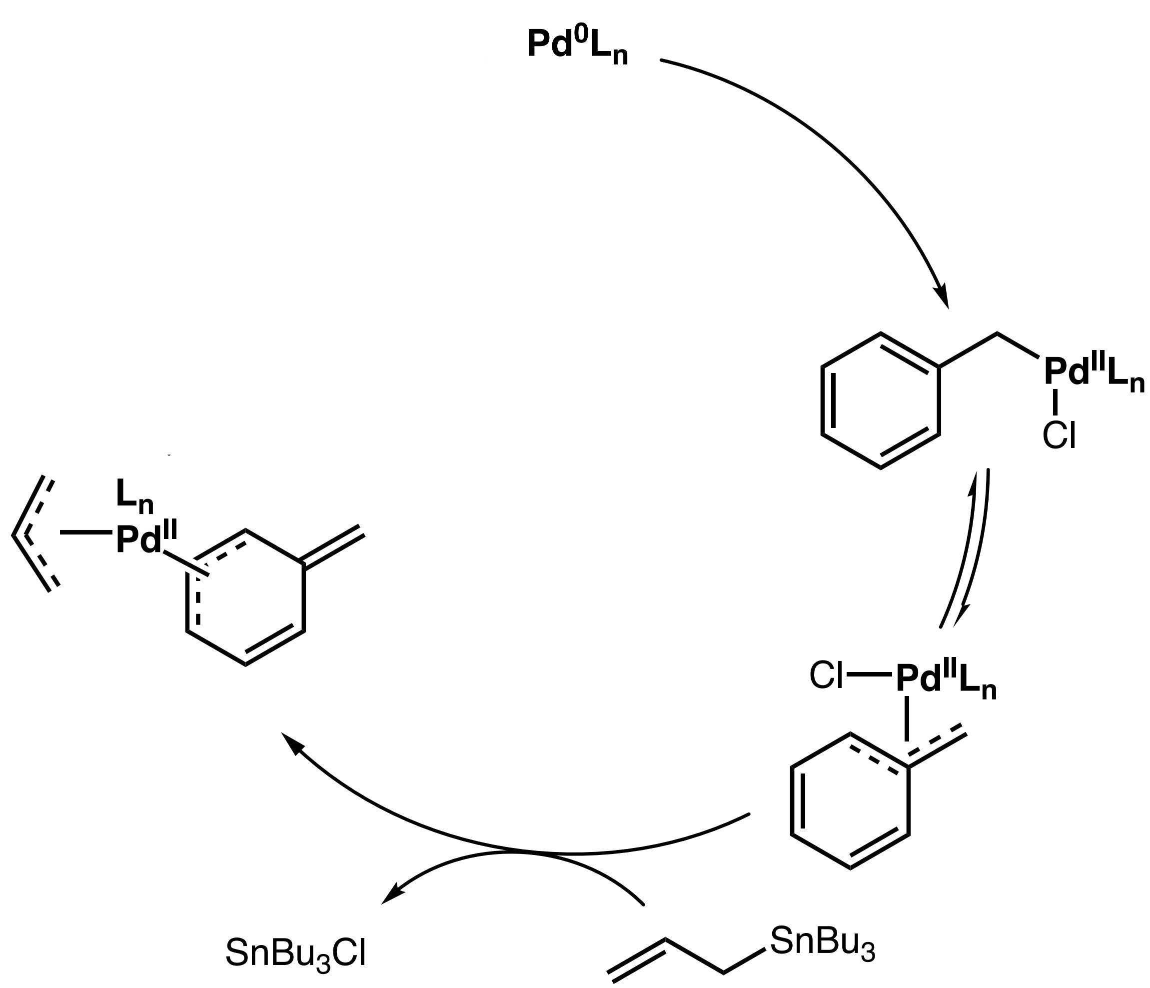

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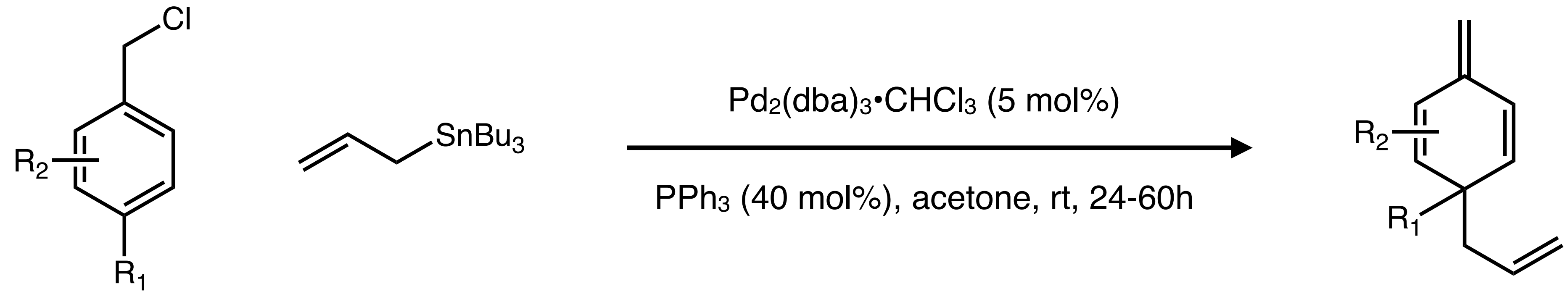

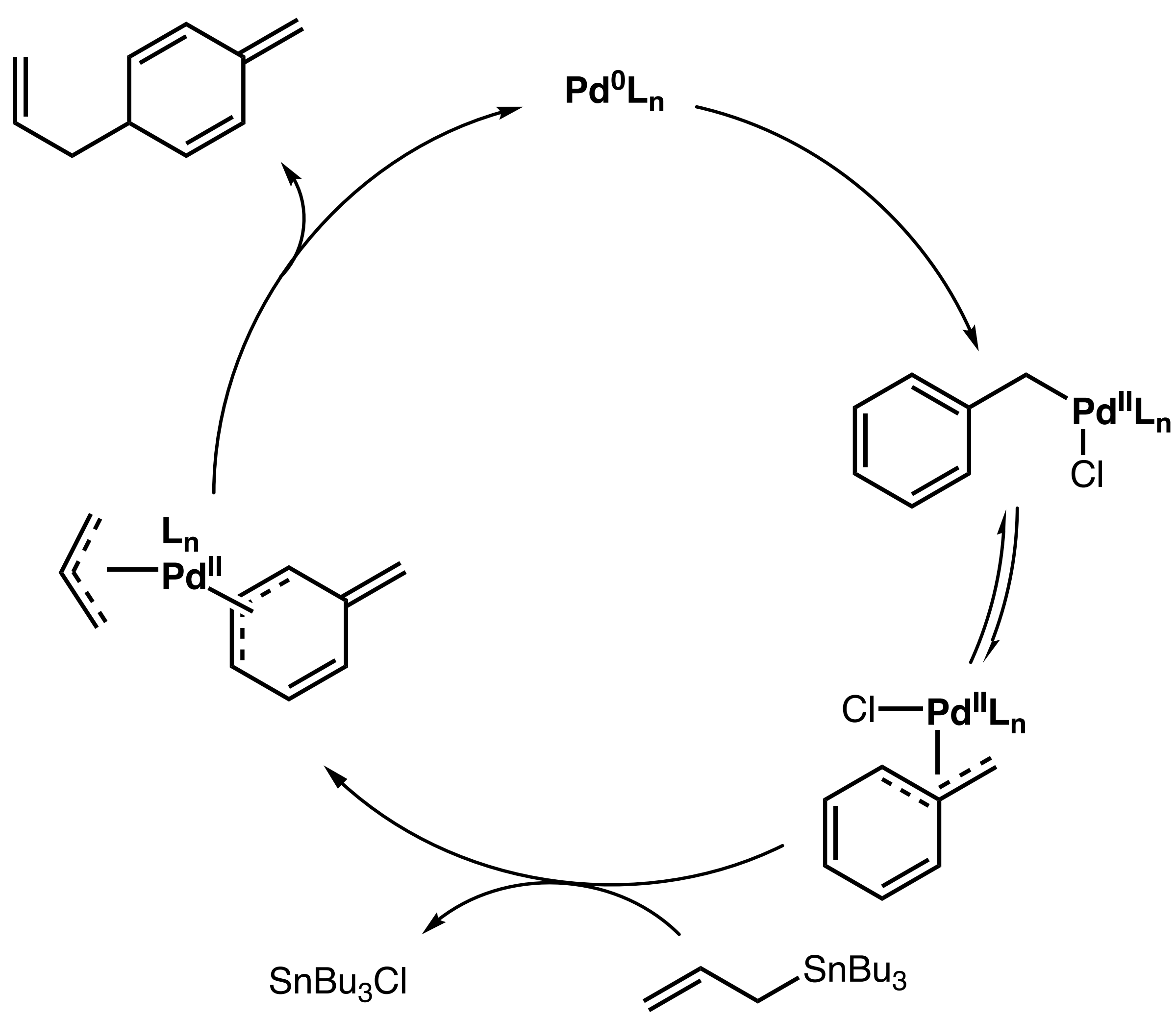

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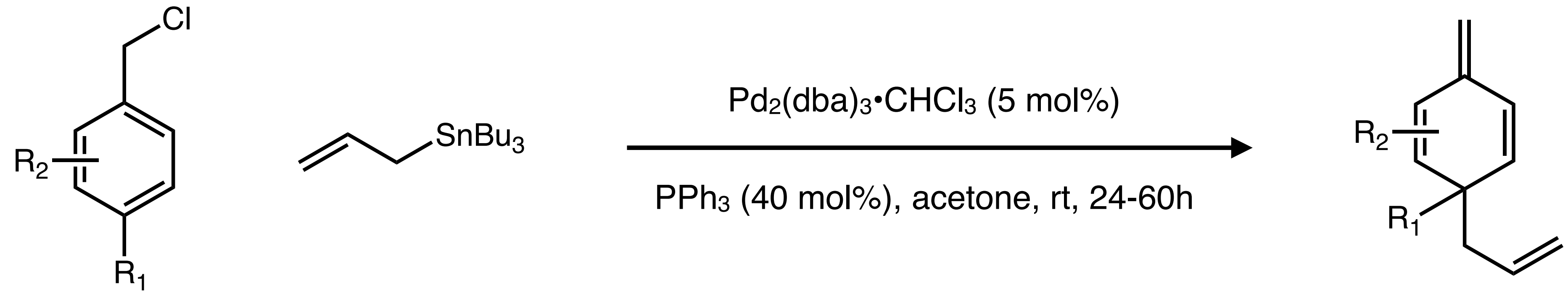

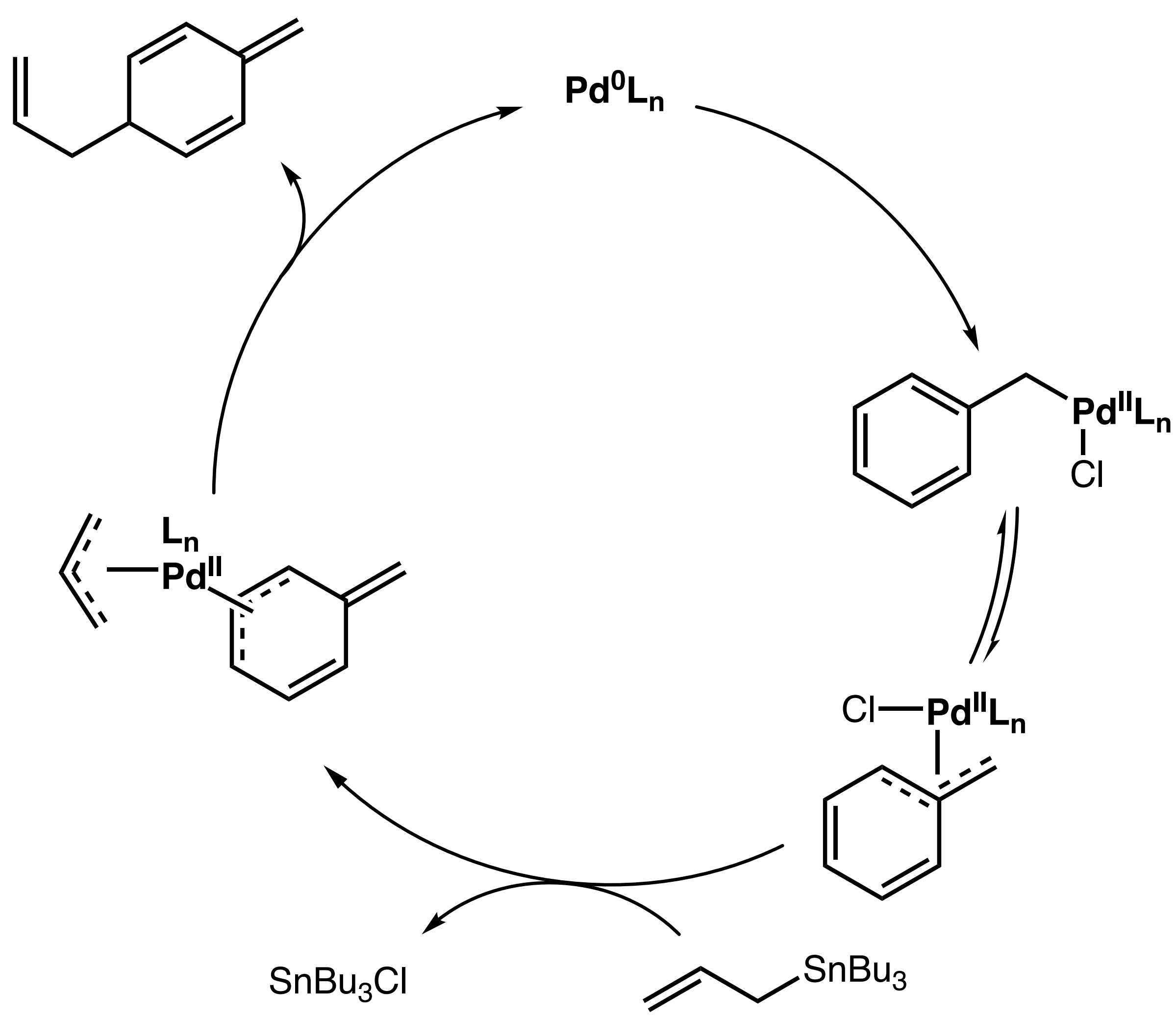

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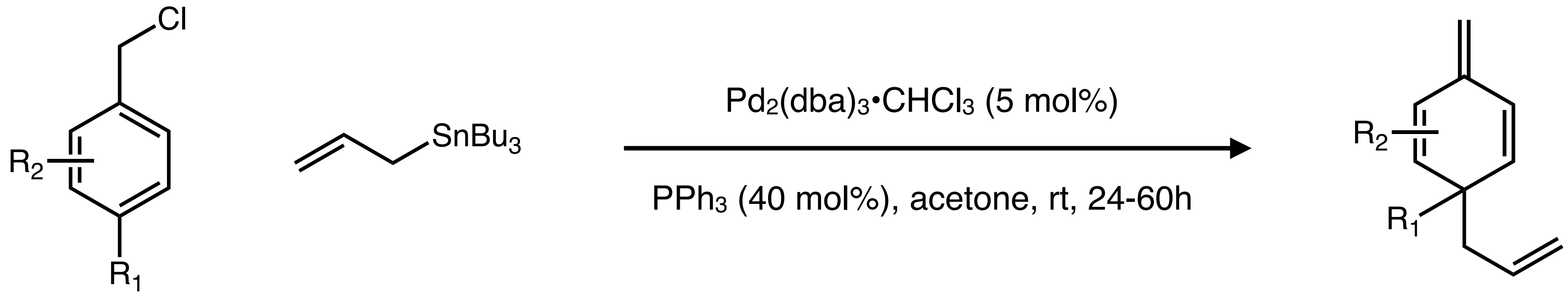

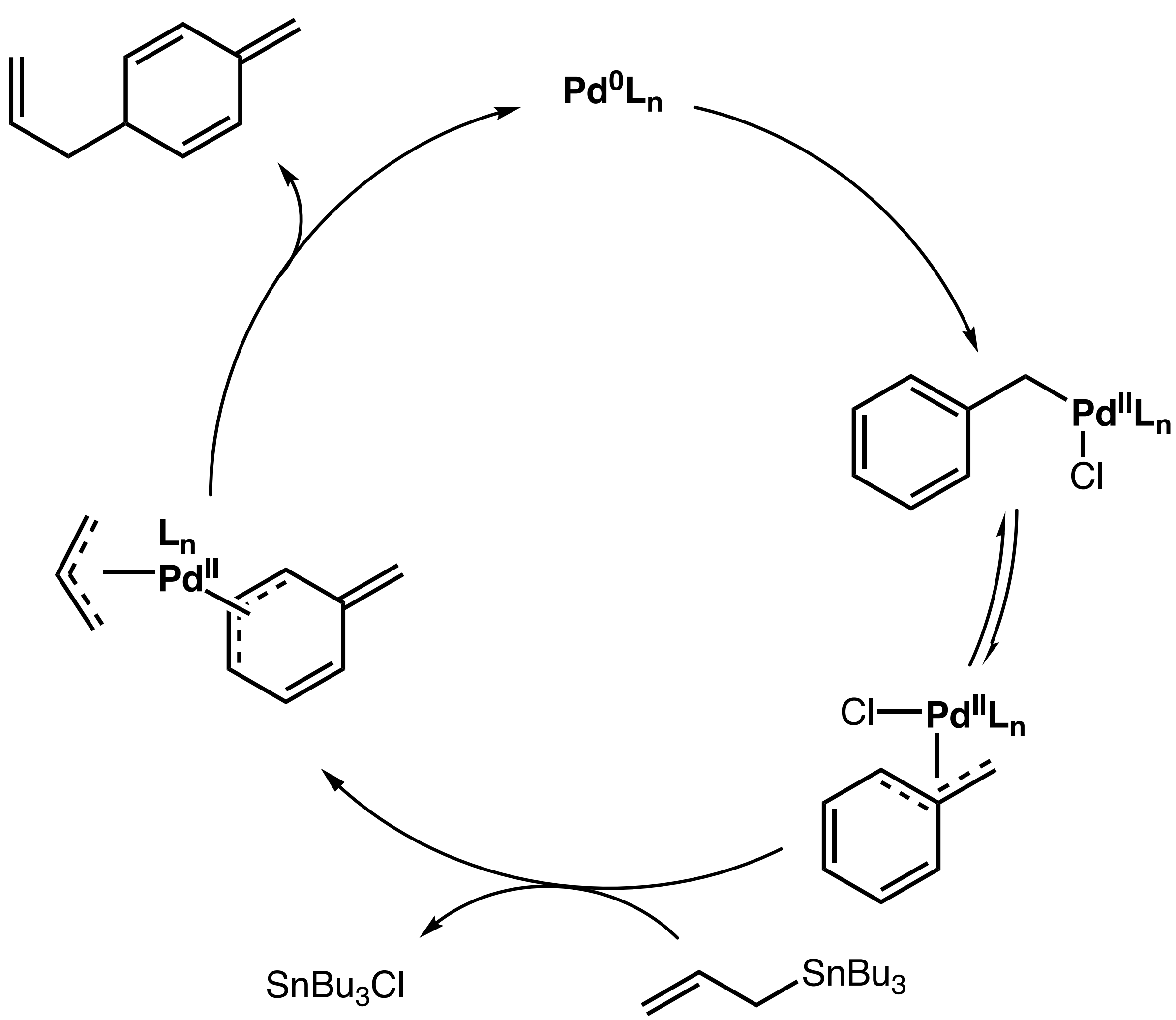

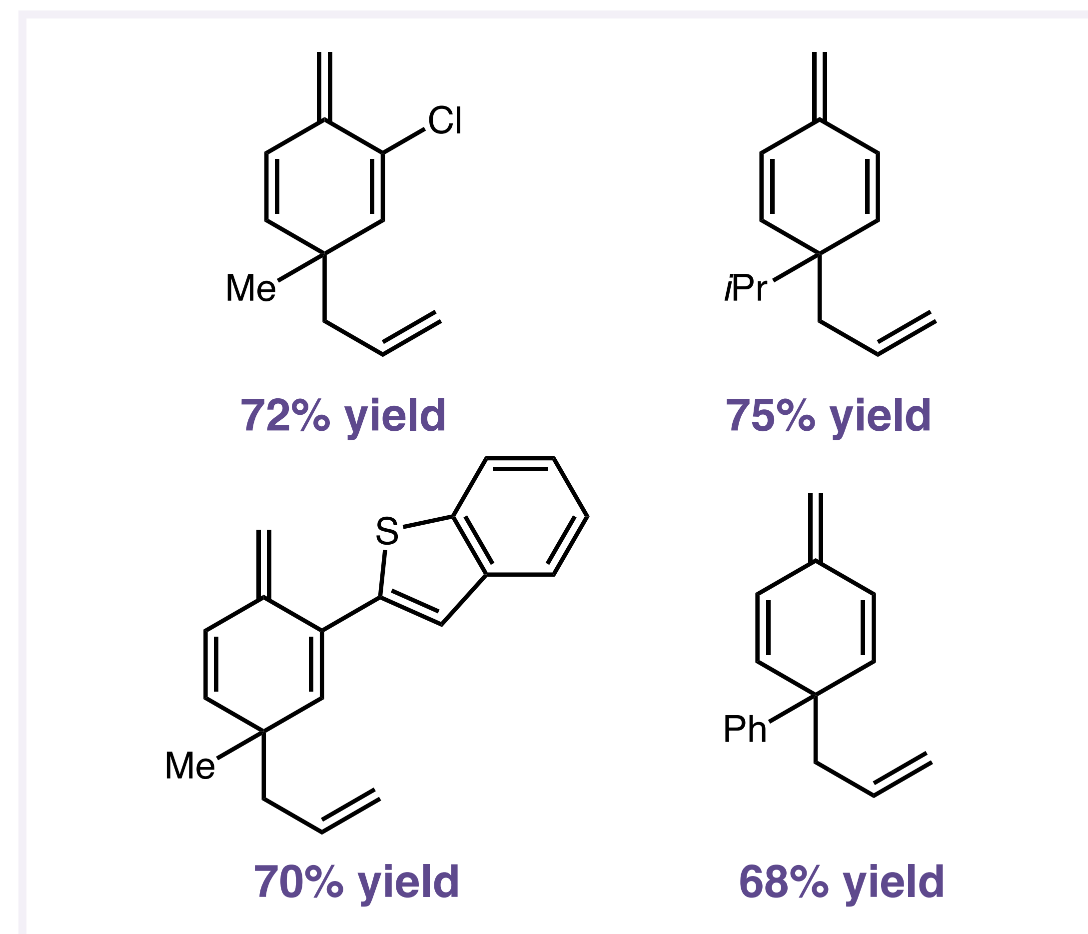

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PRINCETON UNIVERSITY