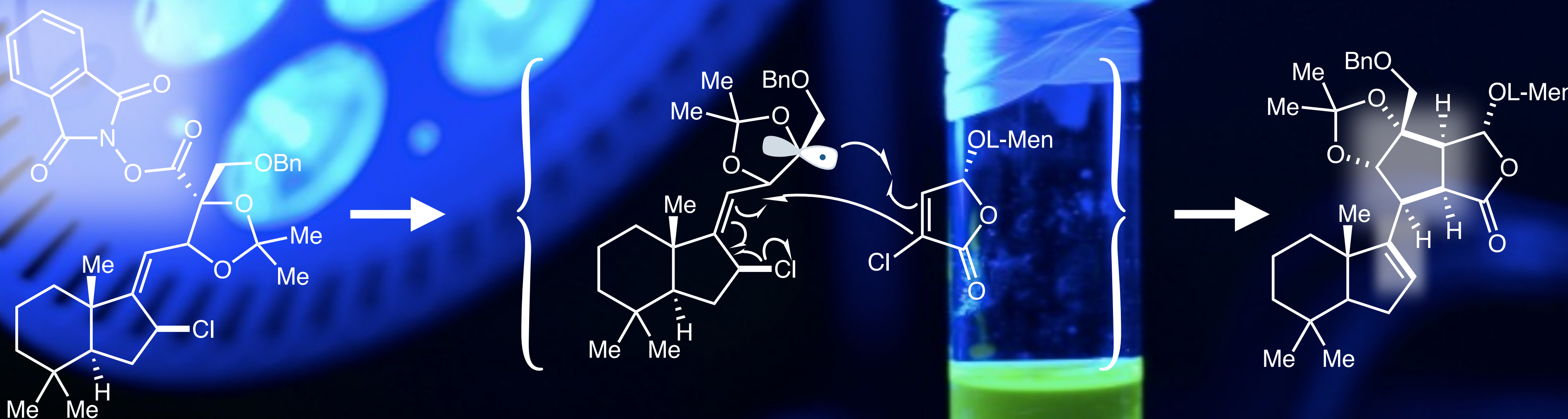
Radical Cyclizations in Total Synthesis via Photoredox Catalysis



Will Zhao

The MacMillan Group

Literature Review

Sept 27th, 2024

Radical Cyclizations: A Short History

The Dawn of Radical Chemistry

Moses Gomberg

AN INSTANCE OF TRIVALENT CARBON: TRIPHENYL-METHYL.

BY M. GOMBERG.

Received October 4, 1900.

[PRELIMINARY PAPER.]

> “*The stereochemical interest attached to [tetraphenylmethane] has induced me to take up the subject once more, in the hope of obtaining larger yields.*”

1900 | 1976 | 2013

Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757.

Radical Cyclizations: A Short History

The Dawn of Radical Chemistry

Moses Gomberg

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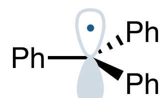


"Trivalent carbon"

1900

1976

2013

Gomberg, M. *J. Am. Chem. Soc.* **1900**, *22*, 757.

Radical Cyclizations: A Short History

The "Classical Antiquity" of Radical Chemistry

1900

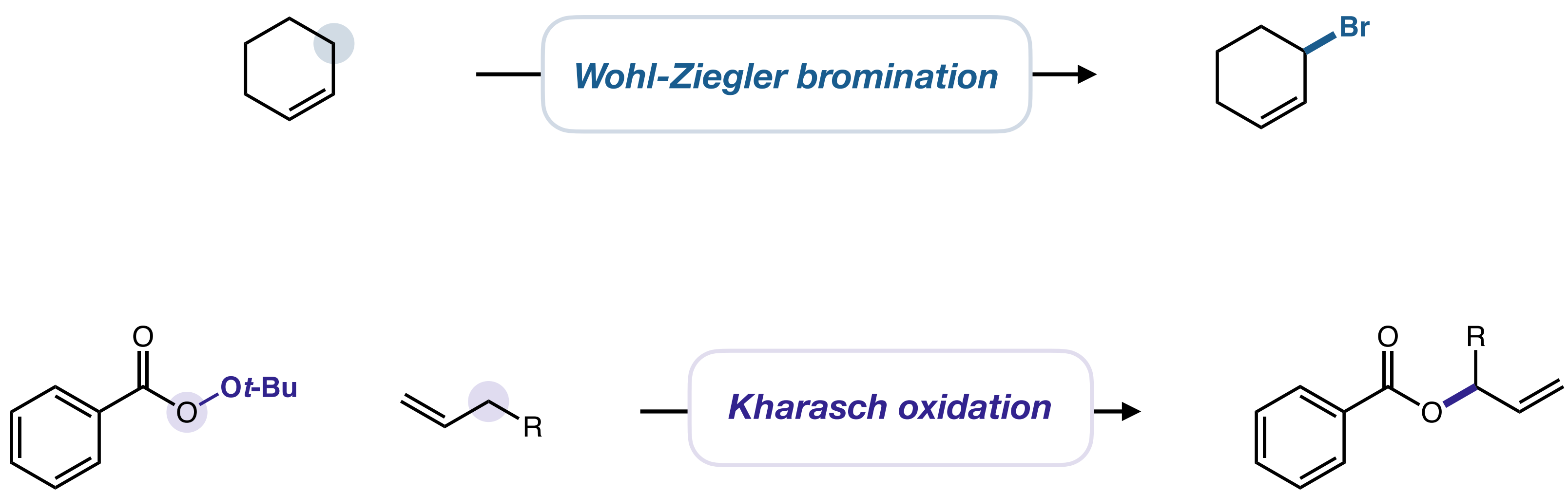
1976

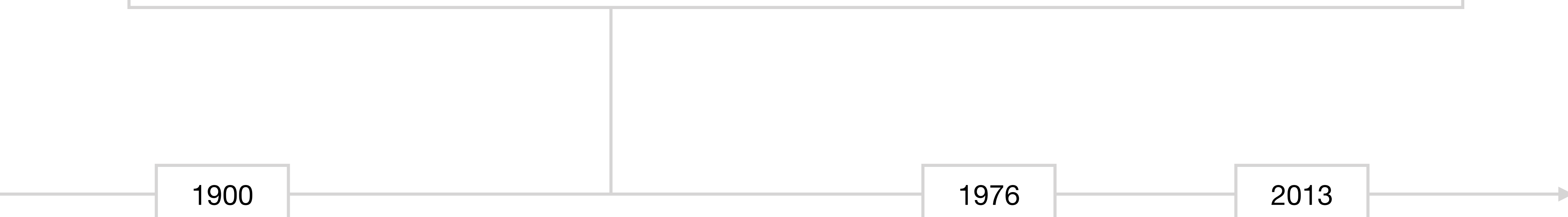
2013

Jasperse, C. P.; Rees, S.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

Radical Cyclizations: A Short History

The "Classical Antiquity" of Radical Chemistry





Jasperse, C. P.; Rees, S.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

Radical Cyclizations: A Short History

The "Classical Antiquity" of Radical Chemistry

- *Mostly functional group transformations*
- *Controlled C-C bond formation reactions remained largely elusive*

"Unruly and uncontrollable"

1900

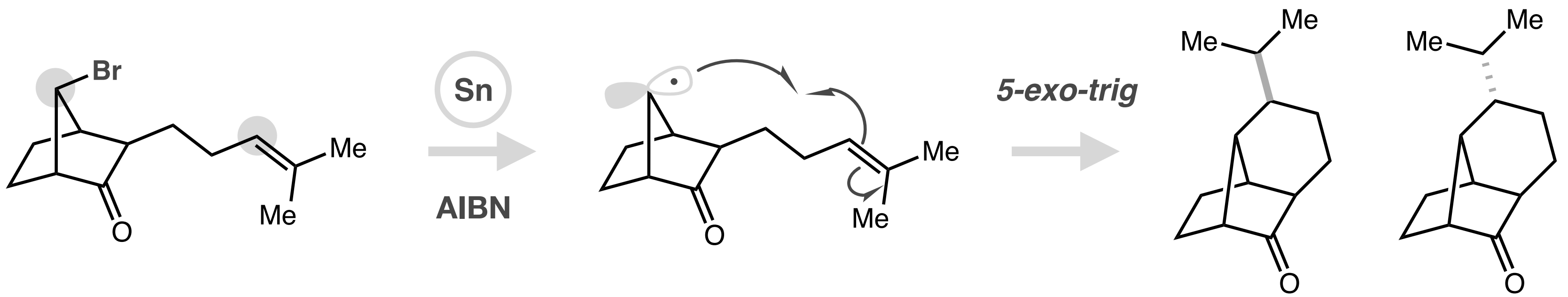
1976

2013

Jasperse, C. P.; Rees, S.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

Radical Cyclizations: A Short History

The "Medieval Era" of Radical Chemistry



Sativene *Cocamphene*

3:2 mixture, 62% yield

Radical cyclization as a strategy in synthetic planning & design

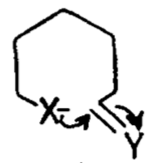
1900 1976 2013

Bakuzi, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261–3264.

Radical Cyclizations: A Short History

Baldwin's Rules

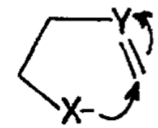
Jack E. Baldwin



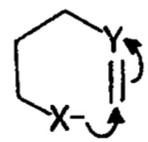
7-Exo-Trig

3-Endo-Trig

4-Endo-Trig



5-Endo-Trig



6-Endo-Trig

7-Endo-Trig

1900

1976

2013

Baldwin, J. E. *J.C.S. Chem. Comm.* **1976**, *8*, 734–736.

Radical Cyclizations: A Short History

Beckwith's Radical Rules

Athel Beckwith

Some Guidelines for Radical Reactions

By ATHELSTAN L J BECKWITH,* CHRISTOPHER J EASTON, and ALGIRDAS K SERELIS
(*Organic Chemistry Department, University of Adelaide, Adelaide, South Australia* 5000)

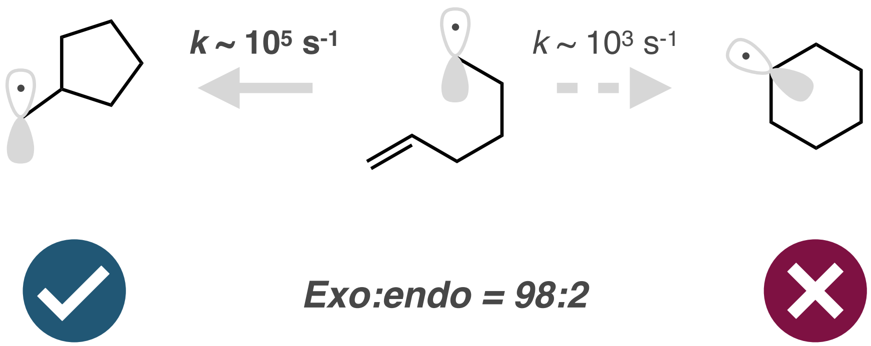
Summary Some generalisations of predictive utility are presented concerning the influence of steric and stereo-electronic effects on radical reactions

1900 — 1980 — 2013

Beckwith, A. L. J. *J.C.S. Chem. Comm.* **1980**, *11*, 482–483.

Beckwith's Rules of Radical Cyclization

*1. Cyclizations containing five linking carbons or less is under **kinetic control** and prefers exo-mode.*



Exo:endo = 98:2

Beckwith's Rules of Radical Cyclization

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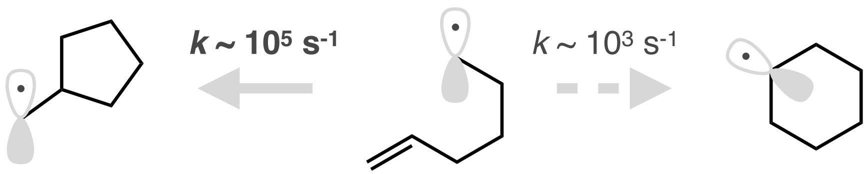
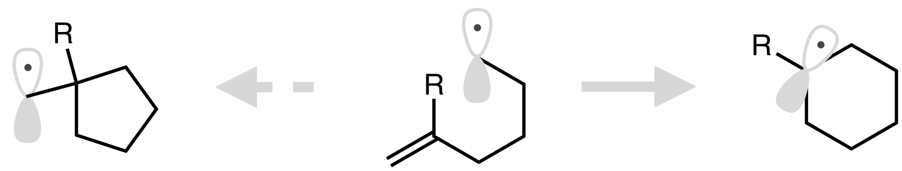


Exo:endo = 98:2

*2. **Substituents** on an olefinic bond **disfavour** homolytic addition at the **substituted** position.*



Endo favoured

exo disfavoured

Beckwith's Rules of Radical Cyclization

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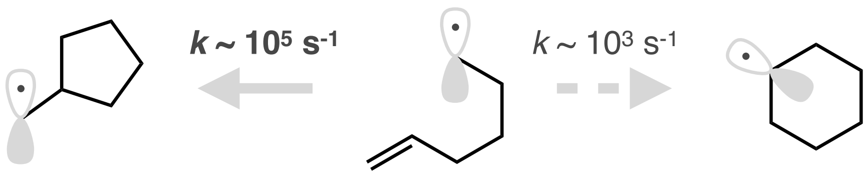

Exo:endo = 98:2

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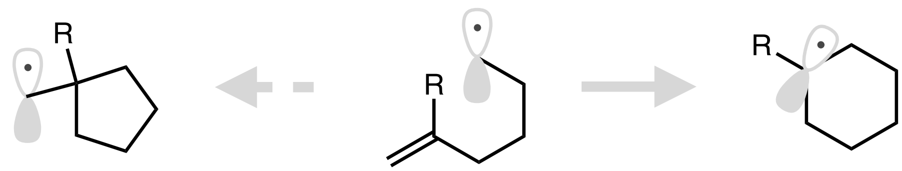
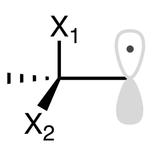


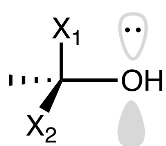
Endo favoured

exo disfavoured

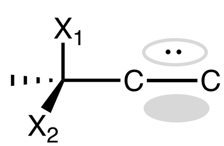
3. Homolytic cleavage is favoured when the bond concerned lies close to ***the plane of an adjacent*** *semi-occupied, filled non-bonding, or π-, orbital.*



semi-occupied



Non-bonding



π-orbital

X_1 favoured in all cases

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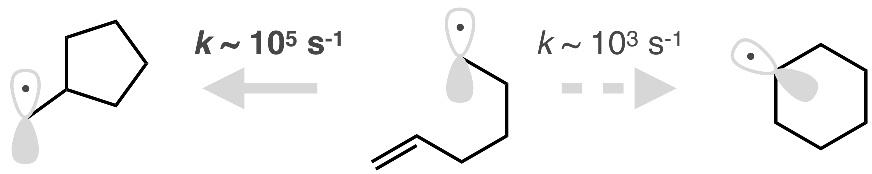

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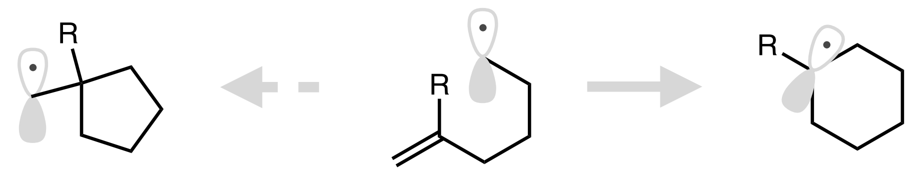

Endo favoured

exo disfavoured

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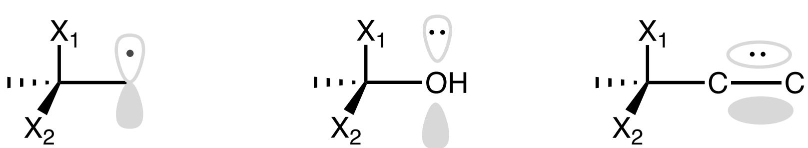
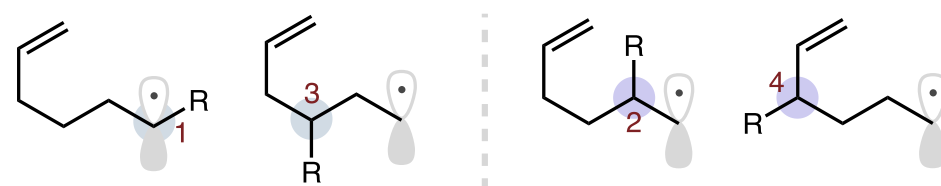


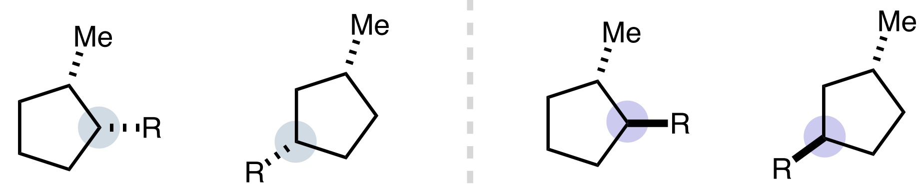
semi-occupied | *Non-bonding* | *π-orbital*

X_1 favoured in all cases

*4. 1,5-Ring closures of substituted hex-5-enyl and related radicals are **stereoselective:***



1,3- prefers cis | ***2,4- prefers trans***



Radical Cyclizations: A Short History

Beckwith's Radical Rules

Athel Beckwith

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By Athelstan L J Beckwith,* Christopher J Easton, and Algirdas K Serelis
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1900

1980

2013

Beckwith, A. L. J. *J.C.S. Chem. Comm.* **1980**, *11*, 482–483.

Radical Cyclizations: A Short History

Three Classes of Radical Cyclization

- Sn AIBN — ***Tin-hydride assisted cyclization***
- Sm + e^- — ***SmI_2 Reductive cyclization***
- Mn – e^- — ***Mn(II) Oxidative cyclization***

1900 — 1980 — 2013

Jasperse, C. P.; Rees, S.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

Radical Cyclizations: A Short History

Three Classes of Radical Cyclization

Sn AIBN

Tin-hydride assisted cyclization

Sm + e^-

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1900 — 1980 — 2013

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Radical Cyclizations: A Short History

Total Synthesis of (±)-Hirsutene: Curran, 1985

Tin-hydride assisted cyclization

80% yield

(±)-Hirsutene

1900

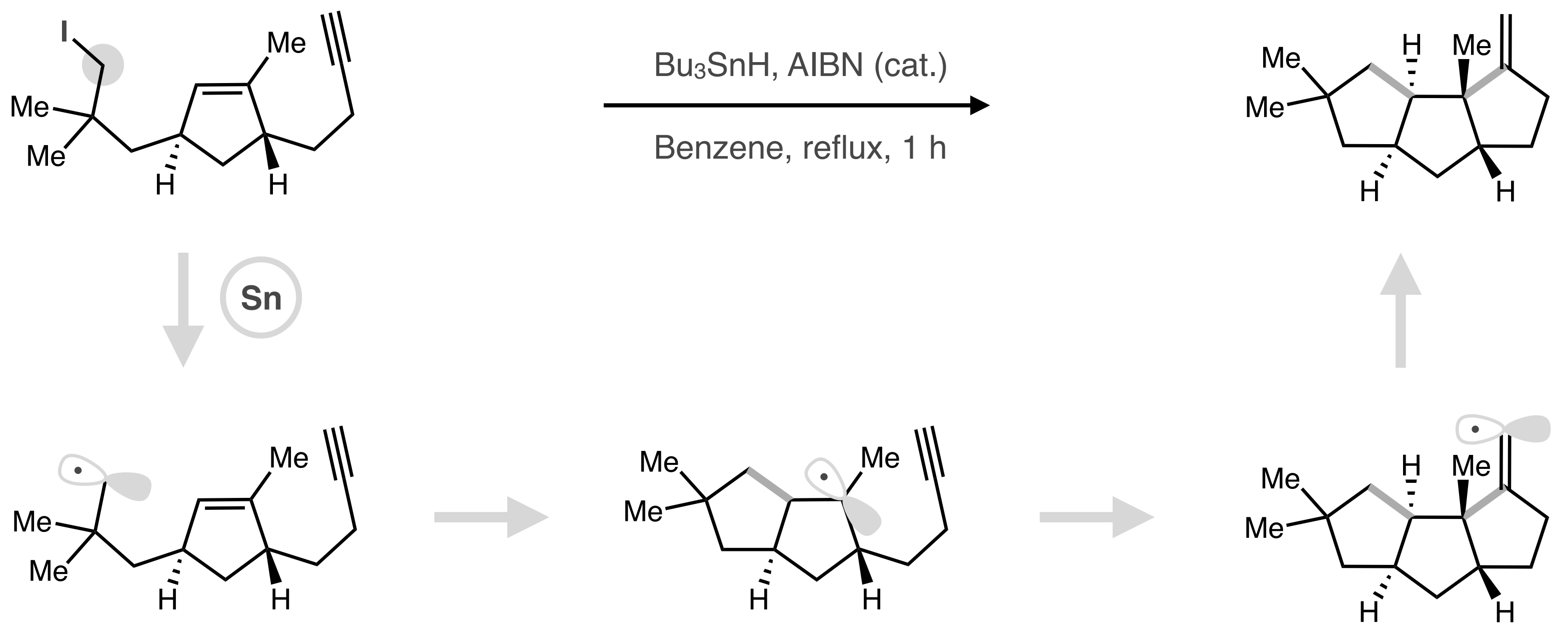
1980

2013

Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

Radical Cyclizations: A Short History

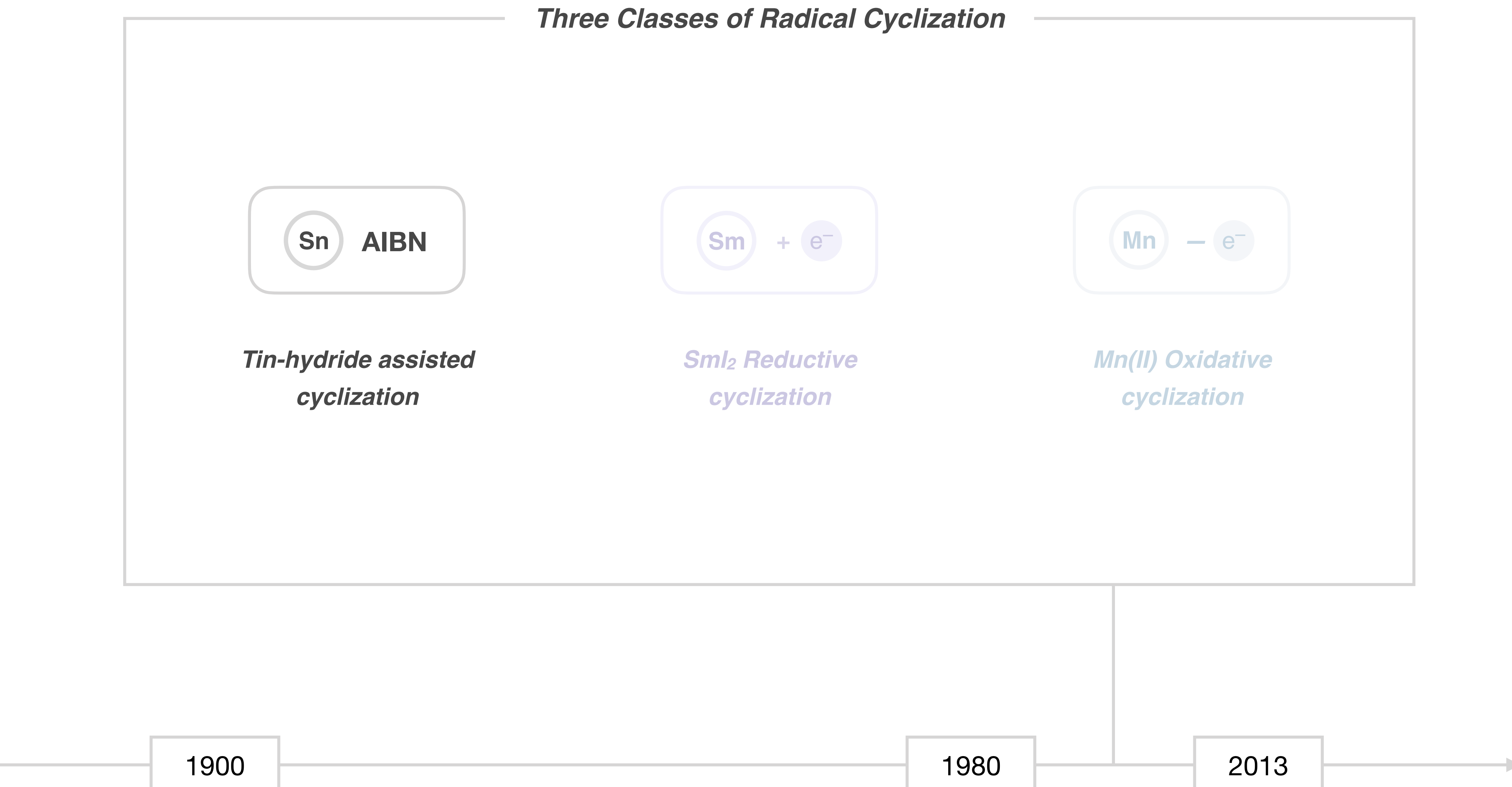
Total Synthesis of (±)-Hirsutene: Curran, 1985



1900 · 1980 · 2013

Curran, D. P.; Rakiewicz, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 1448.

Radical Cyclizations: A Short History



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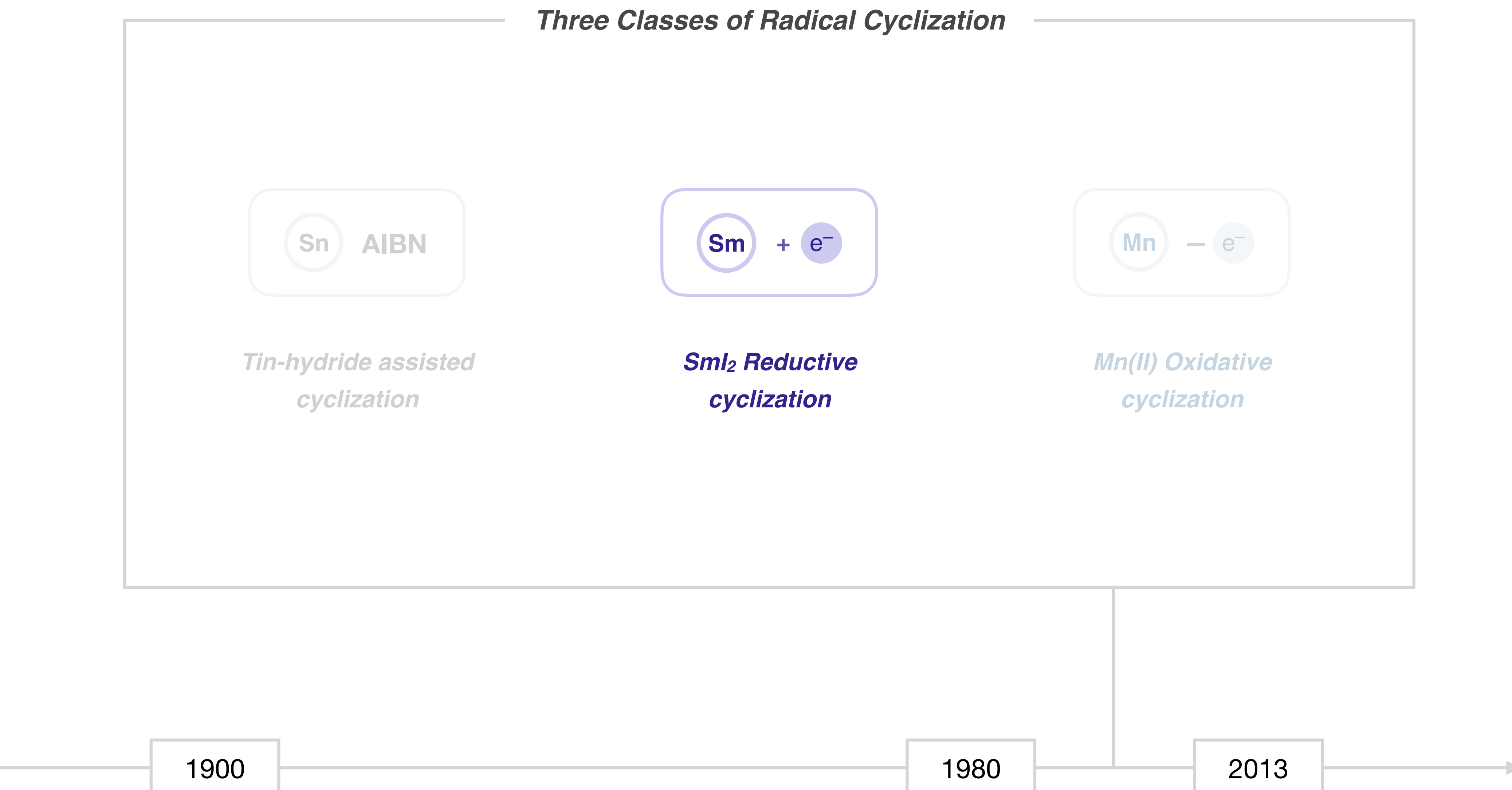
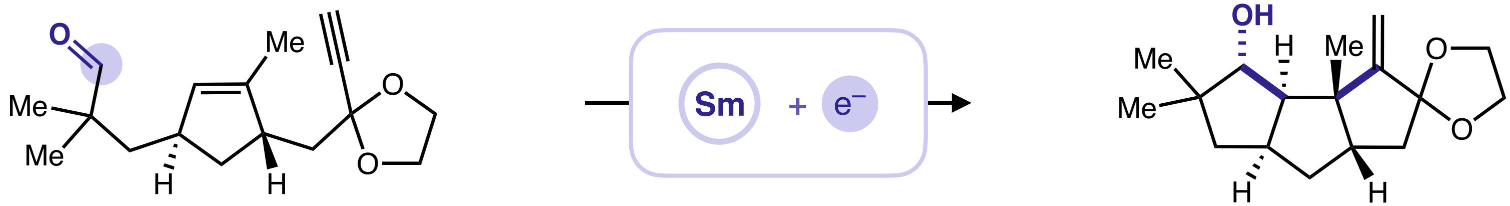


Jasperse, C. P.; Rees, S.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

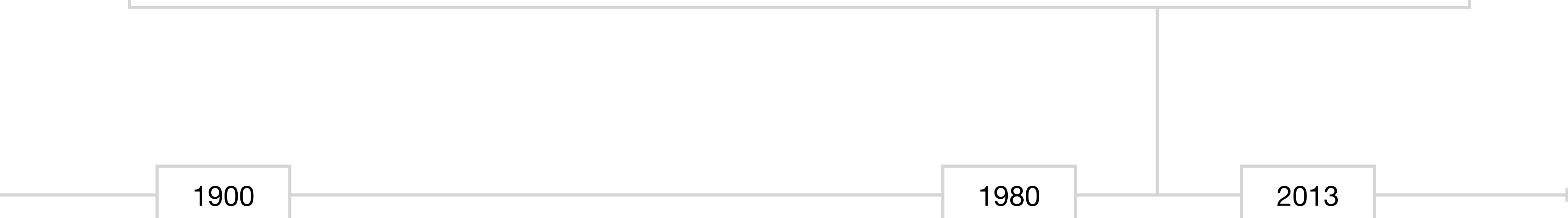
Radical Cyclizations: A Short History

Total Synthesis of (±)-Hypnophilin: Curran, 1988



SmI_2 Reductive cyclization

69% yield



Fevig, T. L.; Elliot, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064–5067.

Radical Cyclizations: A Short History

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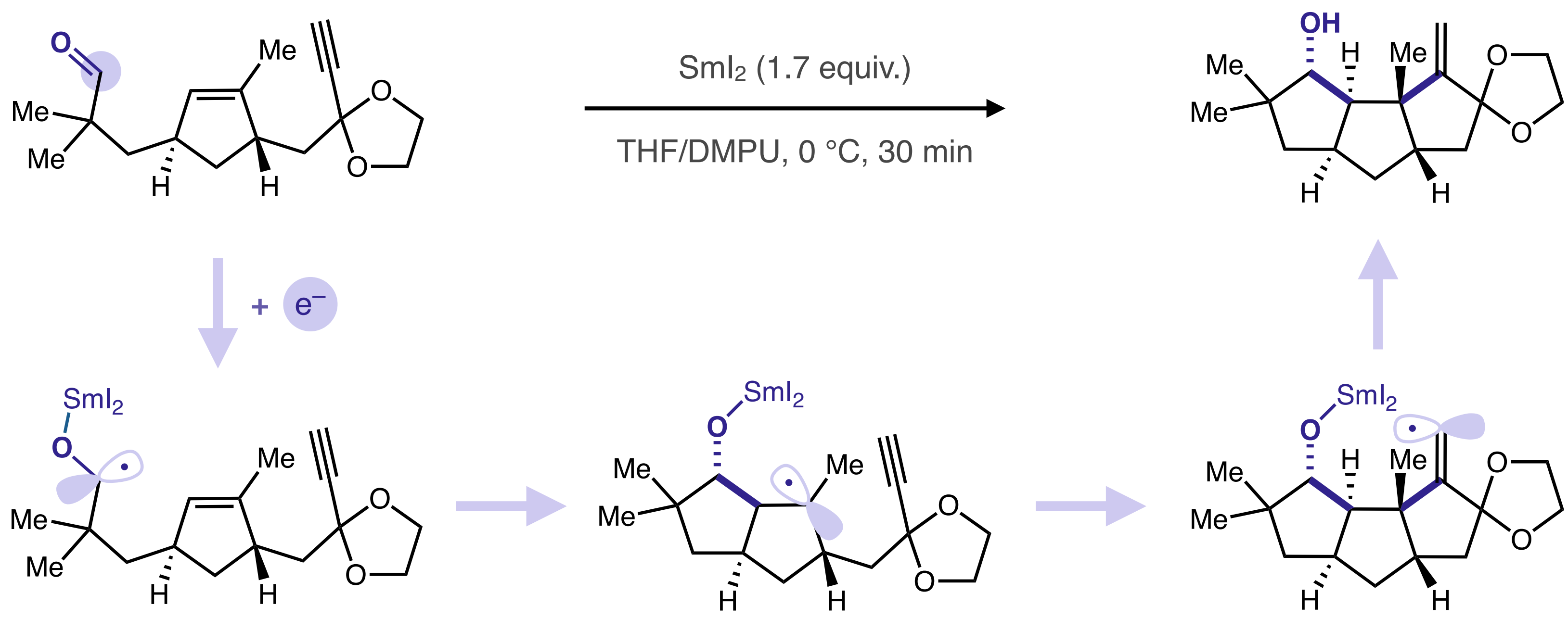

1900

1980

2013

Fevig, T. L.; Elliot, R. L.; Curran, D. P. *J. Am. Chem. Soc.* **1988**, *110*, 5064–5067.

Radical Cyclizations: A Short History

Three Classes of Radical Cyclization

Sn AIBN

Tin-hydride assisted cyclization

Sm + e⁻

SmI_2 Reductive cyclization

Mn – e⁻

Mn(II) Oxidative cyclization

1900 — 1980 — 2013

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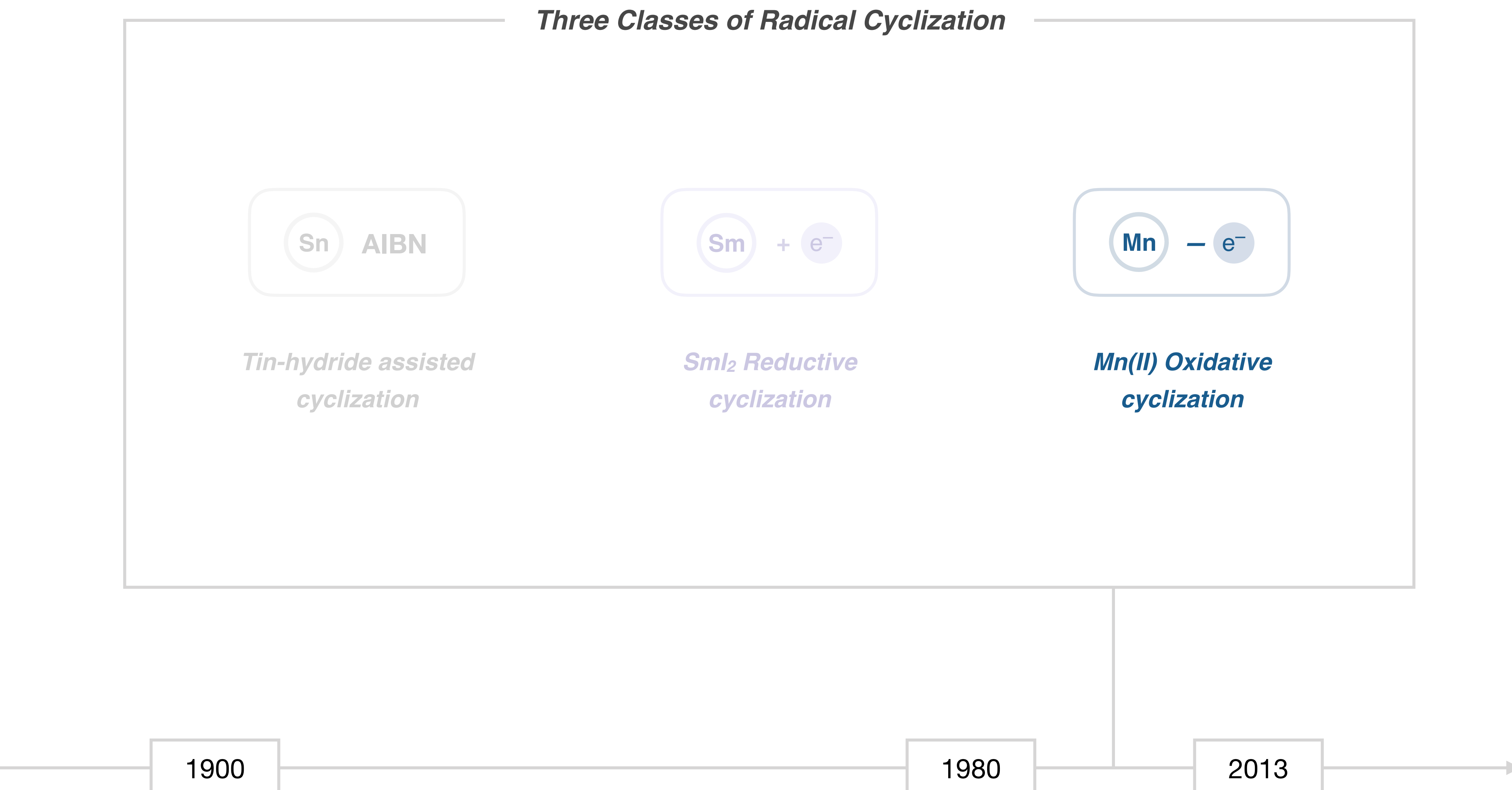
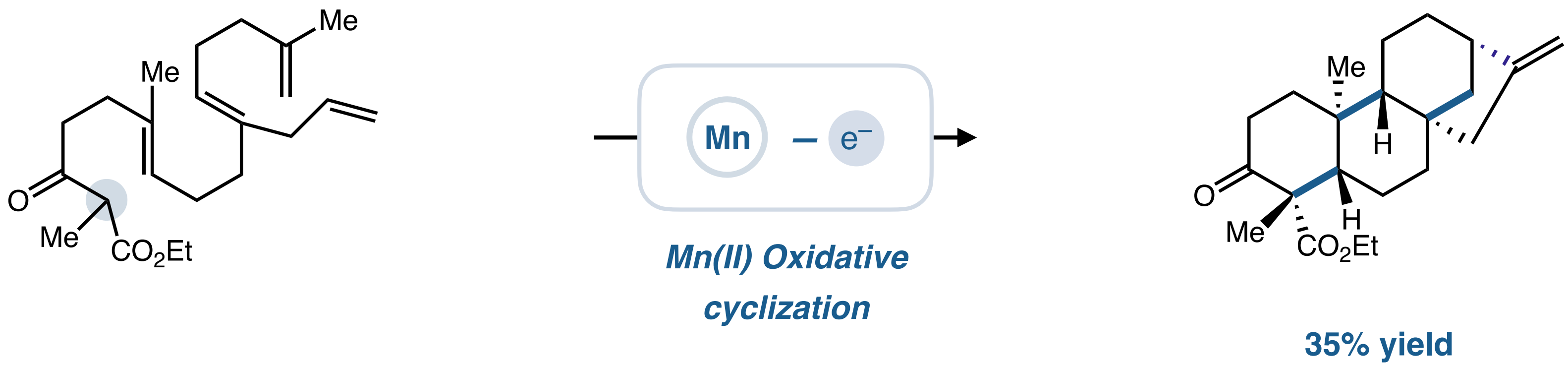


Jasperse, C. P.; Rees, S.; Curran, D. P.; Fevig, T. L. *Chem. Rev.* **1991**, *91*, 1237–1286.

Radical Cyclizations: A Short History

Three Classes of Radical Cyclization

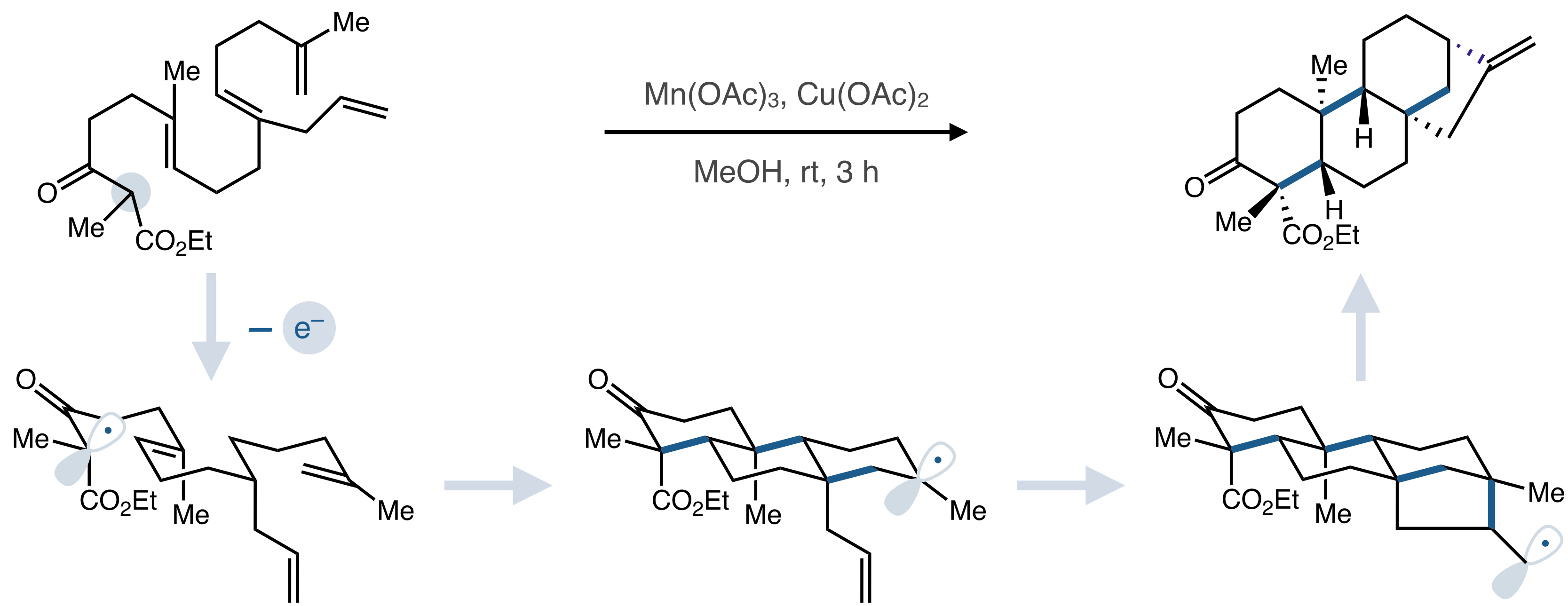


1900 1980 2013

Snider, B. B.; Kiselgof, J. Y.; Foxman, D. M. *J. Org. Chem.* **1990**, *112*, 4003–4008.

Radical Cyclizations: A Short History

Three Classes of Radical Cyclization



1900

1980

2013

Snider, B. B.; Kiselgof, J. Y.; Foxman, D. M. *J. Org. Chem.* **1990**, *112*, 4003–4008.

Radical Cyclizations: A Short History

The "Medieval Era" of Radical Chemistry

Sn

Stoichiometric *activation*

High energy

"The tyranny of tin"

- *Advancements: major paradigmatic shift in synthetic design and planning*
- *Continuity: mild methods allowing general access to the key reactive, high-energy radical intermediates remained limited*

The quest for a new strategy for radical generation

1900 — 1980 — 2013

Crepsi, S.; Fagnoli, M. *Chem. Rev.* **2020**, *120*, 9700–9833.

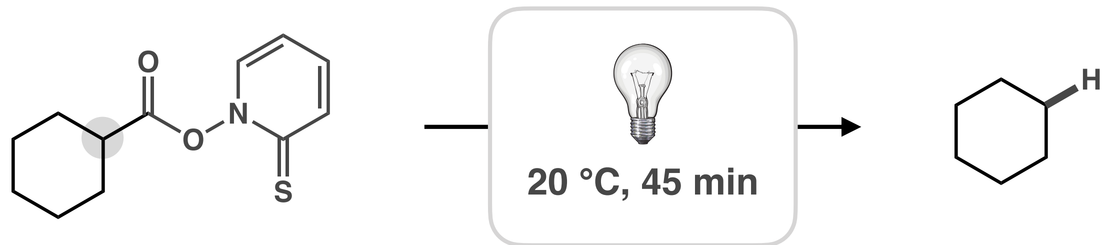
Radical Cyclizations: A Short History

The Photonic Revolution

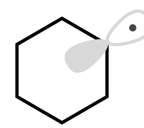
Stoichiometric *activation*

High energy

"The tyranny of tin"



Barton ester

via 

1900 — 1985 — 2008

Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron* **1985**, *41*, 3901–3924.

Radical Cyclizations: A Short History

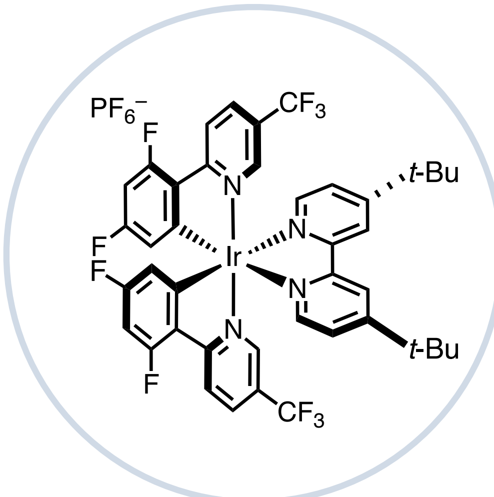
The Photonic Revolution

Sn

***Stoichiometric** activation*

High energy

"The tyranny of tin"



PC

***Catalytic** activation*

Mild, innocuous

"The photon democracy"

1900

1985

2008

Crepsi, S.; Fagnoli, M. *Chem. Rev.* **2020**, *120*, 9700–9833.

Radical Cyclizations: A Short History

The "Modern Era" of Radical Chemistry

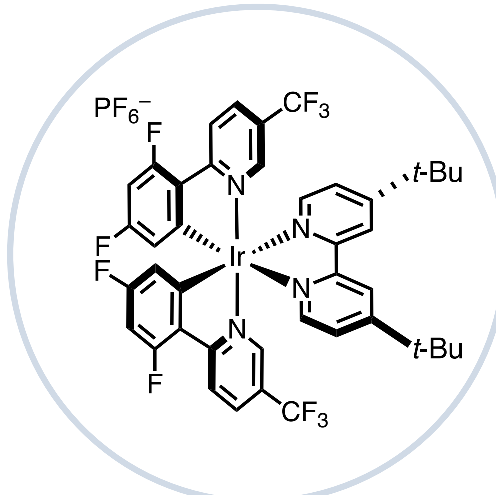
Photoredox catalysis

PC

oxidation

reduction

energy transfer



Visible light irradiation

conversion of photonic energy to chemical energy

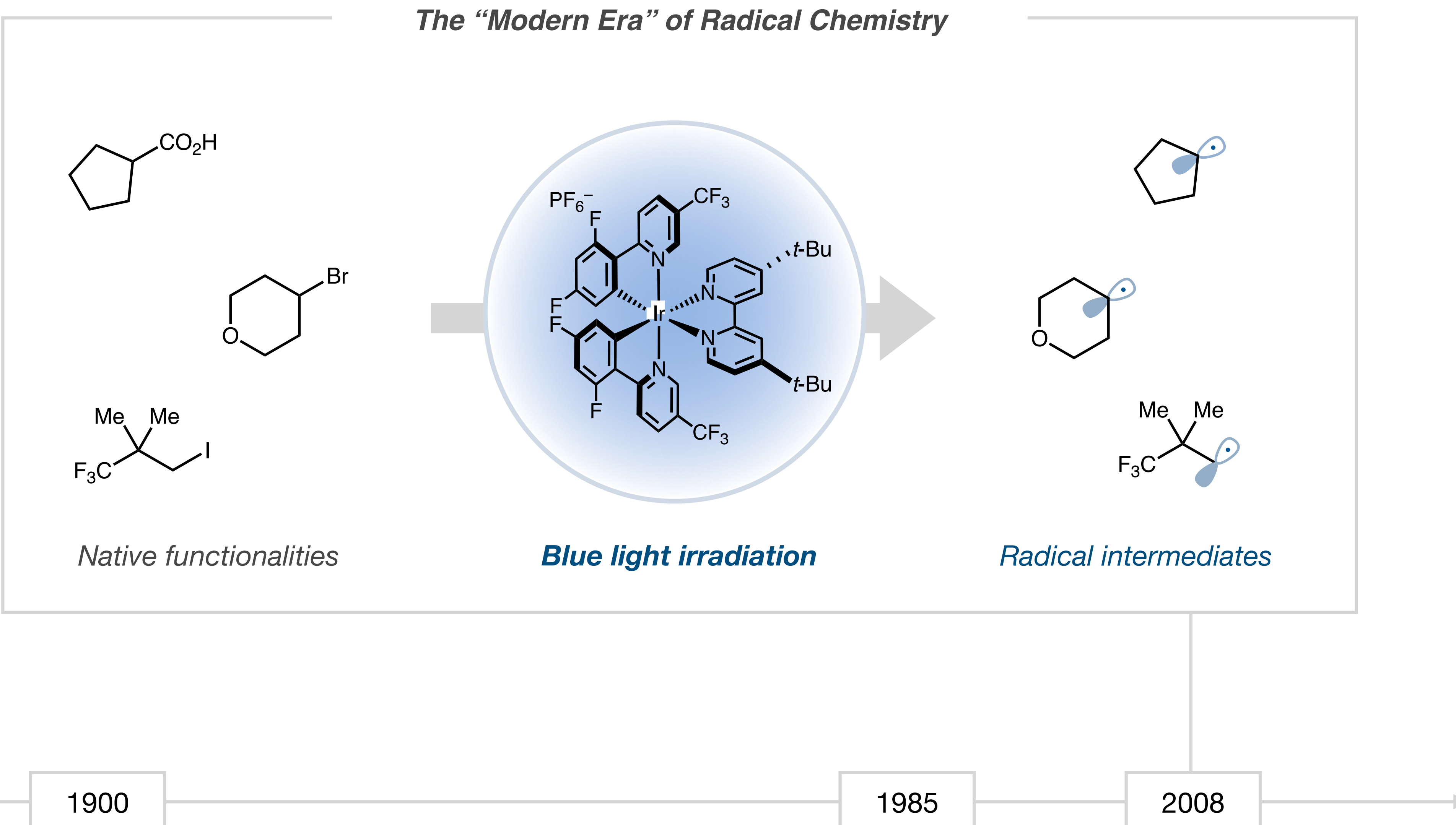
1900

1985

2008

Hughes, J. P.; Rees, S.; Kalindjian, S. B.; Philpott, K. L. *Br. J. Pharmacol.* **2011**, *162*, 1239–1249.

Radical Cyclizations: A Short History



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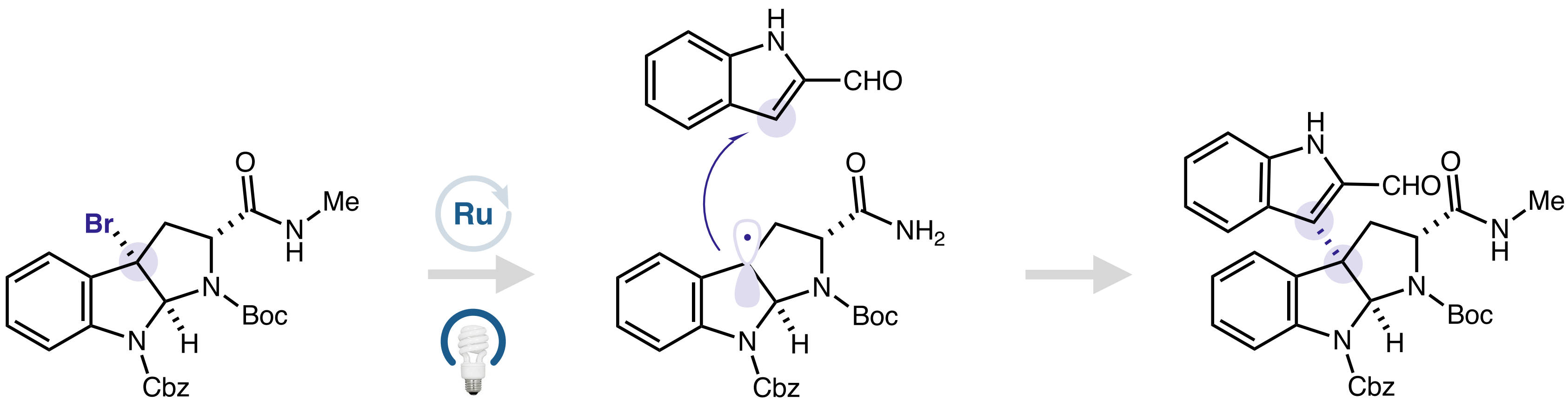
Radical Cyclizations: A Short History

Early Applications of Photoredox in Total Synthesis: Stephenson, 2011



Photoredox reductive dehalogenation

1900

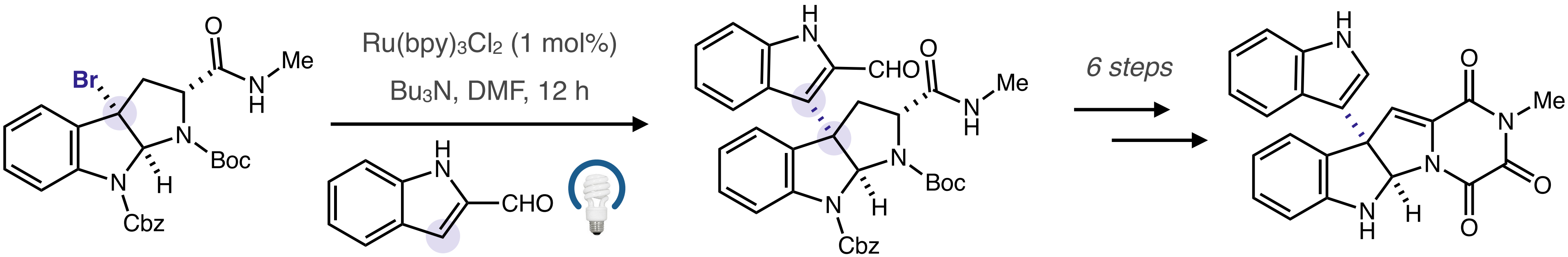
1985

2011

Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem. Intl. Ed.* **2011**, *50*, 9655–9659.

Radical Cyclizations: A Short History

Early Applications of Photoredox in Total Synthesis: Stephenson, 2011



82% yield
gram scale

Glioclandin C
10 steps, 30% overall yield

1900 | 1985 | 2011

Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chem. Intl. Ed.* **2011**, *50*, 9655–9659.

Radical Cyclizations: A Short History

Radical Cyclizations in Total Synthesis via Photoredox

Radical Cyclizations in Total Synthesis

Patricia Zhang →

1900

1985

2013

Radical Cyclizations: A Short History

Radical Cyclizations in Total Synthesis via Photoredox

> *So what is "radical" now?…No* ***photoredox radical cyclyzation in total synthesis*** *yet.*
>
> —Patricia Zhang, *Timeless Methods for Radical Cyclizations in Total Synthesis*, September 25, 2013

1900

1985

2013

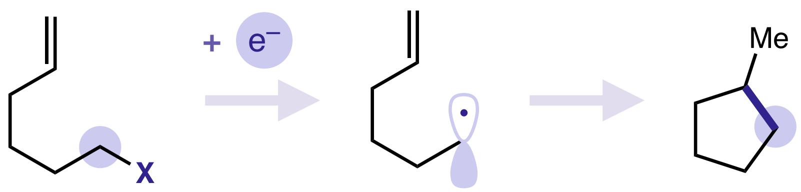
Modern Radical Cyclizations in Total Synthesis via Photoredox

2013

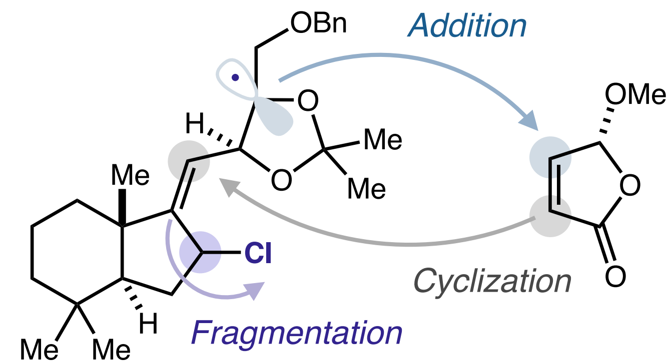
2024

Modern Radical Cyclizations in Total Synthesis via Photoredox

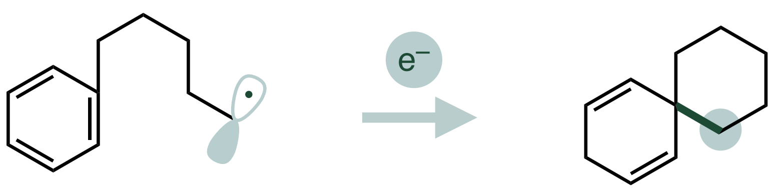
Reductive Dehalogenation



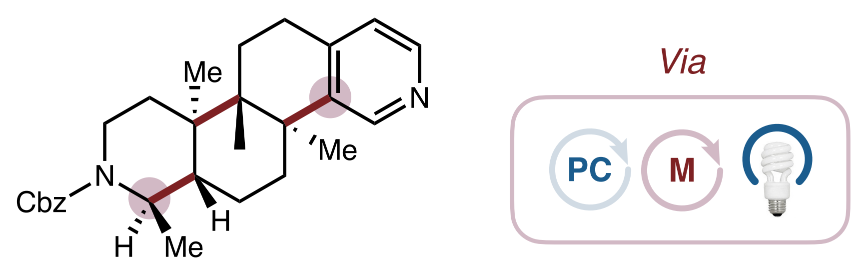
ACF: A Case Study



Spirocyclization—Dearomatization

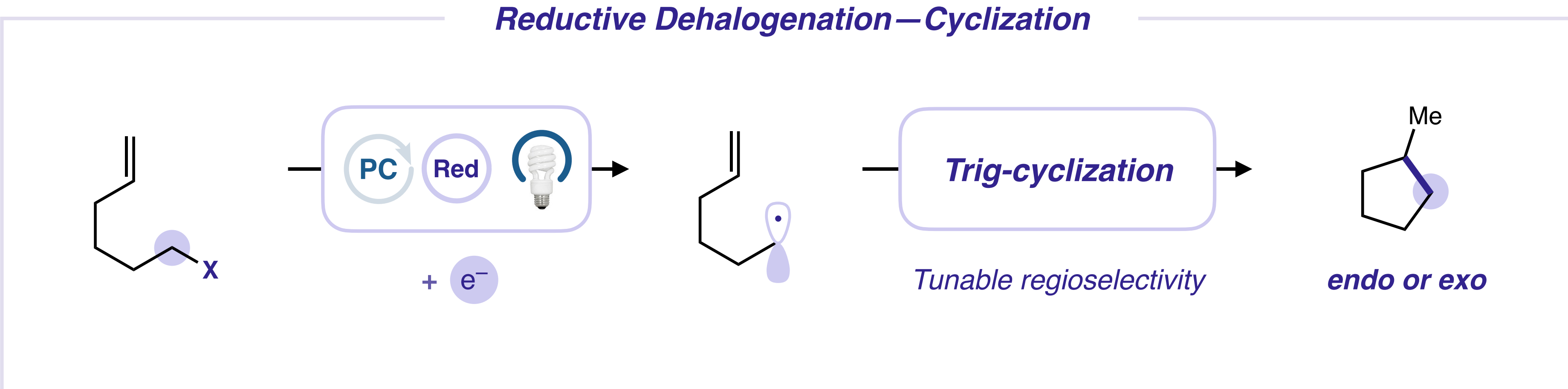


Concluding Remarks & Outlook



Pitre, S. P.; Overman, L. E. *Chem. Rev.* **2022**, *122*, 1717–1751.
Mateus-Ruiz, J. B.; Cordero-Vargas, A. *Synthesis* **2020**, *52*, 3111–3128.

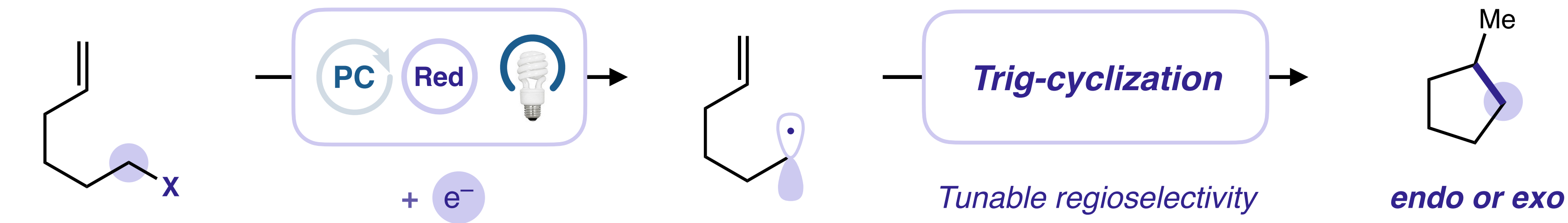
Radical Cyclizations via Photoredox Reductive Dehalogenation



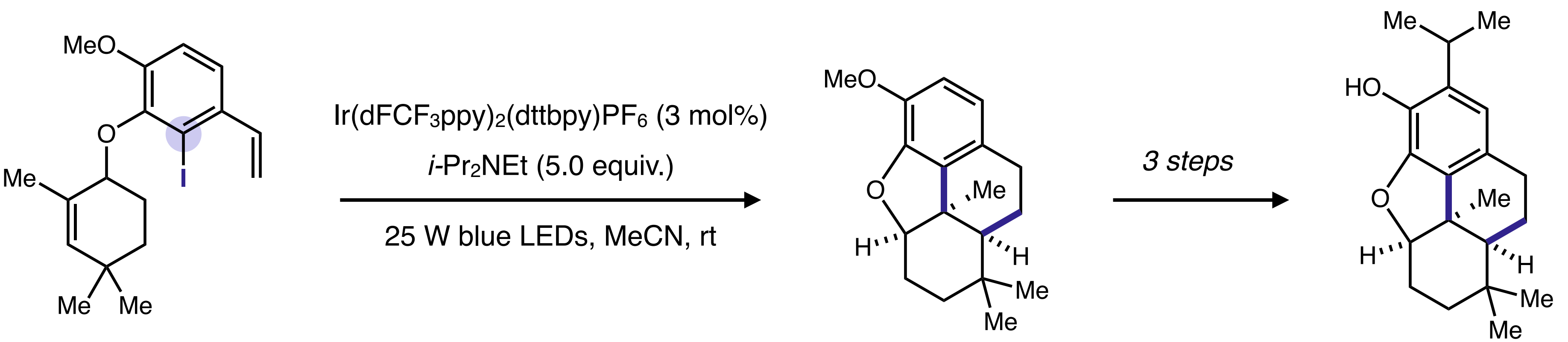
- *Reliable and most **common** mode of radical generation in **cyclization cascades***
- ***Tertiary amines** as sacrificial **reductants***
- *Homolysis of **aryl iodides**, **vinyl iodides**, and **activated alkyl iodides + bromides***
- *Can be interfaced with other radical processes **(e.g., 1,5-HAT)***

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Aryl radical from iodides

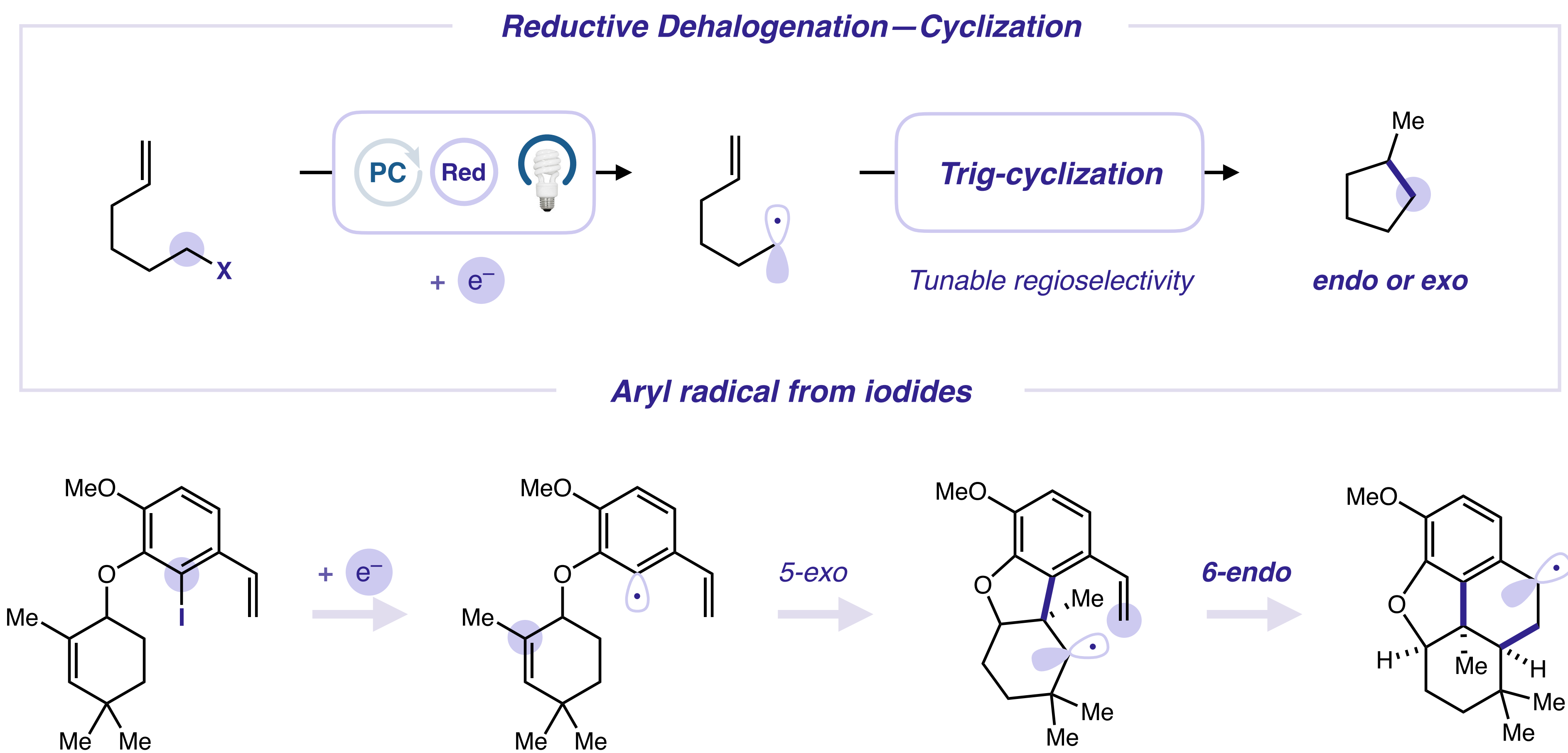


70% yield

10-epi-epoxyhinokiol

Xiao, J.; Wu, H.; Liang, J.-R.; Wu, P.; Guo, C.; Wang, Y.-W.; Wang, Z.-Y.; Peng, Y. *Org. Lett.* **2024**, *26*, 3481–3486.

Radical Cyclizations via Photoredox Reductive Dehalogenation



Benzylic** stabilization & **conformational
*constraint **exclusively favours 6-endo***

Xiao, J.; Wu, H.; Liang, J.-R.; Wu, P.; Guo, C.; Wang, Y.-W.; Wang, Z.-Y.; Peng, Y. *Org. Lett.* **2024**, *26*, 3481–3486.

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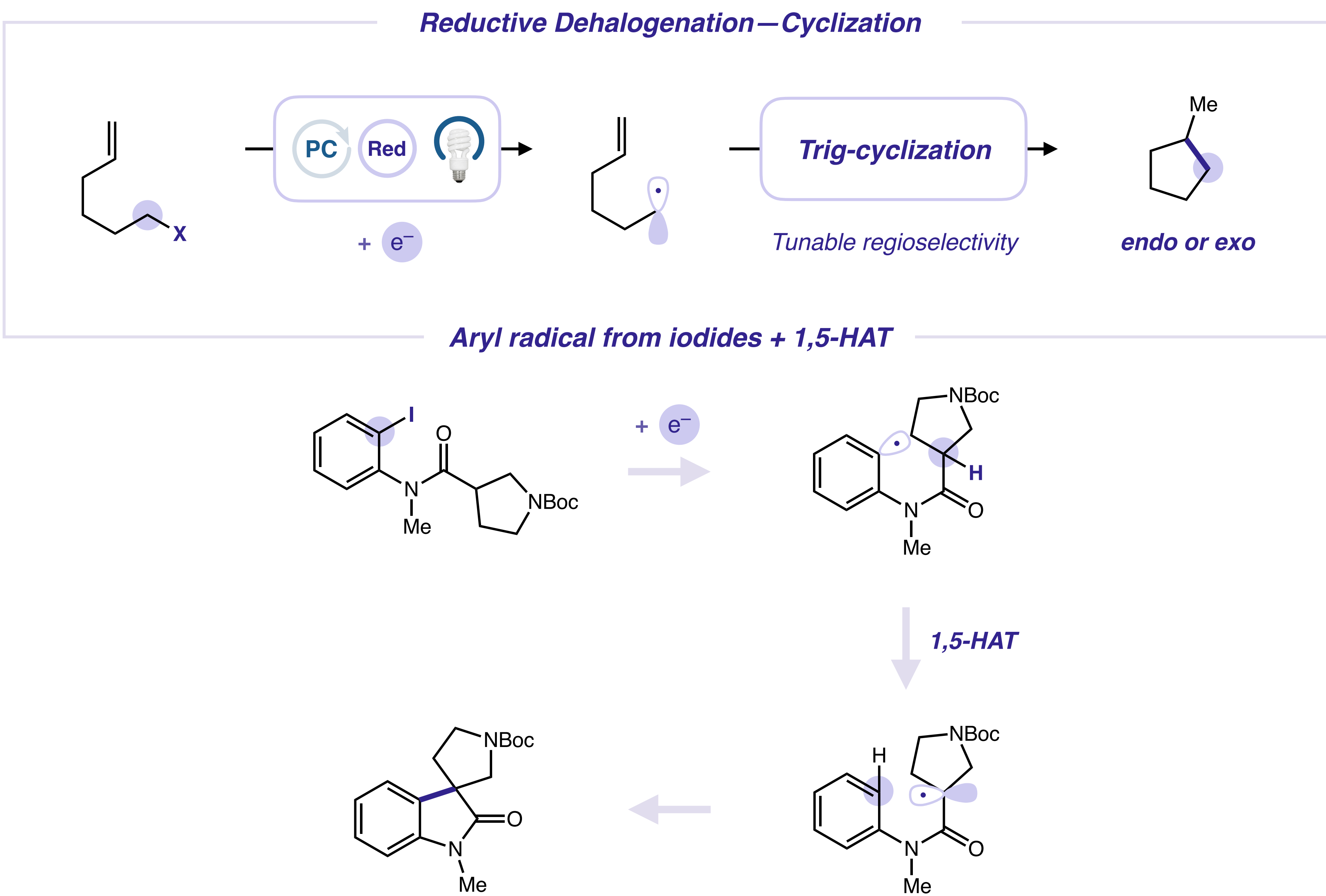
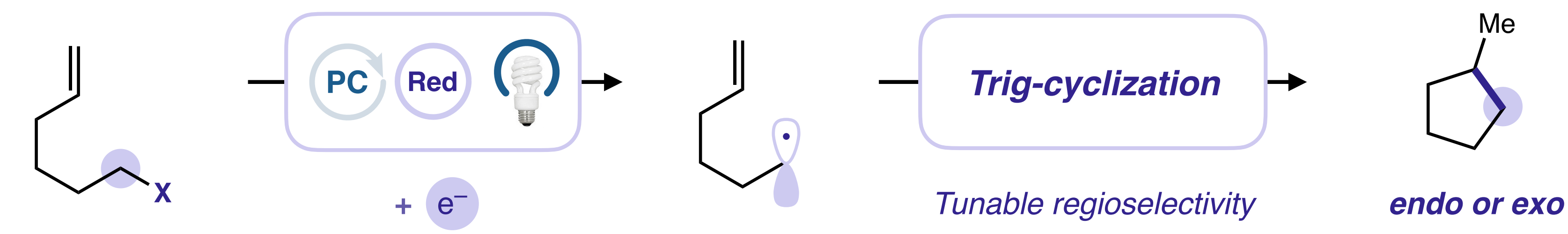


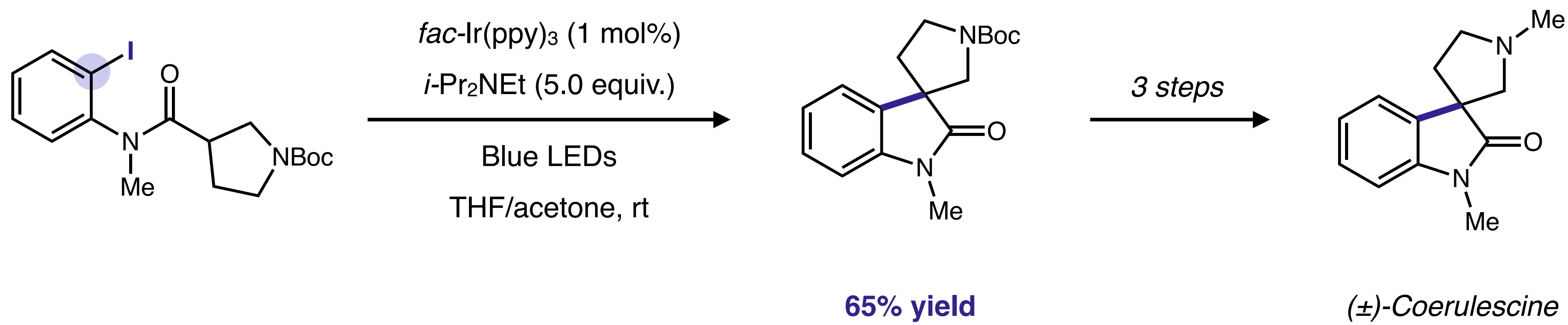
Xiao, J.; Wu, H.; Liang, J.-R.; Wu, P.; Guo, C.; Wang, Y.-W.; Wang, Z.-Y.; Peng, Y. *Org. Lett.* **2024**, *26*, 3481–3486.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization

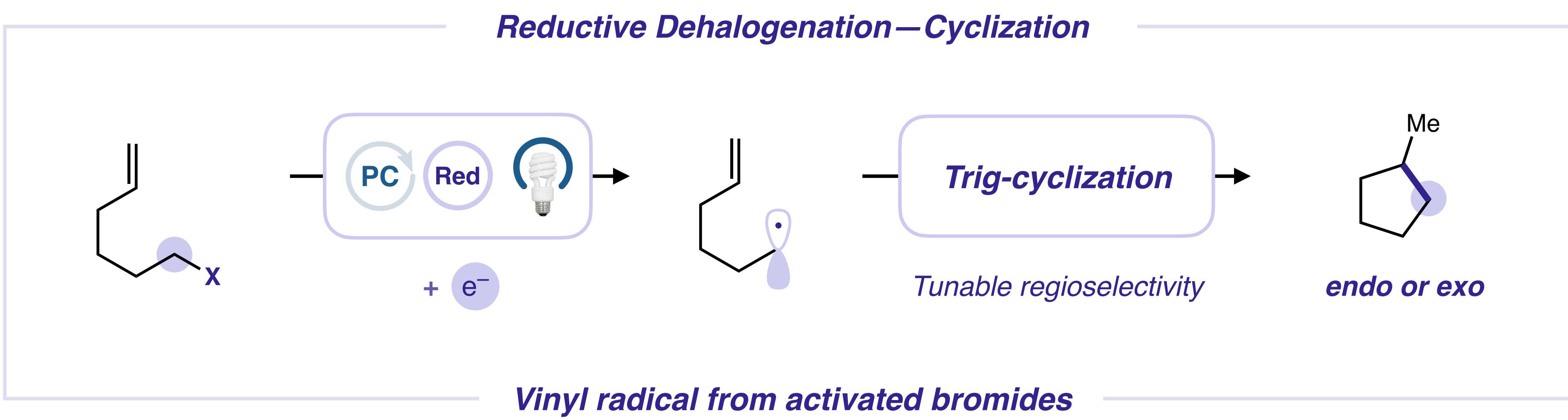


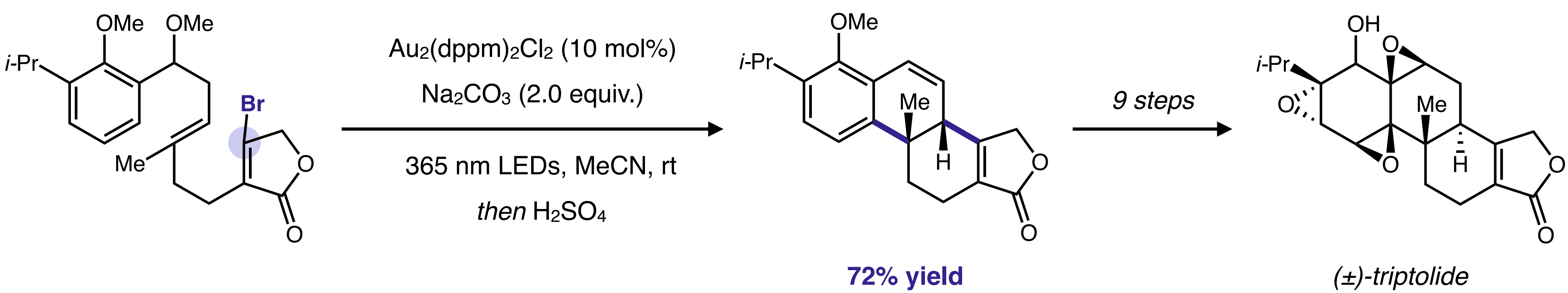
Aryl radical from iodides + 1,5-HAT



Xiao, J.; Wu, H.; Liang, J.-R.; Wu, P.; Guo, C.; Wang, Y.-W.; Wang, Z.-Y.; Peng, Y. *Org. Lett.* **2024**, *26*, 3481–3486.

Radical Cyclizations via Photoredox Reductive Dehalogenation

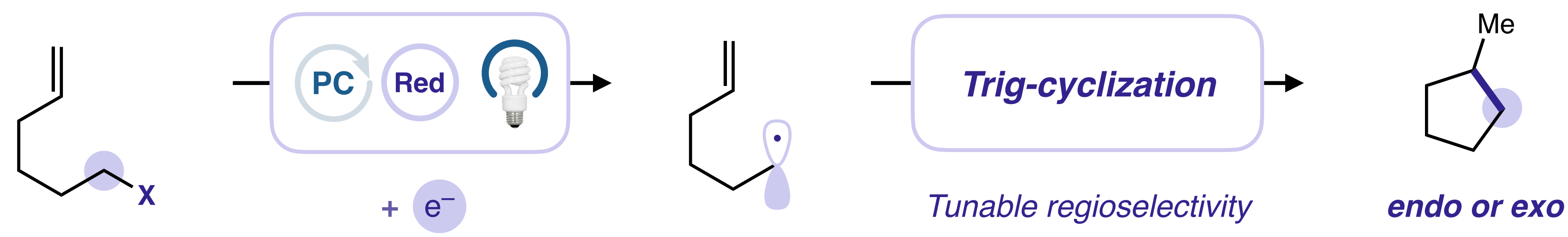




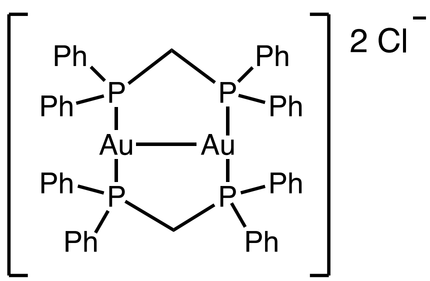
Canillo, A.; Schwantje, T. R.; Bégin, M.; Barabé. F.; Barriault, L. *Org. Lett.* **2016**, *18*, 2592–2595.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Vinyl radical from activated bromides



$Au_2(dppm)_2Cl_2$

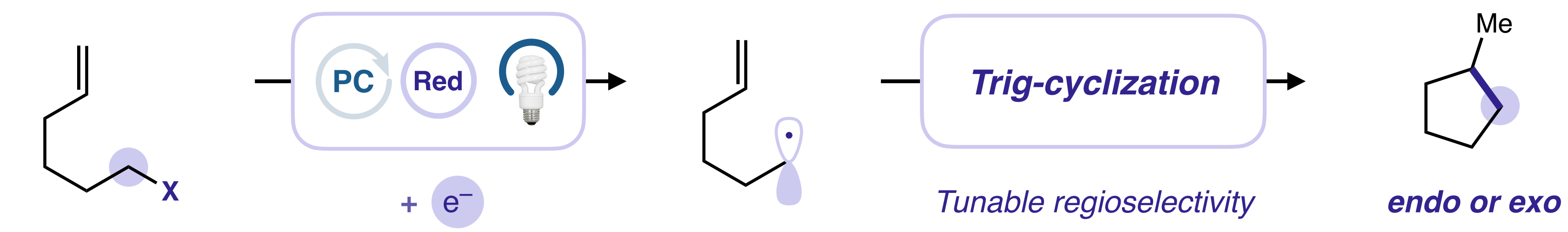
- *Absorbs UVA very strongly, reaction can be run* ***under sunlight***
- ***First C—C bond formation*** *reaction discovered in* ***1992***
- *Use for dehalogenative radical* ***cyclization*** *by* ***Louis Barriault in 2013***

> *"Let the sunshine in!"*
>
> *—Louis Barriault, 2013*

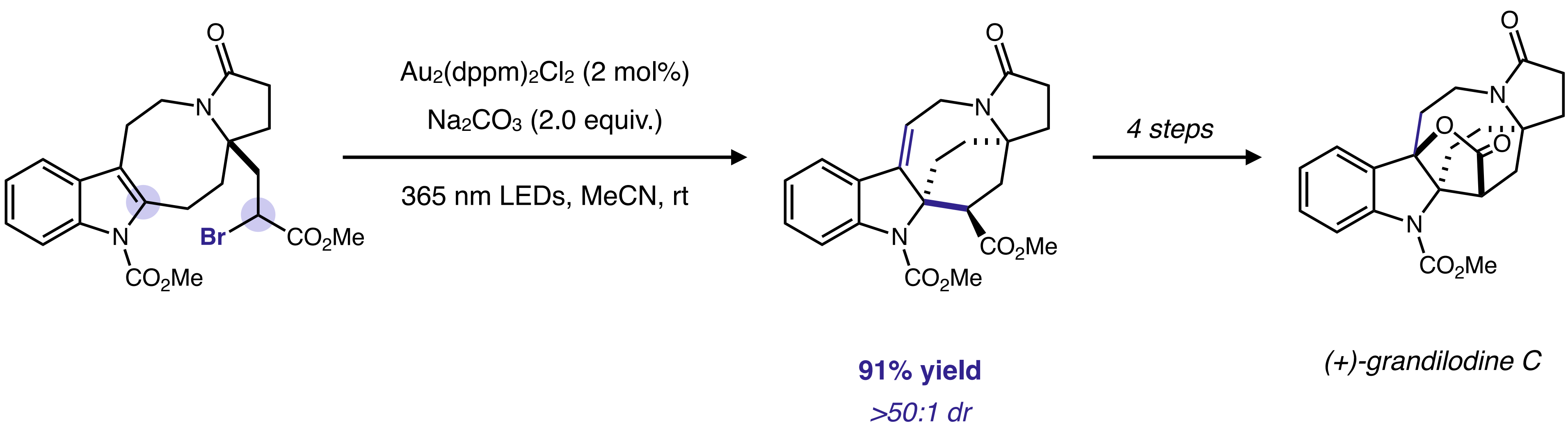
Revol, G.; McCallum, T.; Morin, M.; Gagosz. F.; Barriault, L. *Angew. Chem. Int. Ed.* **2013**, *52*, 13342–13345.
Li, D.; Che, C.-M.; Kwong, H.-L.; Yam, V. W.-W. *J. Chem. Soc. Dalton Trans.* **1992**, *23*, 3325–3329.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization

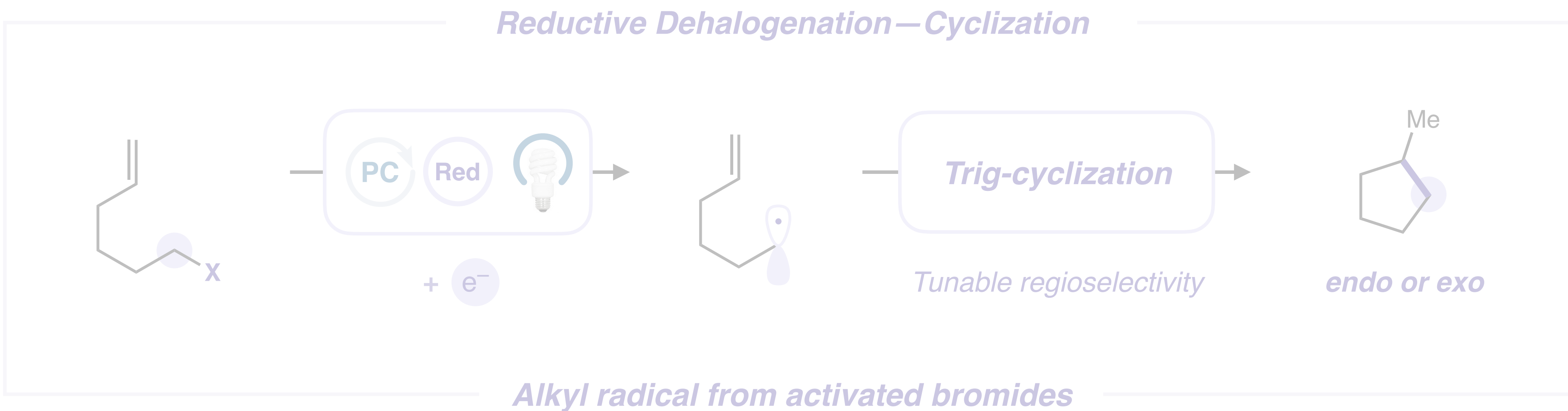


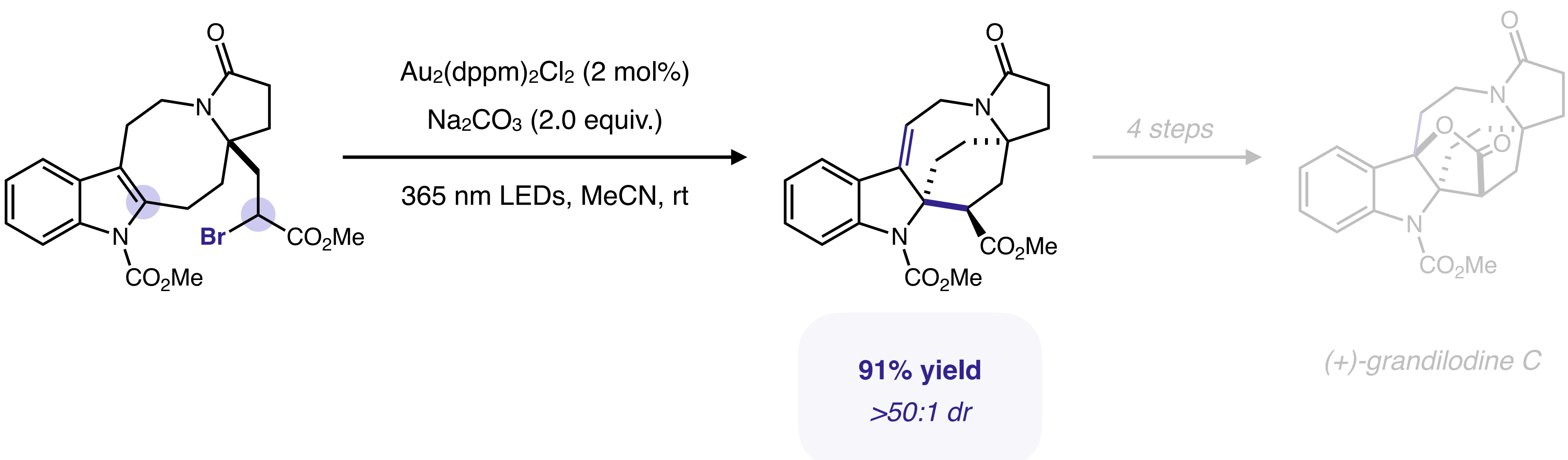
Alkyl radical from activated bromides



Miloserdov, F. M.; Che, C.-M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.

Radical Cyclizations via Photoredox Reductive Dehalogenation





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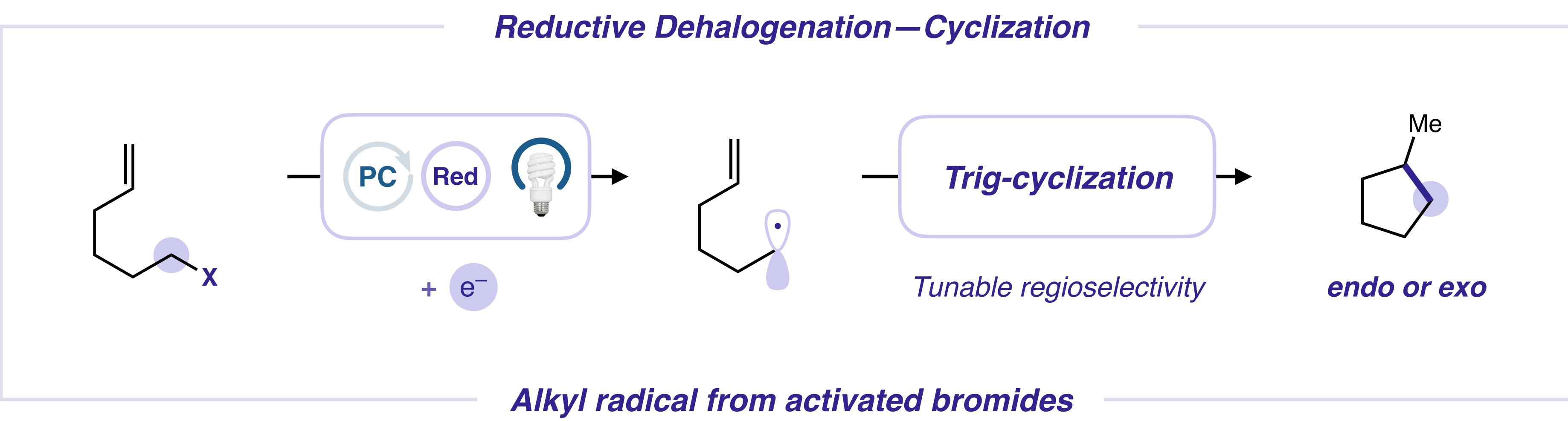
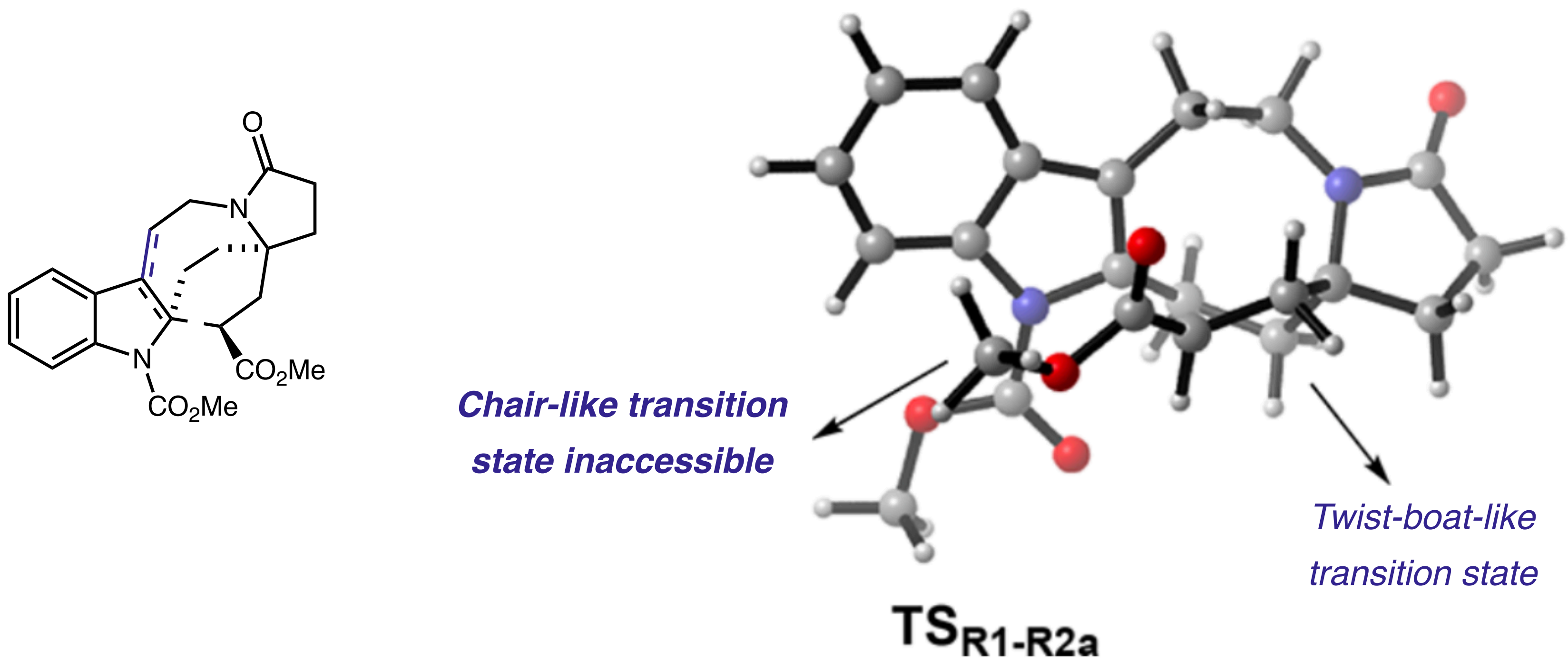
Radical Cyclizations via Photoredox Reductive Dehalogenation

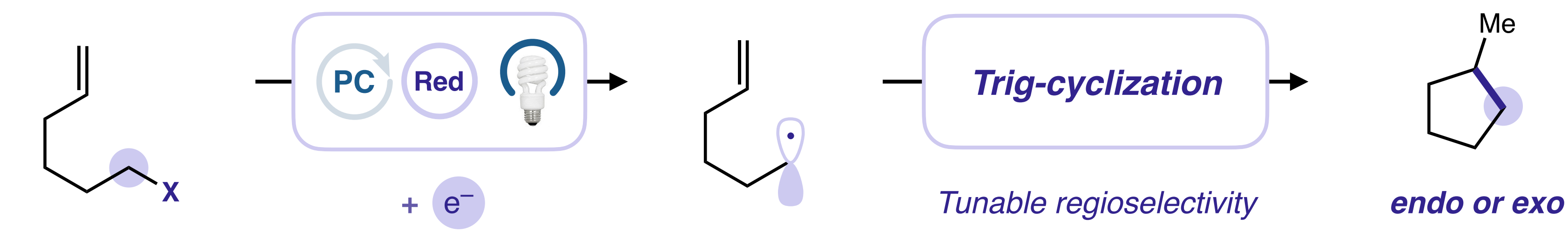




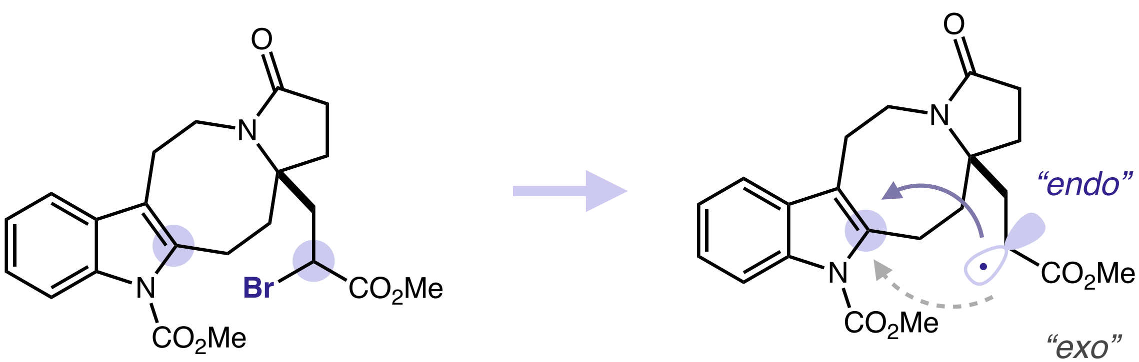
Miloserdov, F. M.; Che, C.-M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Alkyl radical from activated bromides



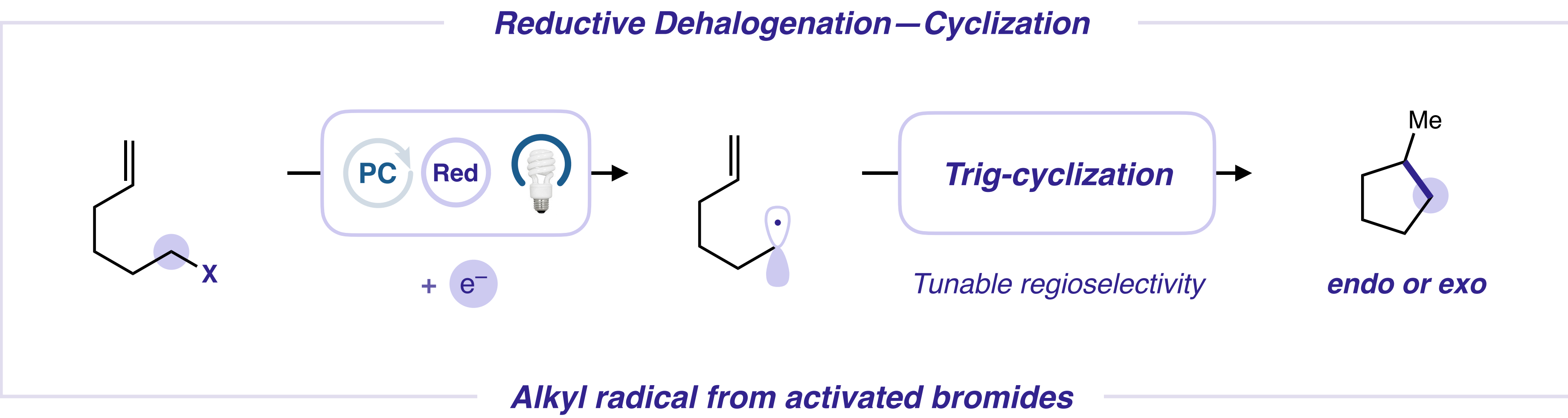
ΔG° (endo) = +1.7 kcal/mol

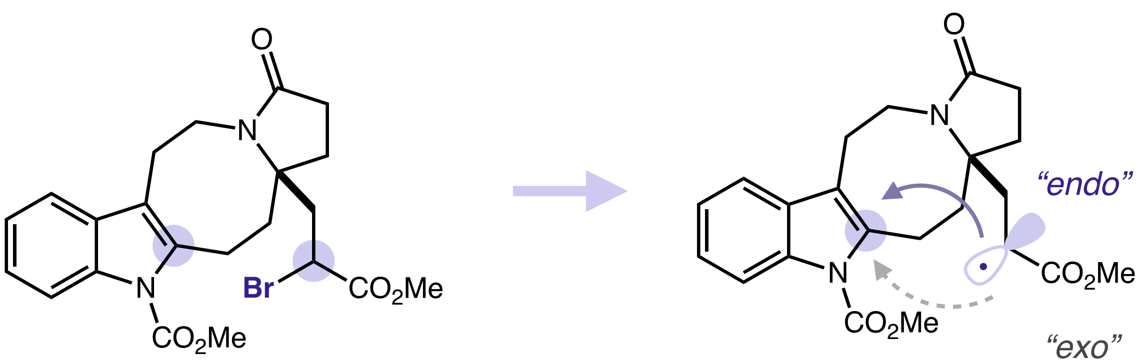
ΔG° (exo) = +7.5 kcal/mol

Cyclization energetically uphill

Miloserdov, F. M.; Che, C.-M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.

Radical Cyclizations via Photoredox Reductive Dehalogenation





$\Delta G^{\ddagger}$ (endo) = 20.2 kcal/mol

$\Delta G^{\ddagger}$ (exo) = 23.2 kcal/mol

Endo favoured by 3.0 kcal/mol

Miloserdov, F. M.; Che, C.-M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.

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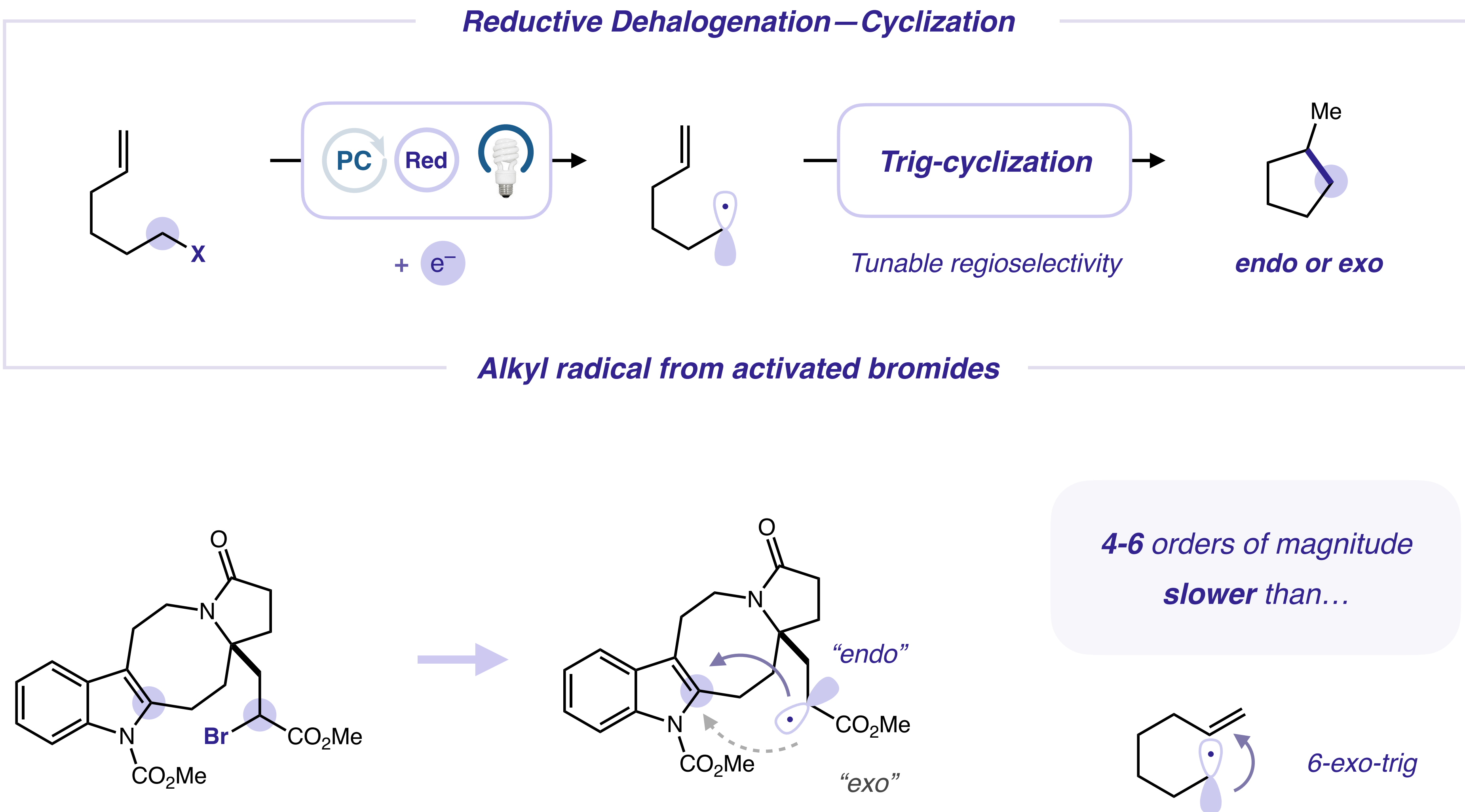

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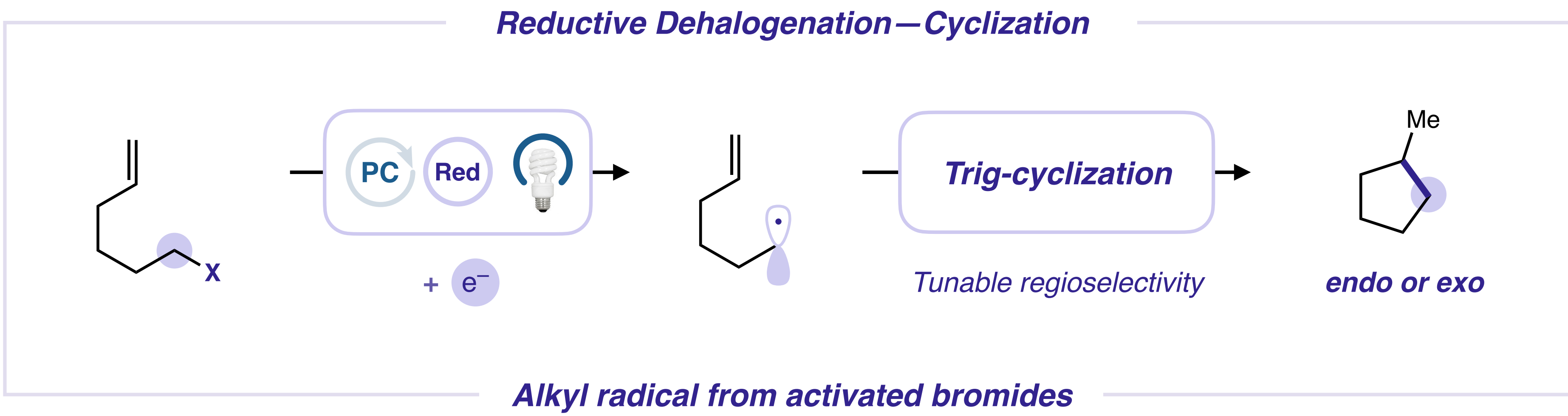
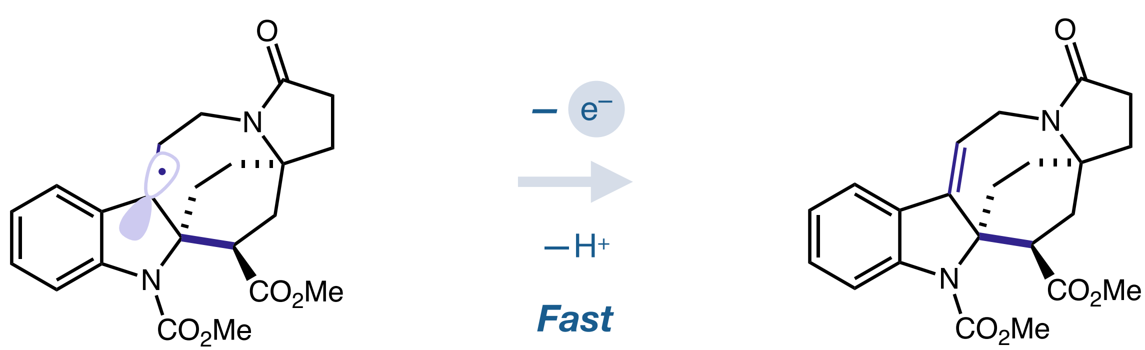
Radical Cyclizations via Photoredox Reductive Dehalogenation



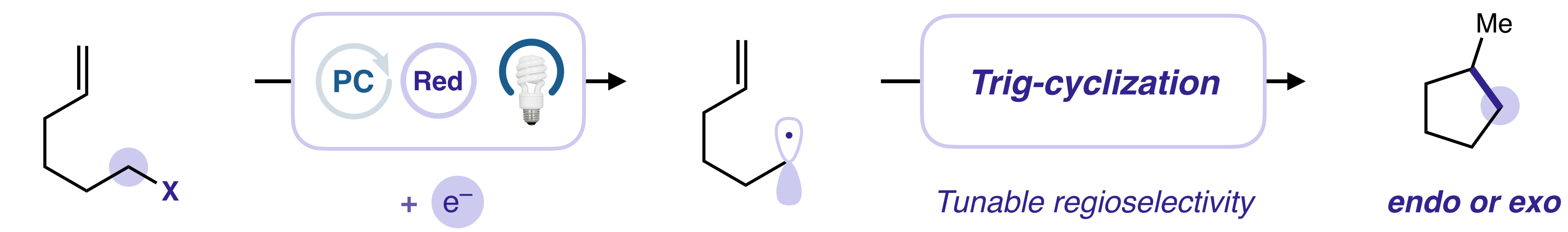


***Fast oxidation** serves as the major driving force*

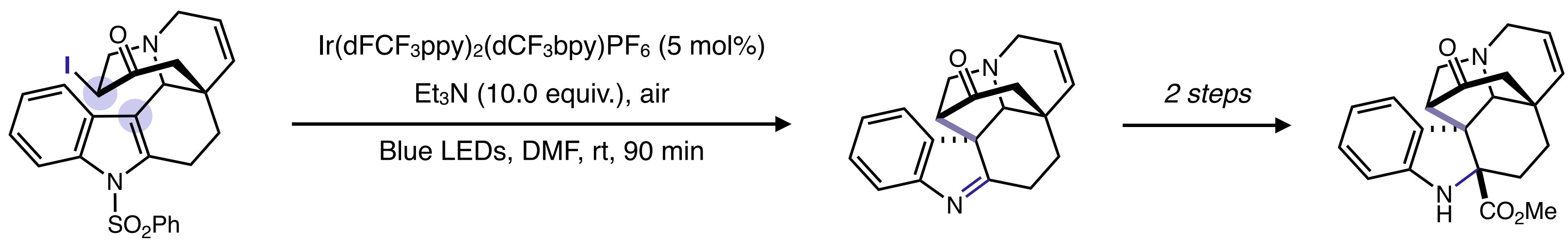
Miloserdov, F. M.; Che, C.-M.; Kirillova, M. S.; Muratore, M. E.; Echavarren, A. M. *J. Am. Chem. Soc.* **2018**, *140*, 5393–5400.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Alkyl radical from activated iodides



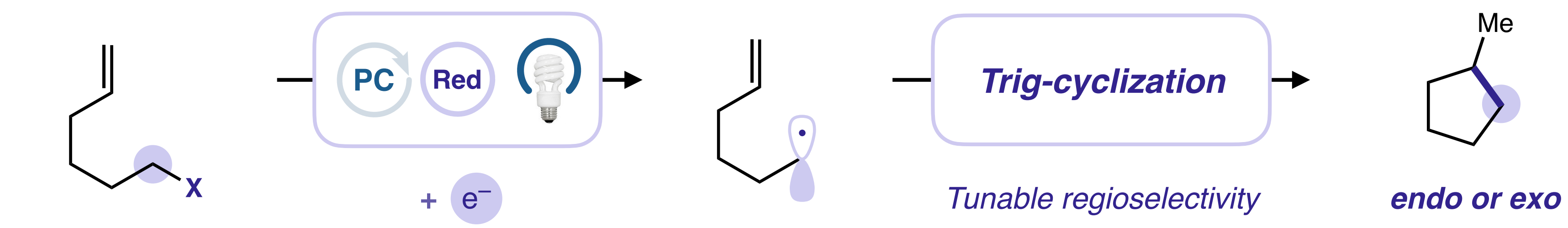
77% yield

(+)-flavisiamine F

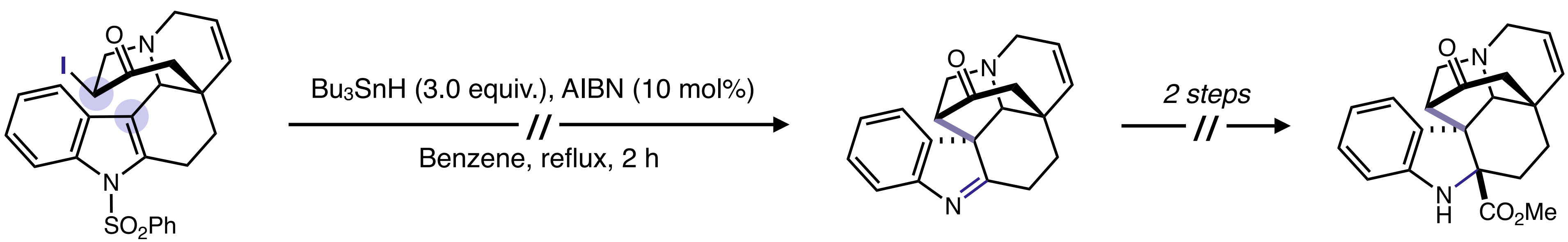
Tong, X.; Shi, B.; Liang, K.; Liu, Q.; Xia, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 5443–5446.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Alkyl radical from activated iodides



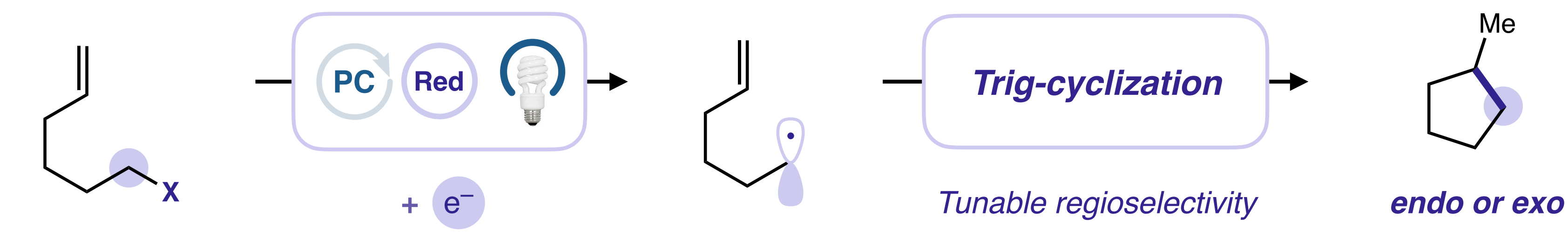
0% yield

(+)-flavisiamine F

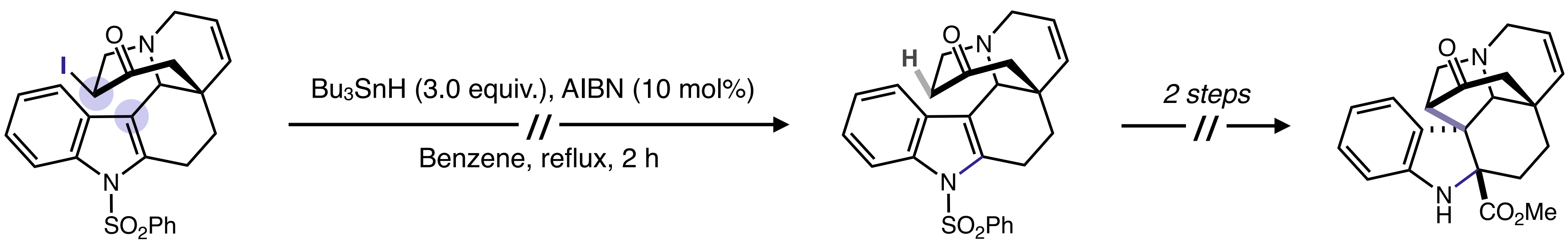
Tong, X.; Shi, B.; Liang, K.; Liu, Q.; Xia, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 5443–5446.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Alkyl radical from activated iodides



Premature reduction

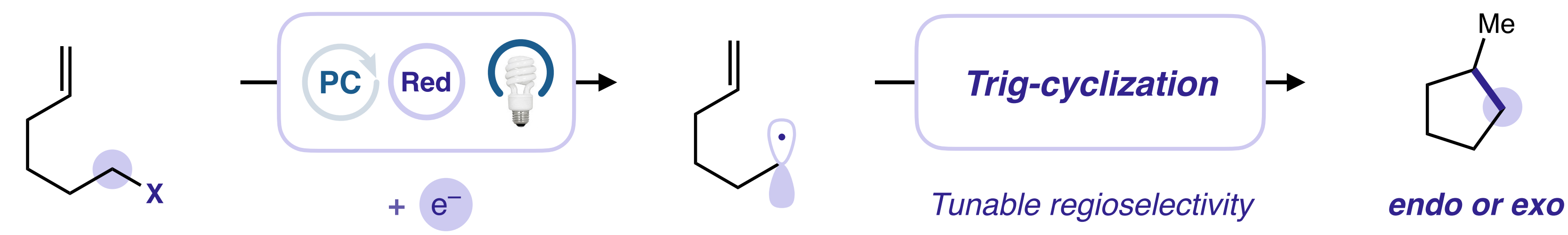
92% yield

(+)-flavisiamine F

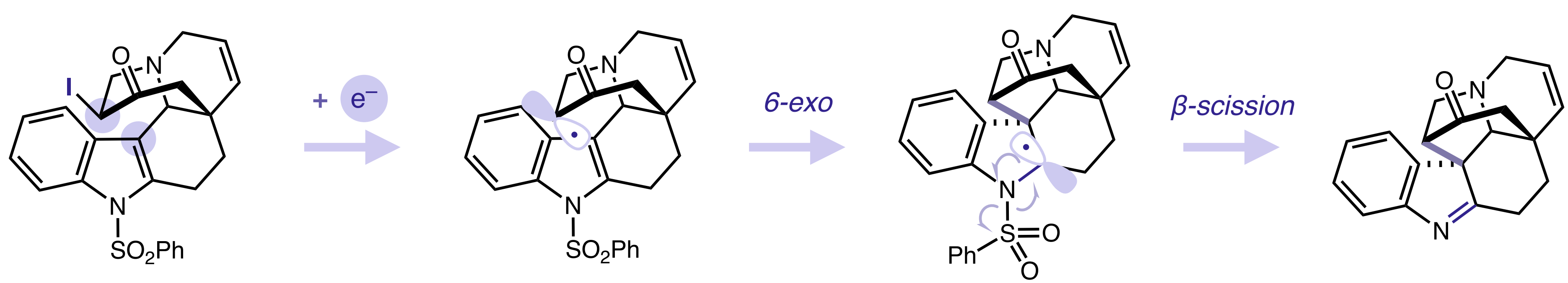
Tong, X.; Shi, B.; Liang, K.; Liu, Q.; Xia, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 5443–5446.

Radical Cyclizations via Photoredox Reductive Dehalogenation

Reductive Dehalogenation—Cyclization



Alkyl radical from activated iodides

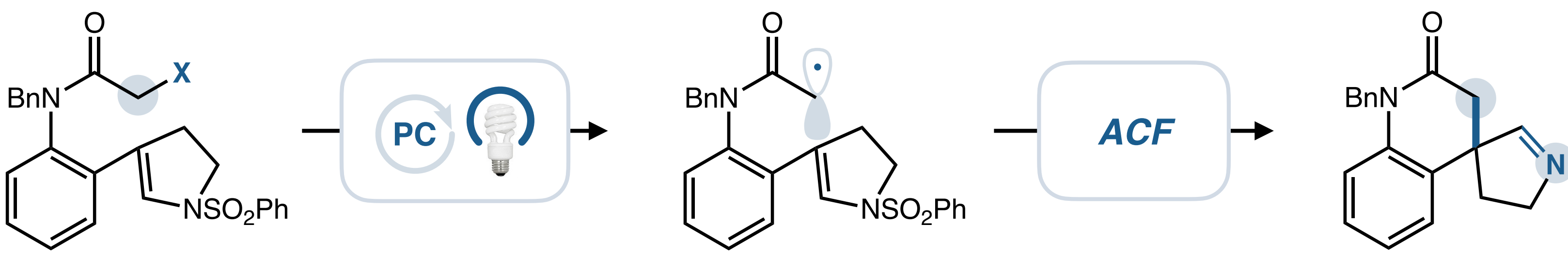


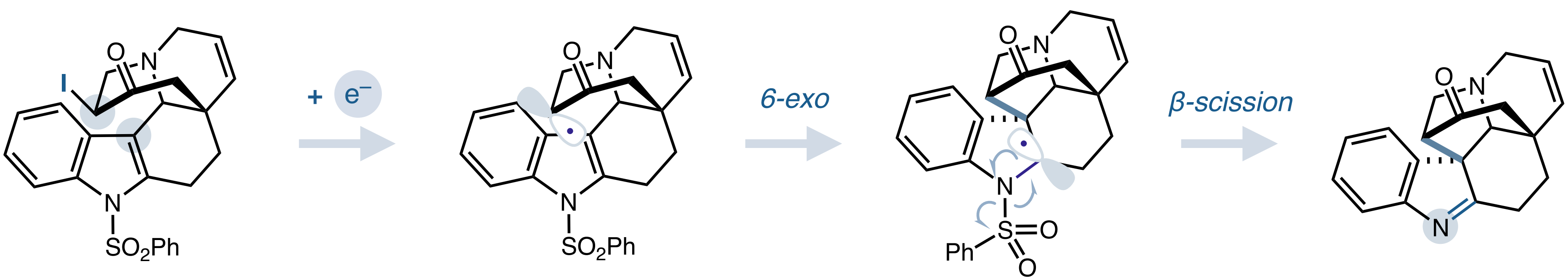
Addition ***Cyclization*** ***Fragmentation***

Tong, X.; Shi, B.; Liang, K.; Liu, Q.; Xia, C. *Angew. Chem. Int. Ed.* **2019**, *58*, 5443–5446.

Radical Cyclizations via ACF

Addition—Cyclization—Fragmentation (ACF)

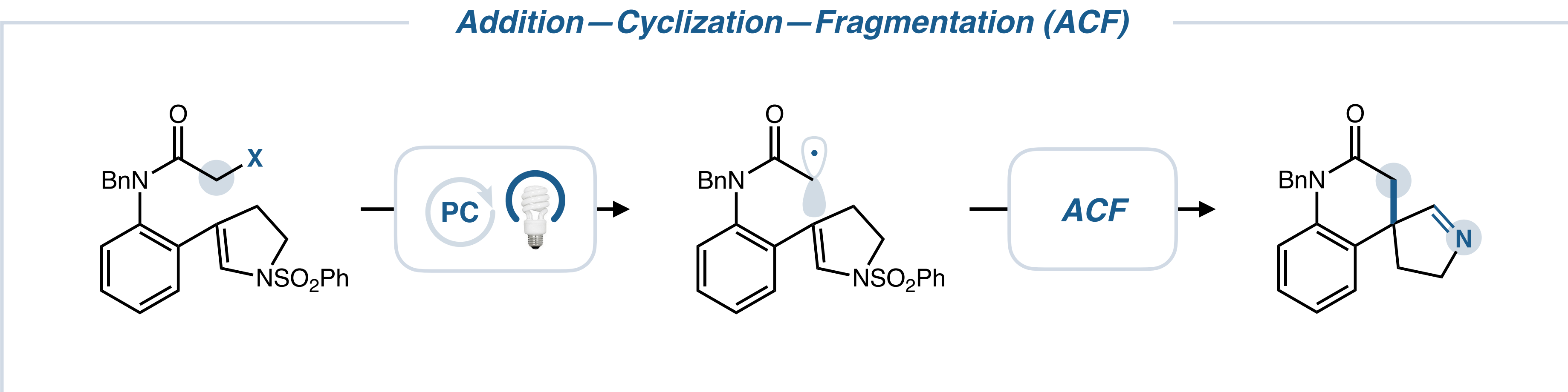




Addition ***Cyclization*** ***Fragmentation***

Zhang, H.; Hay, E. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2013**, *135*, 16610–16617.

Radical Cyclizations via ACF



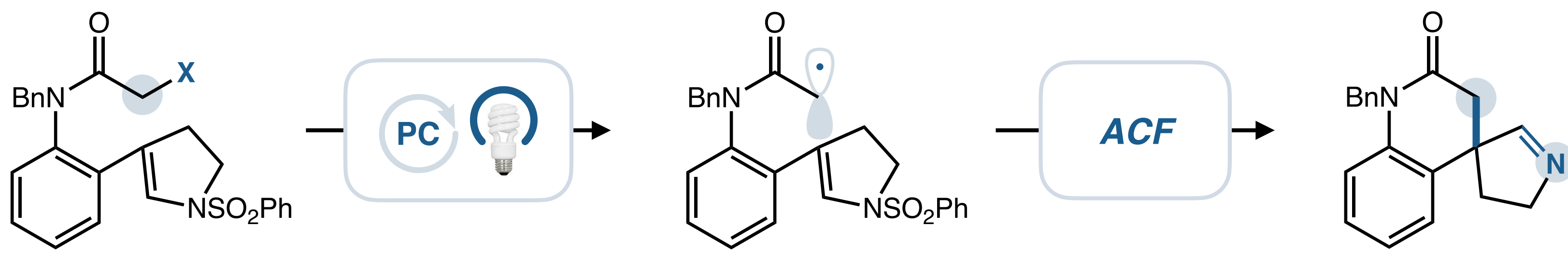
Dennis P. Curran

> *The ability to made **imines** by a sulfonyl radical elimination, especially when coupled with a **prior radical reaction** (here, the **cyclizations**), provides a **powerful alternative** to the usual condensation route.*

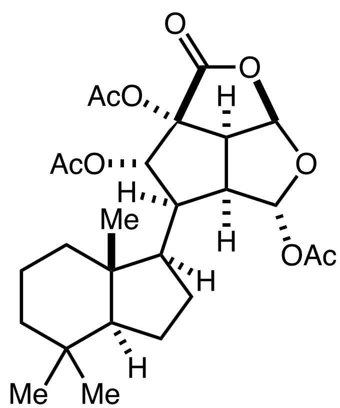
Zhang, H.; Hay, E. B.; Geib, S. J.; Curran, D. P. *J. Am. Chem. Soc.* **2013**, *135*, 16610–16617.

Radical Cyclizations via ACF

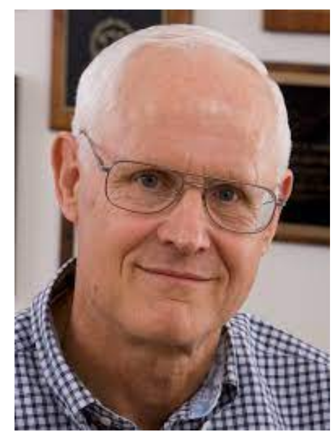
Addition—Cyclization—Fragmentation (ACF)



Case Study: Total Synthesis of (—)-Chromodorolide B



(—)-Chromodorolide B

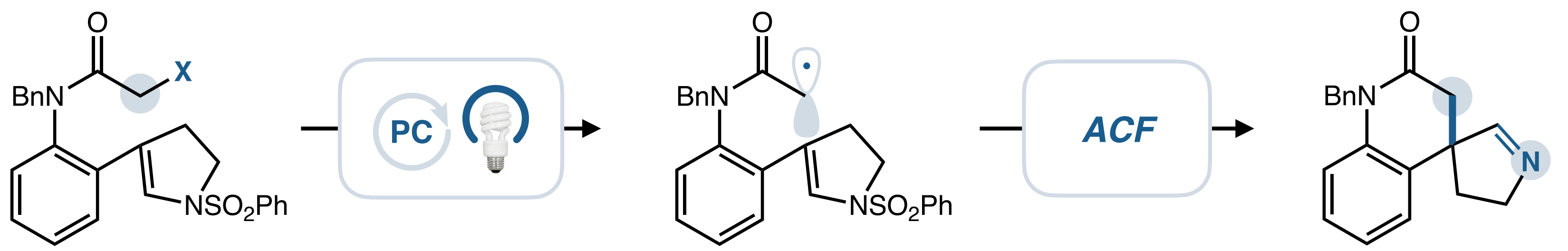


Larry E. Overman

Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

Radical Cyclizations via ACF

Addition—Cyclization—Fragmentation (ACF)



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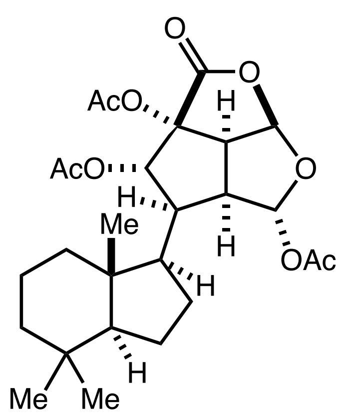


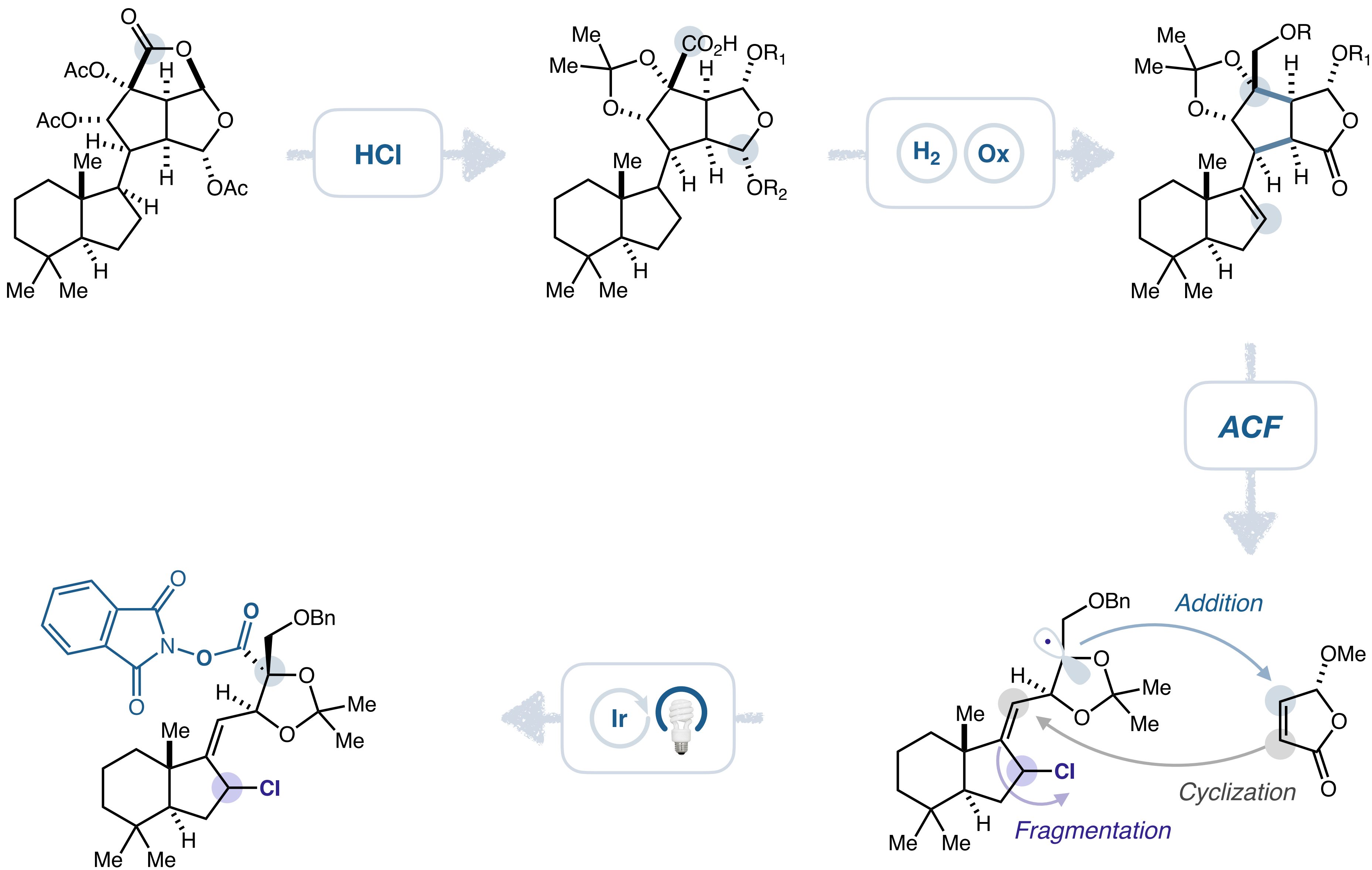
(—)-Chromodorolide B

- ***Most structurally intricate*** *of the spongian diterpenoids; largely isolated from marine sources*
- ***Ten contiguous stereocentres*** *arrayed upon the pentacyclic ring system*
- *Modest in vitro* ***anti-tumour, nematocidal, and antimicrobial*** *activities*

Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

Radical Cyclizations via ACF

Overman's Total Synthesis of (—)-Chromodorolide B



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Radical Cyclizations via ACF

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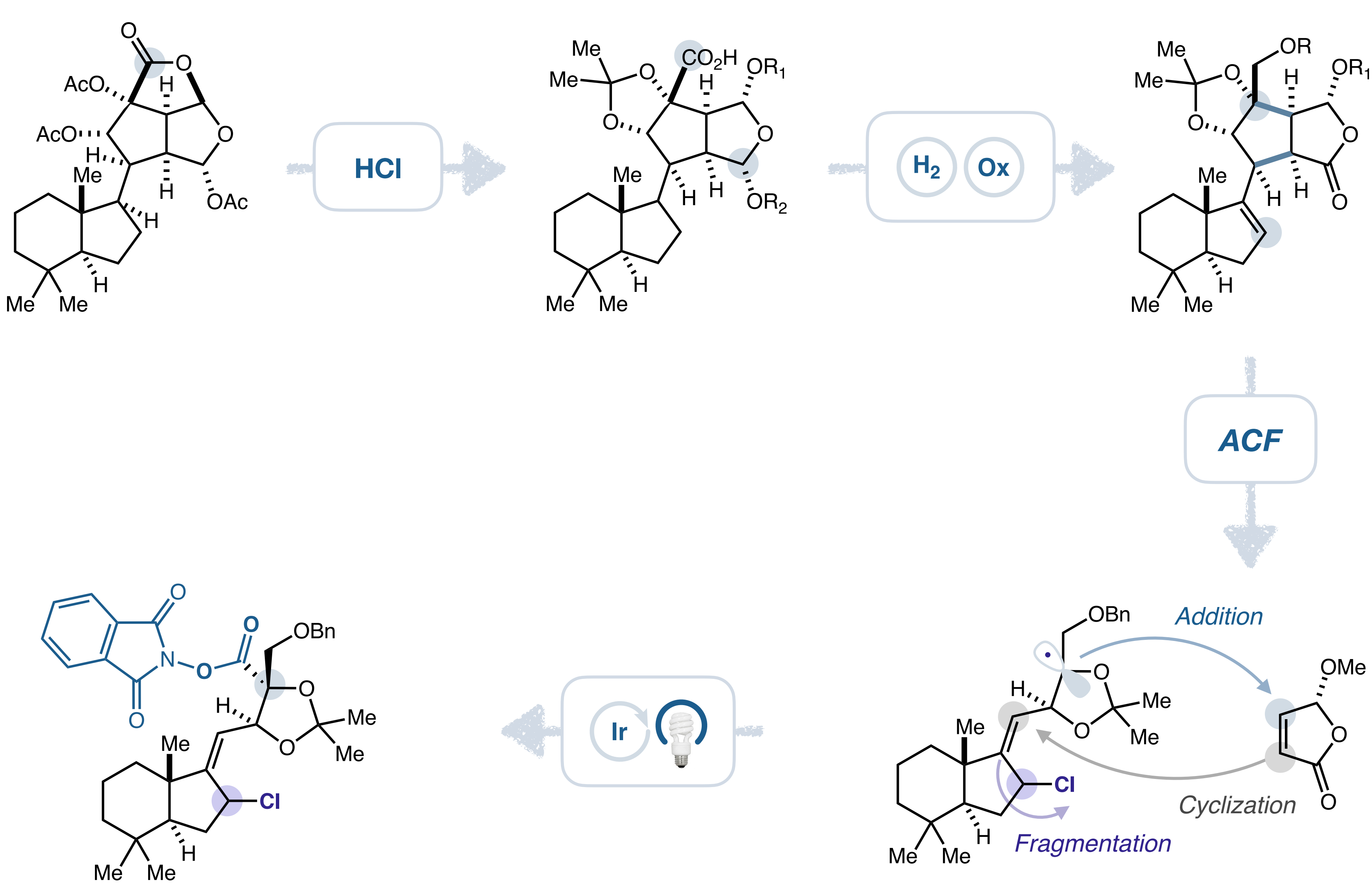

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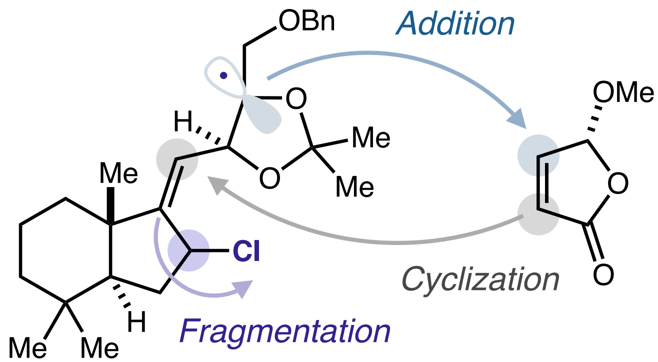

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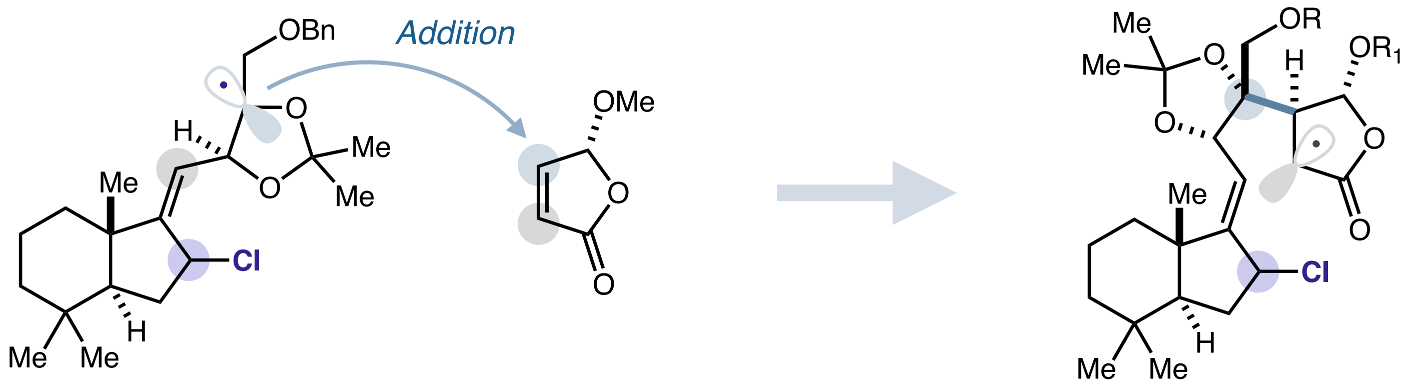

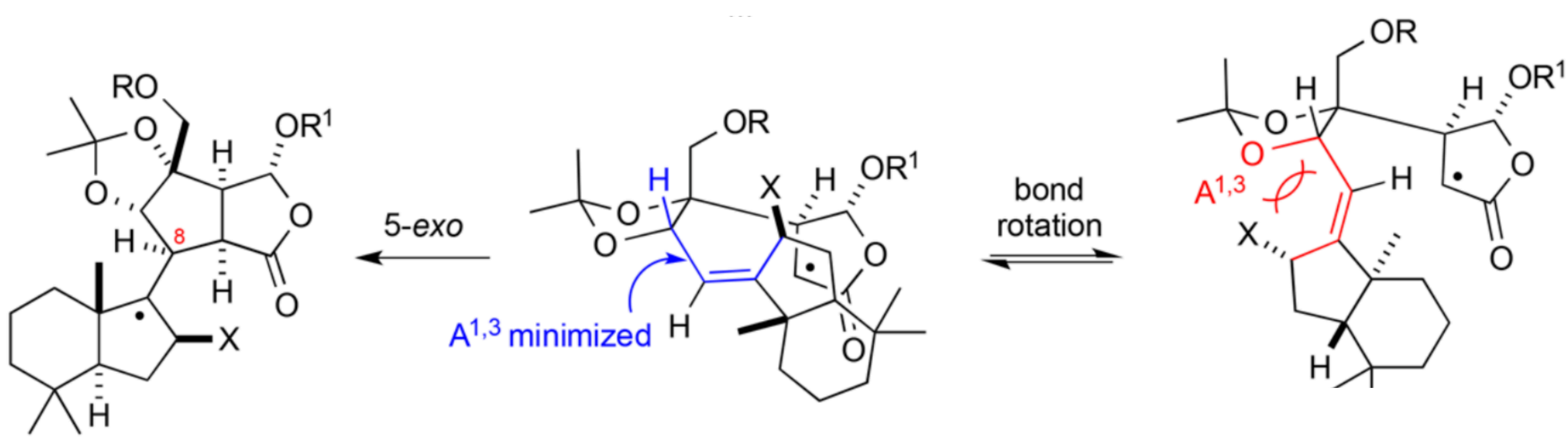

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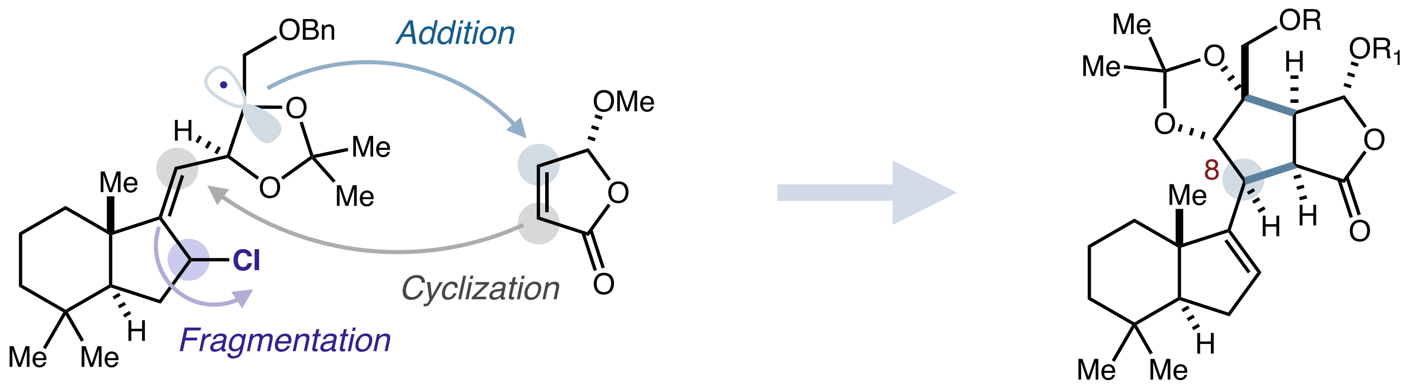

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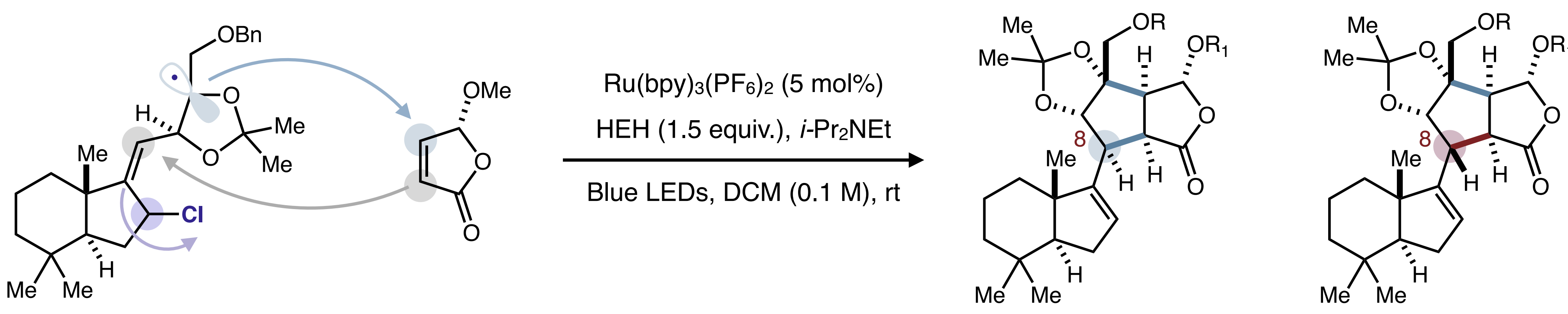
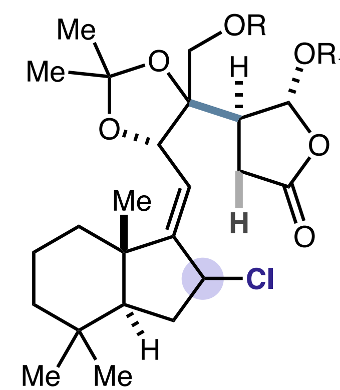
Radical Cyclizations via ACF

Overman's Total Synthesis of (—)-Chromodorolide B



Product | *Undesired epimer*

Modifications	*Product*	*Undesired epimer*	*Alk-H*
None	**20%**	35%	40%

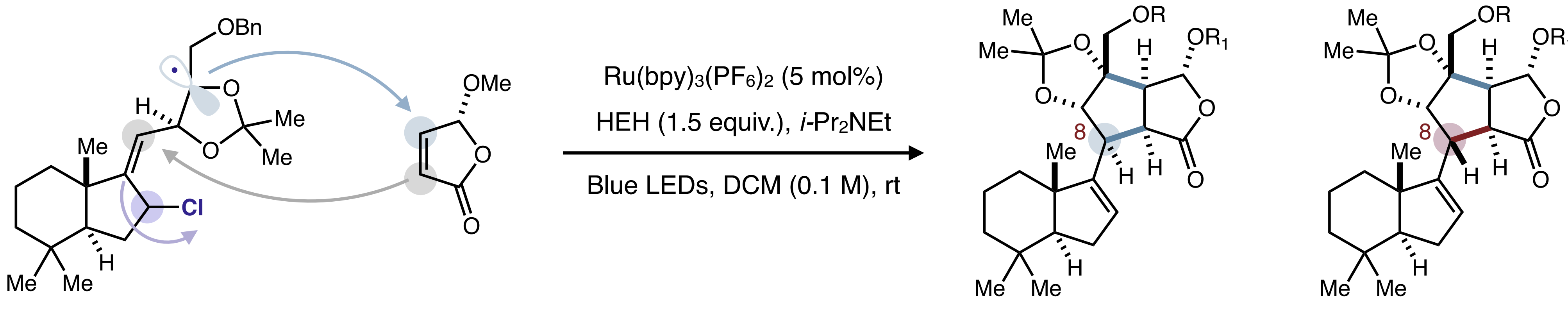


Alk-H

Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

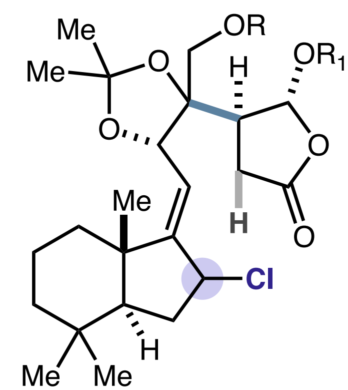
Radical Cyclizations via ACF

Overman's Total Synthesis of (—)-Chromodorolide B



Product — *Undesired epimer*

Modifications	Product	Undesired epimer	Alk-H
None	20%	35%	40%
No *i*-Pr$_2$NEt	18%	34%	21%

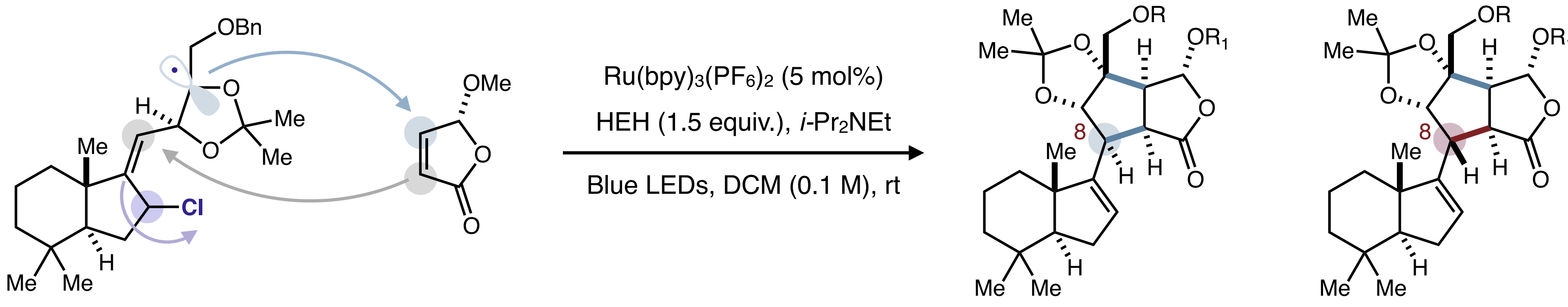


Alk-H

Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

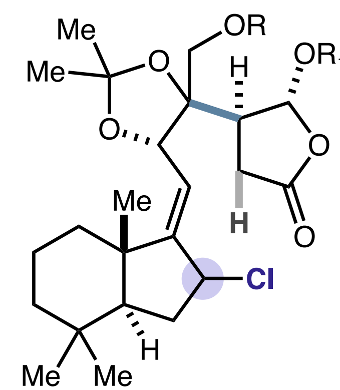
Radical Cyclizations via ACF

Overman's Total Synthesis of (—)-Chromodorolide B



Product — *Undesired epimer*

Modifications	*Product*	*Undesired epimer*	*Alk-H*
None	**20%**	35%	40%
No *i*-Pr$_2$NEt	**18%**	34%	21%
No *i*-Pr$_2$NEt, DCM (0.02 M)	**16%**	29%	9%



Alk-H

Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

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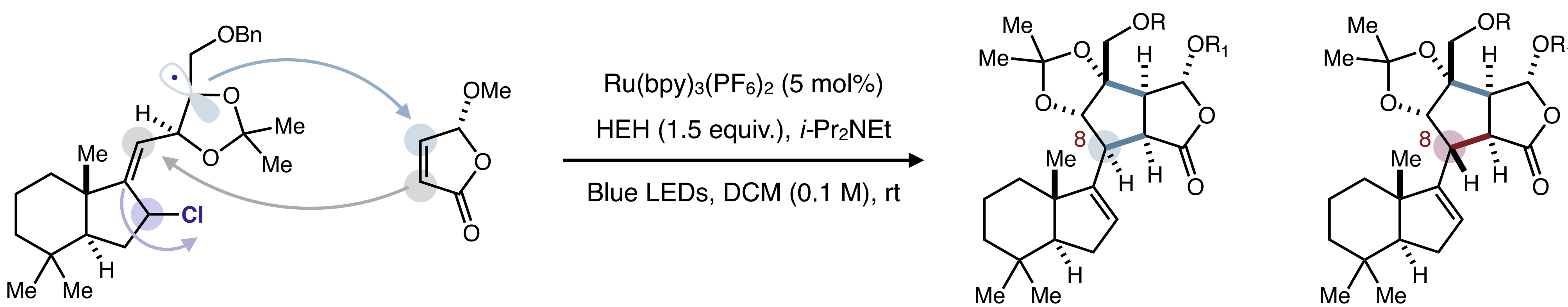

Product ***Undesired epimer***

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No *i*-Pr_2NEt	**18%**	34%	21%
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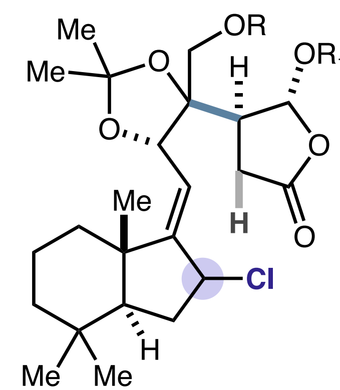
No *i*-Pr_2NEt, d_2-HEH	**25%**	45%	16% (d_1)



Alk-H

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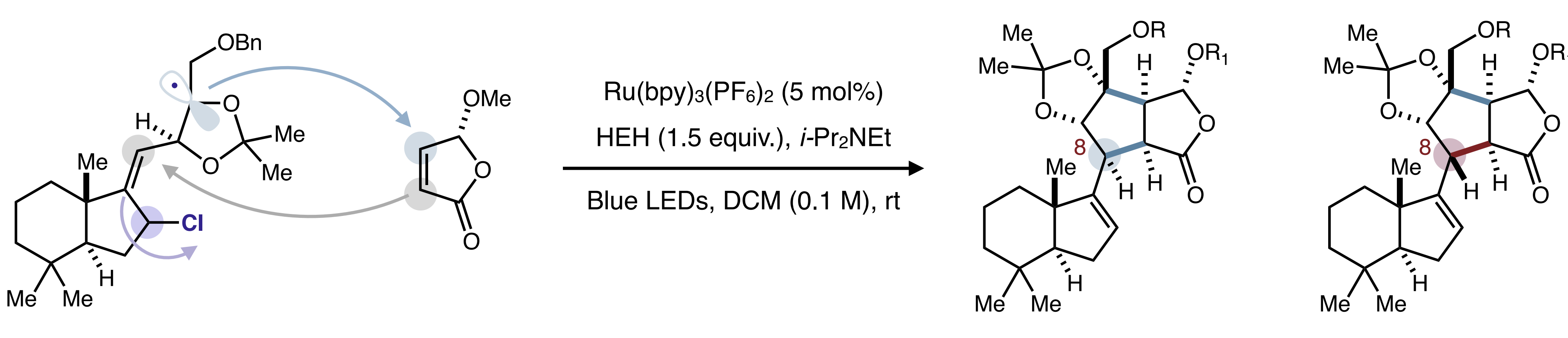

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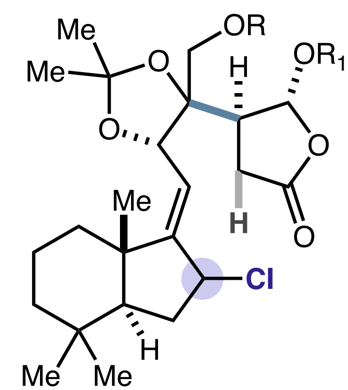
No *i*-Pr_2NEt, d_2-HEH, MeCN	**27%**	37%	21% (d_1)



Alk-H

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Radical Cyclizations via ACF

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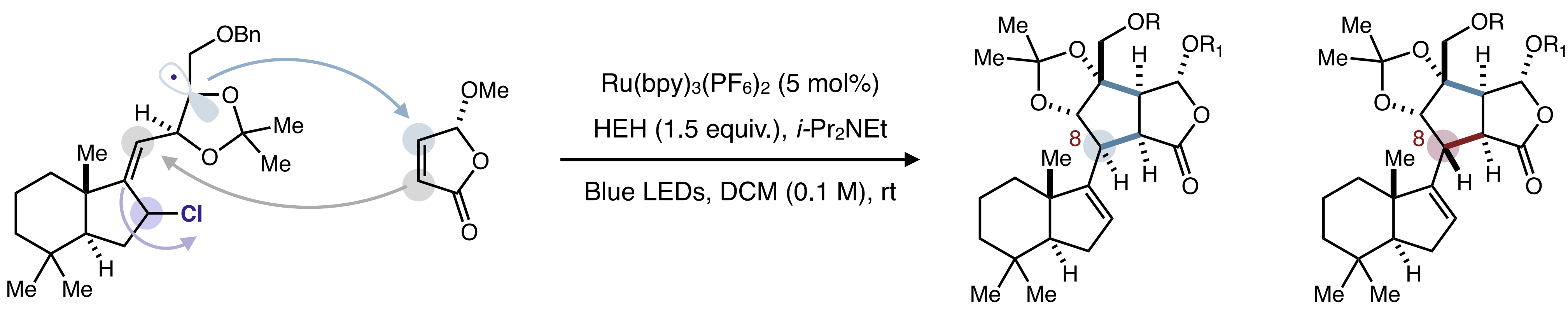

Product | *Undesired epimer*

Modifications	***Product***	***Undesired epimer***	***Alk-H***
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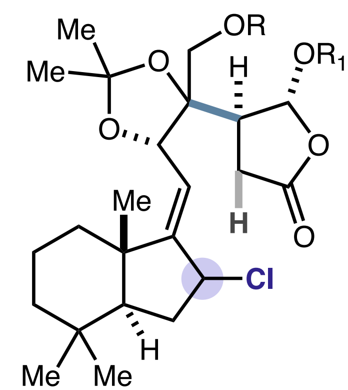

Alk-H

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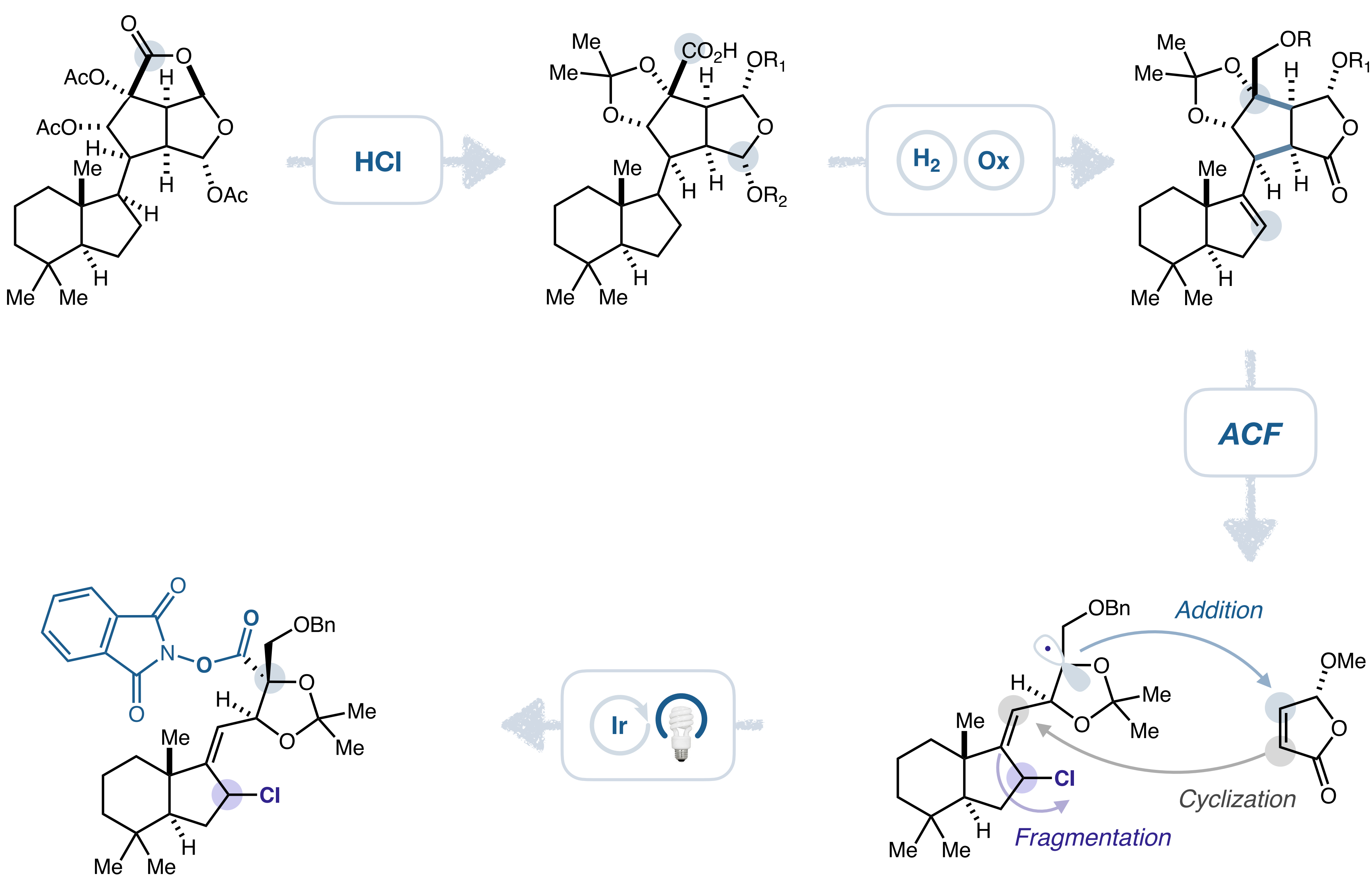

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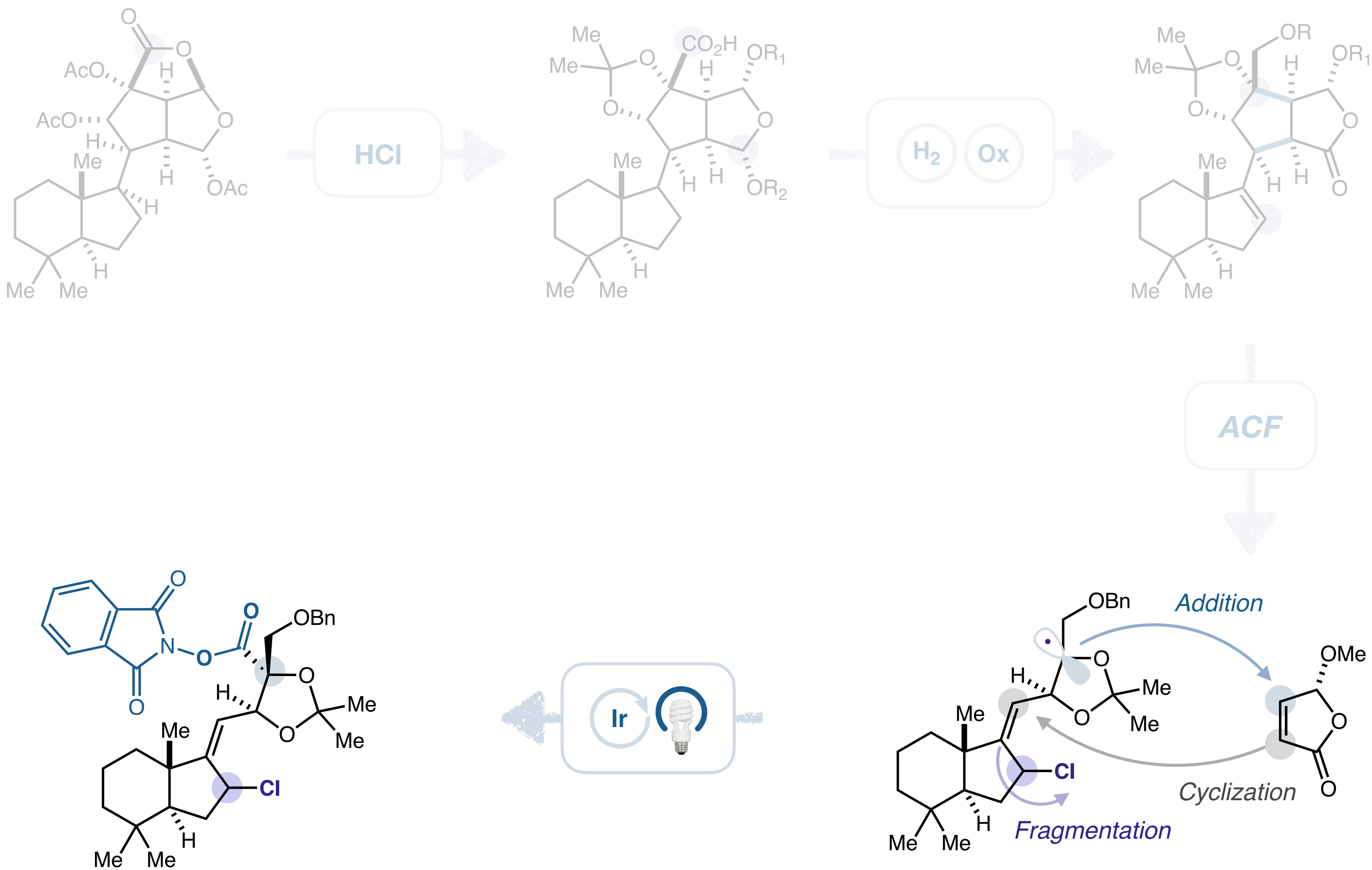

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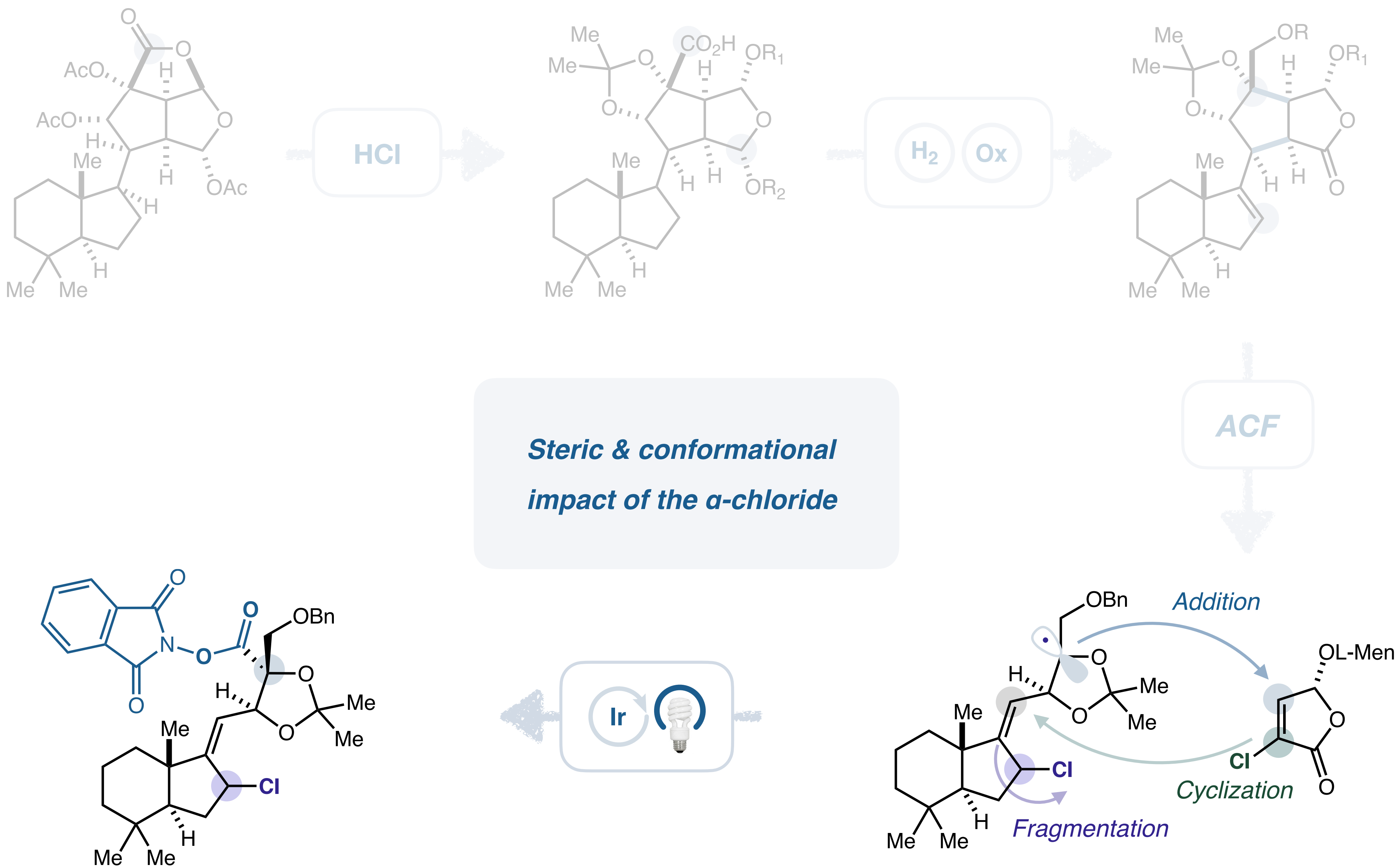

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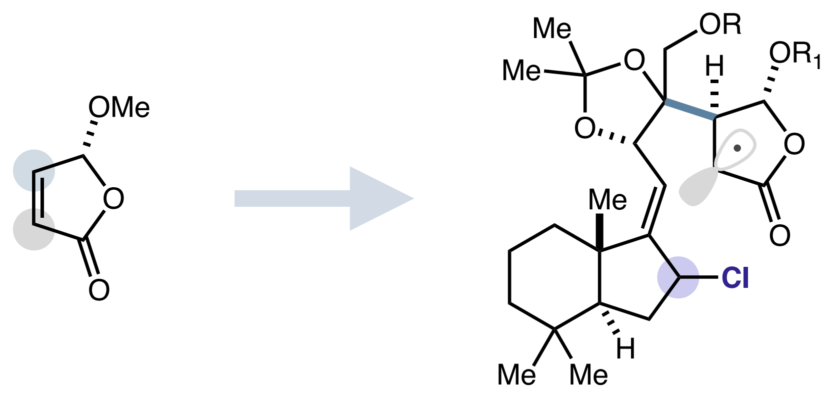
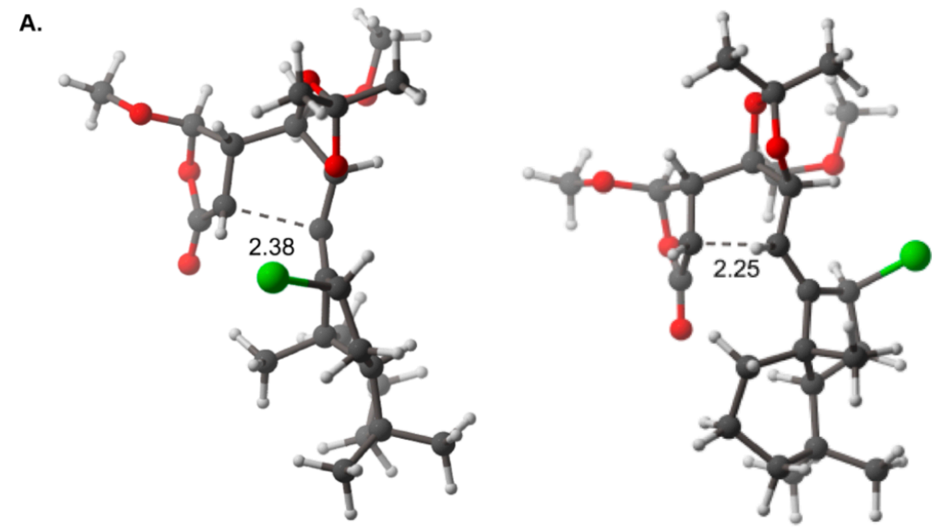
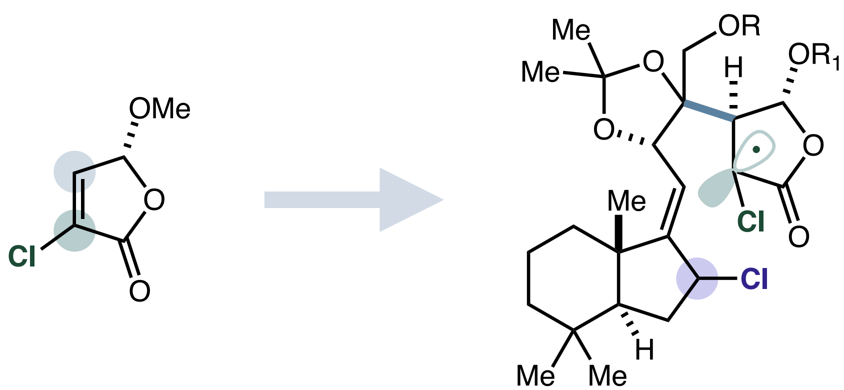
Radical Cyclizations via ACF

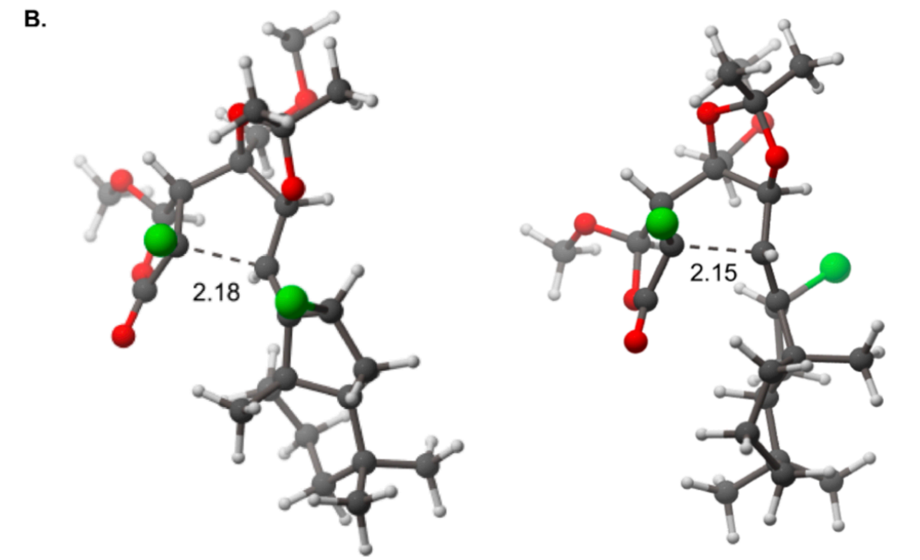
Overman's Total Synthesis of (—)-Chromodorolide B





TS-A-*trans* (0 kcal/mol) **TS-A-*cis*** (1.0 kcal/mol)



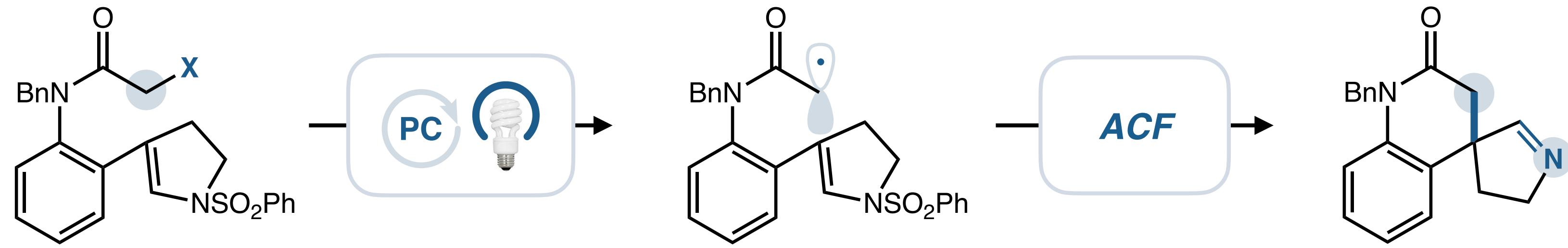


TS-B-*trans* (2.0 kcal/mol) **TS-B-*cis*** (0 kcal/mol)

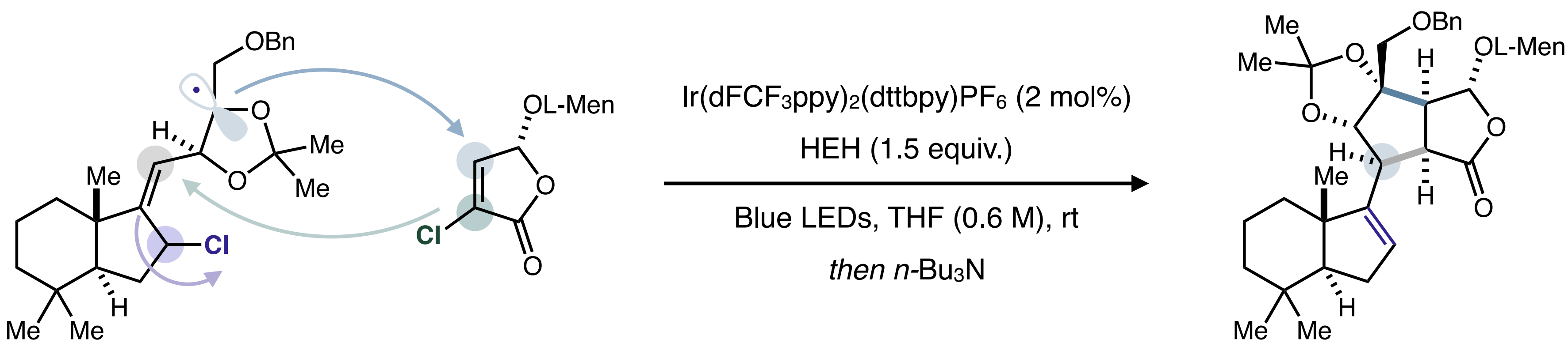
Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, F., Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

Radical Cyclizations via ACF

Addition—Cyclization—Fragmentation (ACF)



Case Study: Total Synthesis of (—)-Chromodorolide B



One ring, two C—C bonds, four stereocentres

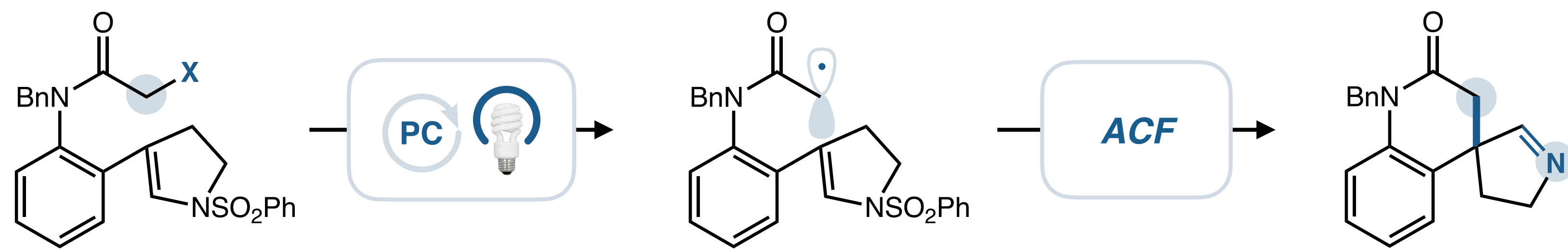
58% yield

Undesired epimer not detected

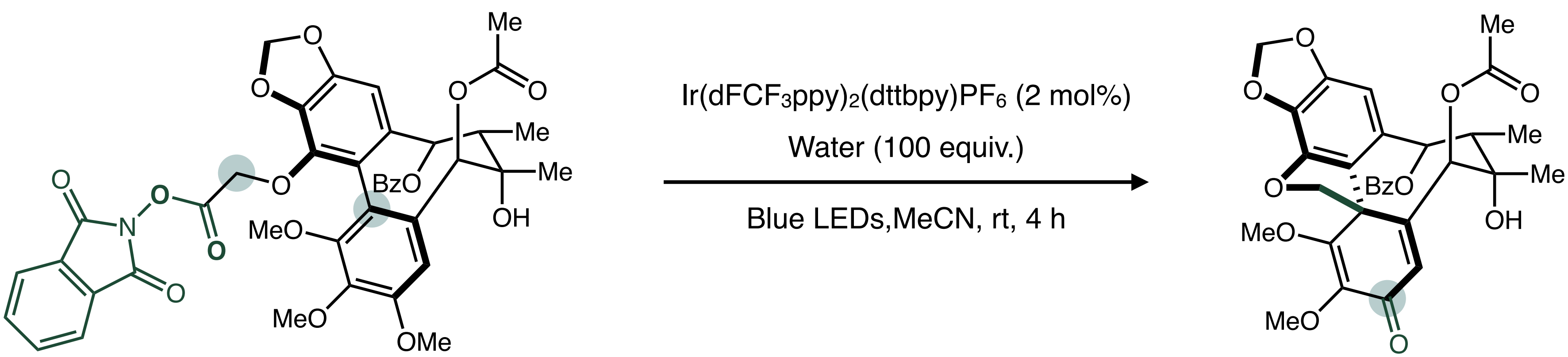
Tao, D. J.; Slutskyy, Y.; Muuronen, M.; Le, A.; Kohler, P.; Overman, L. E. *J. Am. Chem. Soc.* **2018**, *140*, 3091–3102.

Radical Cyclizations via ACF

Addition—Cyclization—Fragmentation (ACF)



Decarboxylation via RAE: (—)-kadsulignan E



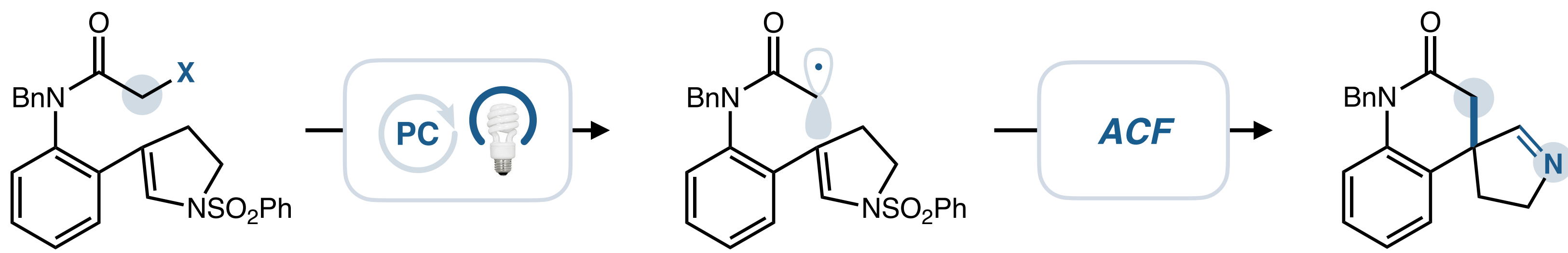
43% yield

(—)-kadsulignan E

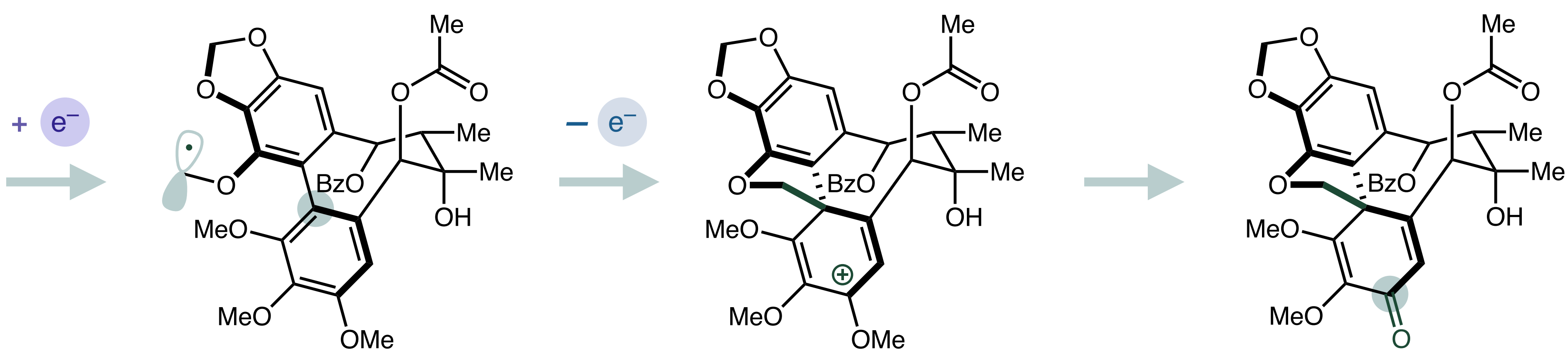
Zheng, H.; Lumb J.-L. *Nat. Chem.* **2021**, *13*, 24–32.

Radical Cyclizations via ACF

Addition—Cyclization—Fragmentation (ACF)



Decarboxylation via RAE: (—)-kadsulignan E



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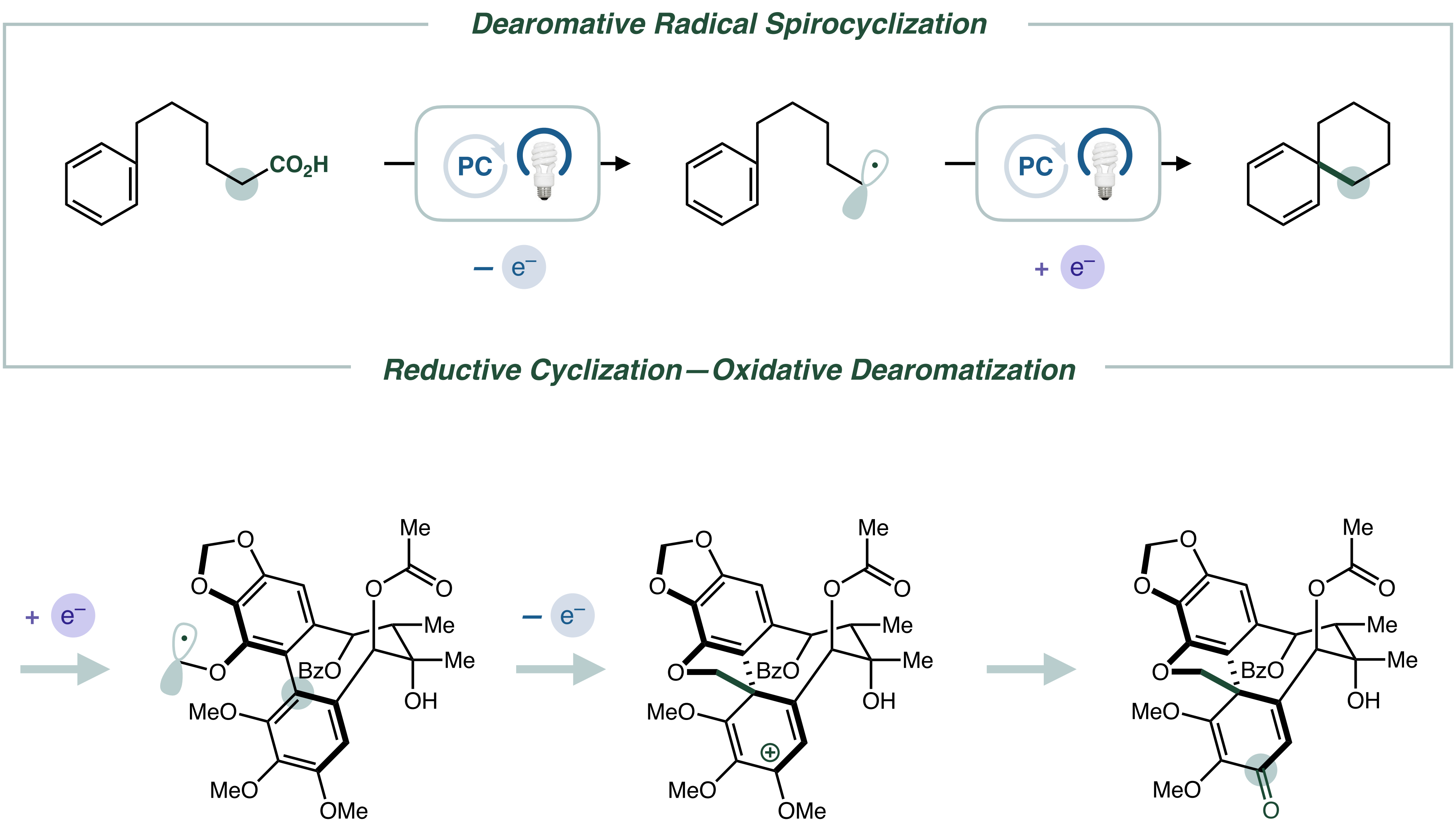
Redox-neutral Radical Cyclization—Dearomatization



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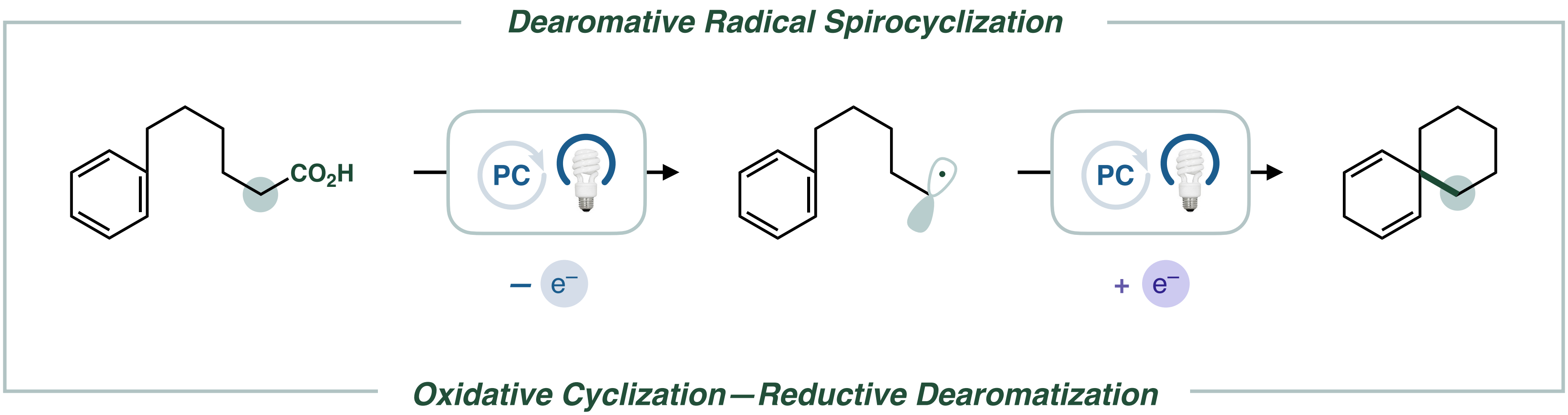
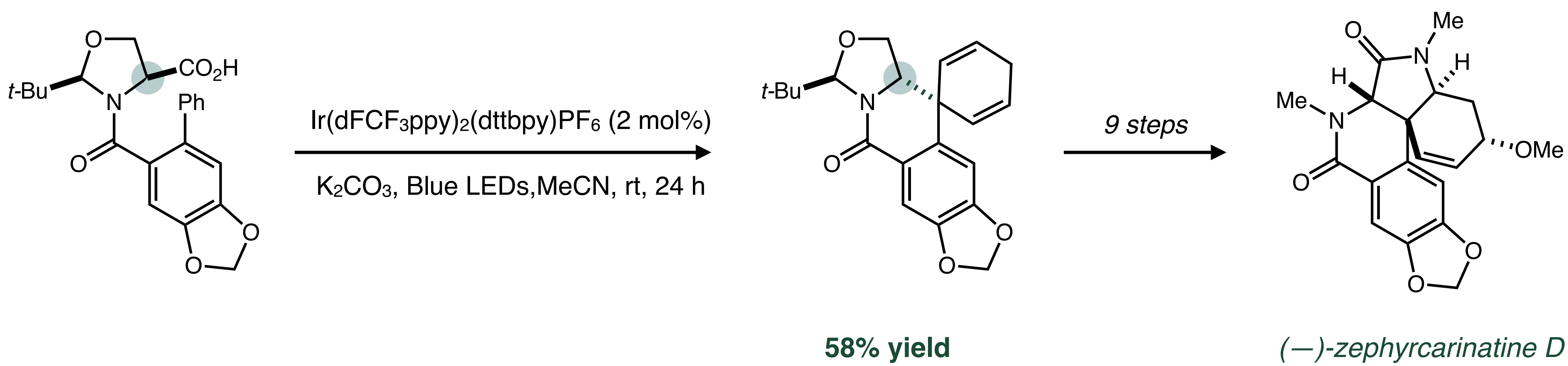




Takeuchi, H.; Inuki, S.; Nakagawa, K.; Kawabe, T.; Ichimua, A.; Oishi, S.; Ohno, H. *Angew. Chem. Int. Ed.* **2020**, *59*, 21210–21215.

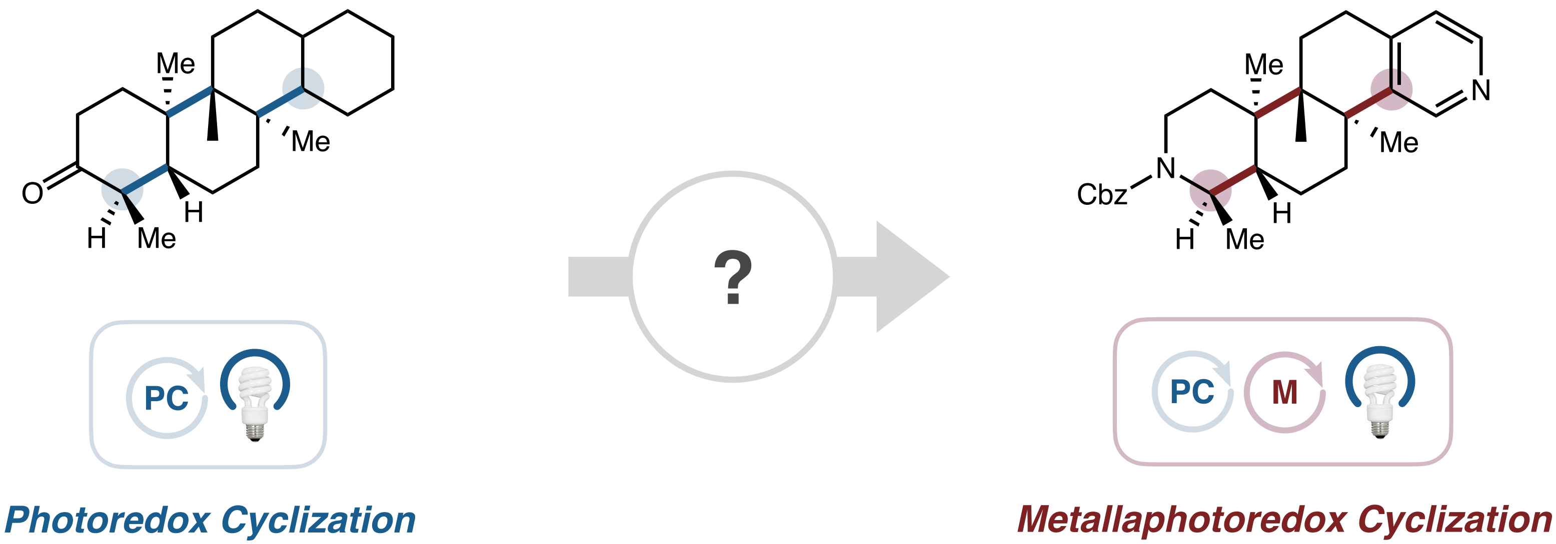
Radical Cyclizations: The Future

2013 → 2024

Pitre, S. P.; Overman, L. E. *Chem. Rev.* **2022**, *122*, 1717–1751.
Mateus-Ruiz, J. B.; Cordero-Vargas, A. *Synthesis* **2020**, *52*, 3111–3128.

Radical Cyclizations: The Future

Conclusion & outlook: The Future of Photoredox in Total Synthesis



2024

Pitre, S. P.; Overman, L. E. *Chem. Rev.* **2022**, *122*, 1717–1751.
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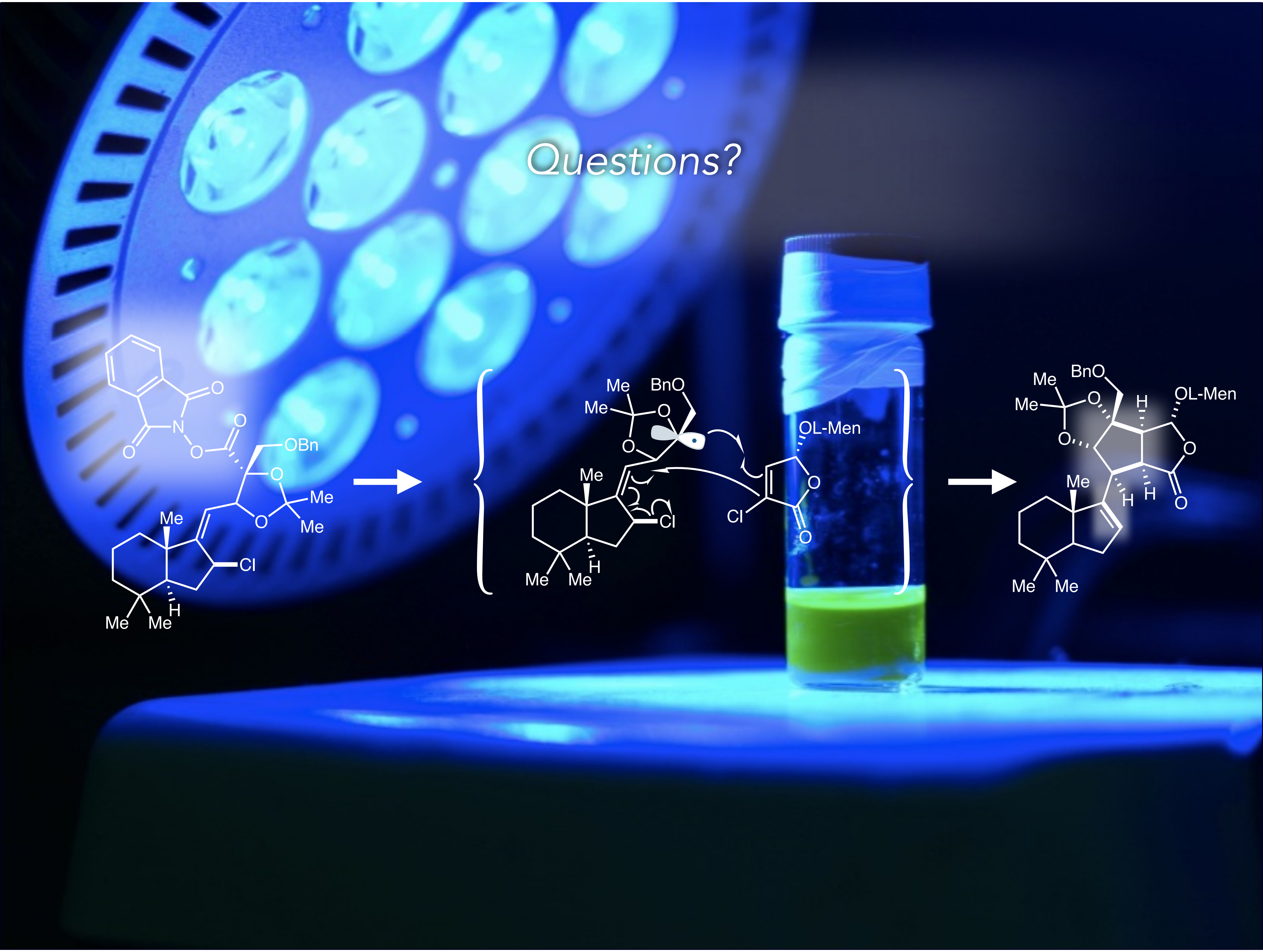
Questions?
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