Constructing Four-Membered Carbocycles and Heterocycles via Photochemical 1,5-HAT

Seminar

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Supervisor: Prof. Ping Lu (陆平 教授)

2026-4-10

Contents

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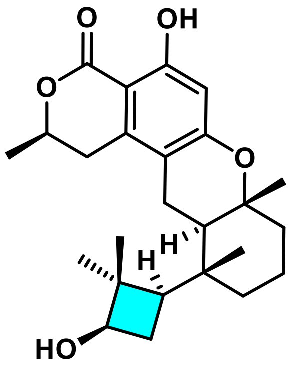
Part 1

Introduction

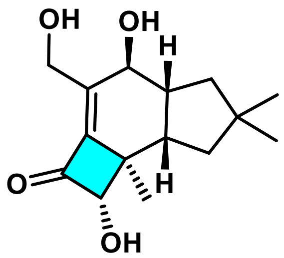
1. Introduction

➢ Strained Four-Membered Rings in Bioactive Molecules

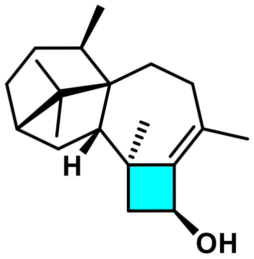
❒ Carbocyclic Four-Membered Rings



(+)-talaromyolides D
potent antiviral activity
against PRV

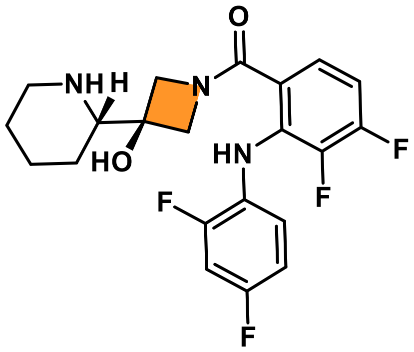


(-)-tsugicoline A
isolated from *L. tsugicola*

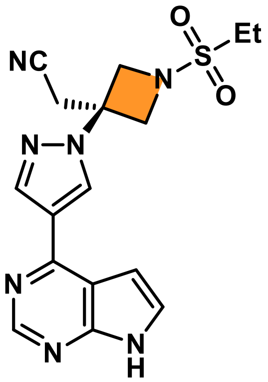


9-harzien-11-ol
isolated from *Taxus baccata*

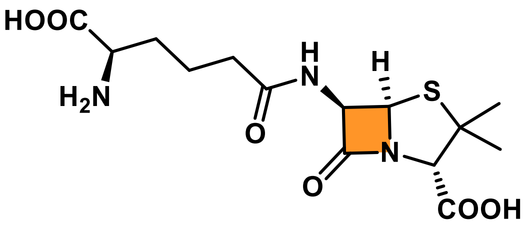
❒ Azacyclic Four-Membered Rings



cobimetinib
MEK1 inhibitor



baricitinib
for arthritis



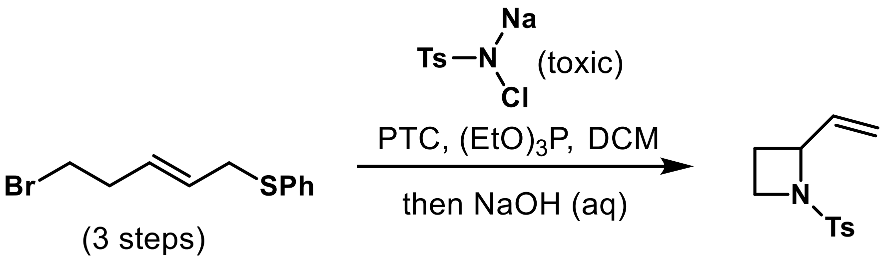
penicillin N
antibiotic

B. Wu *et al*., *Org. Lett*. **2019**, *21*, 6539; G. Nasini *et al*., *Tetrahedron* **1995**, *51*, 13357; J. Ouazzani *et al*., *Phytochemistry* , **2014**, *97*, 55; N. Aay *et al*., WO2007/44515 A1, **2007**; P. A. Friedman *et al*., WO2010/39939 A1, **2010**; M. Castells *et al*., *N. Engl. J. Med.* **2019**, *381*, 2338.

1. Introduction

➢ Current Strategies towards Four-Membered Rings and Limitations

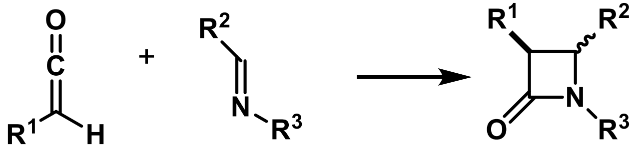
❒ Nucleophilic substitution



lengthy routines

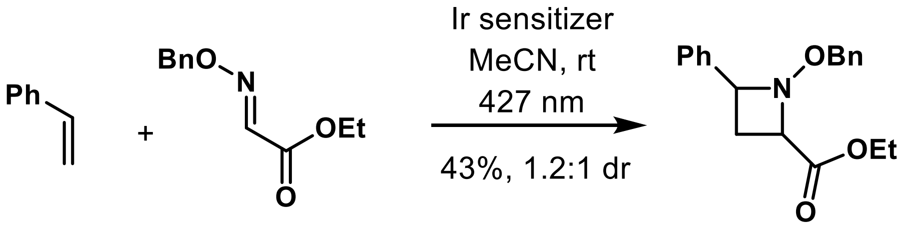
❒ [2+2]-Cycloaddition (ground state)

The Staudinger reaction



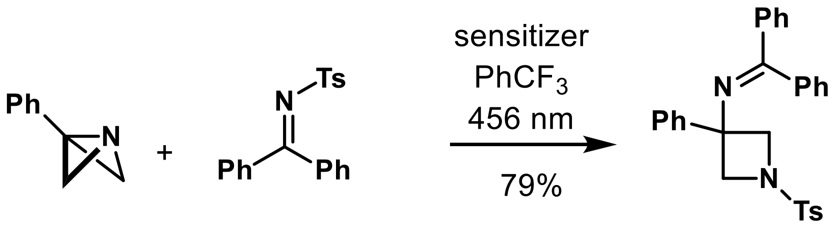
in situ formed ketenes

❒ [2+2]-Cycloaddition (excited state)



diastereoselectivity issue; activated alkenes

❒ Strain-release reaction



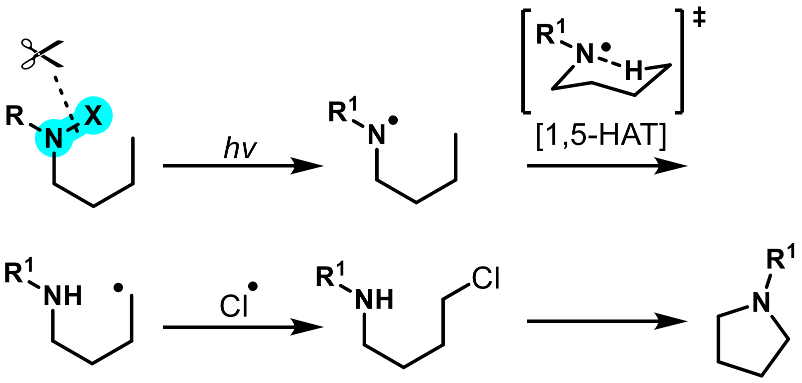
substrates with highly-strained rings

R. E. Dolle *et al.*, *Tetrahedron Lett.* **1989**, *30*, 4723; H. Staudinger, *Justus Liebigs Ann. Chem.* **1907**, *356*, 51;
C. S. Schindler *et al.*, *Science*, **2024**, *384*, 1468; Luca Dell’Amico *et al.*, *Nat. Catal.* **2024**, *7*, 1223.

1. Introduction

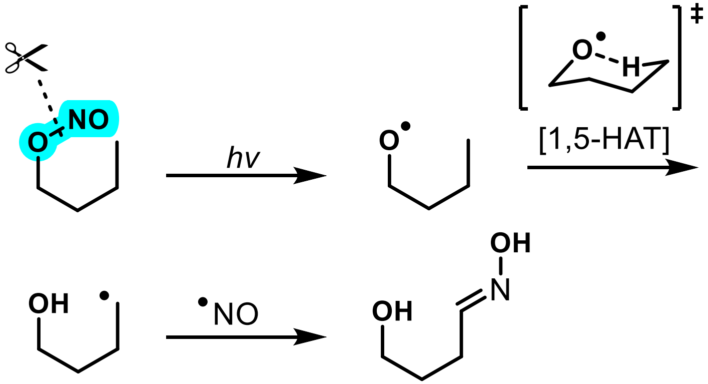
➢ Photochemical Remote C–H Functionalisation Promoted by 1,5-HAT

Hoffman-Löffler-Freytag reaction 1883



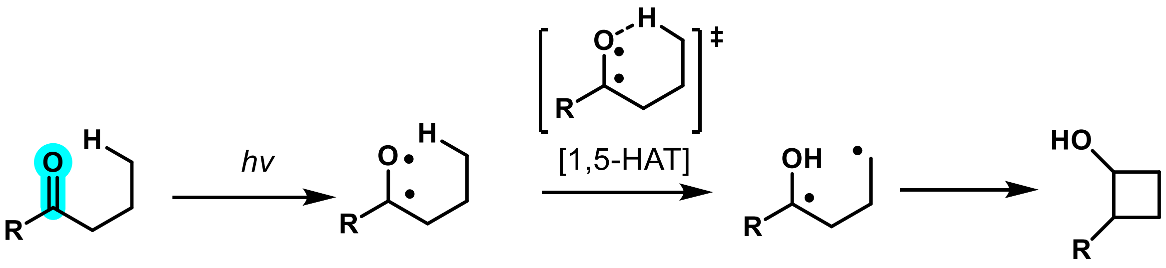
A. W. Hofmann, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 558.

Barton reaction 1960



D. H. R. Barton *et al.*, *J. Am. Chem. Soc.* **1960**, *82*, 2640.

Norrish-Yang Cyclization 1958

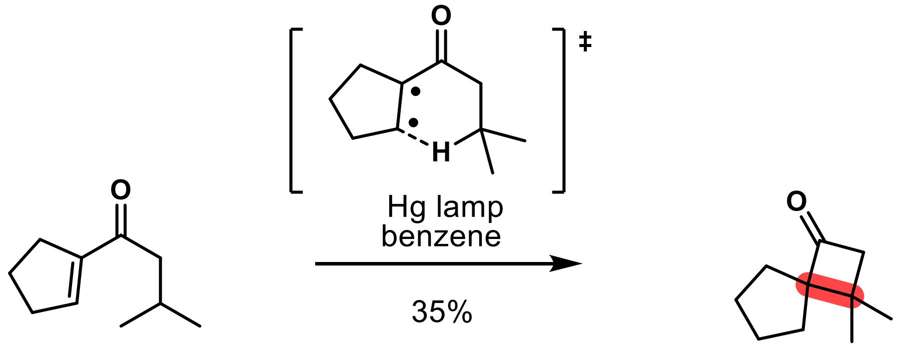


- **1,5-HAT promoted by C–O-centered biradical species**
- **construction of four-membered carbocycles**

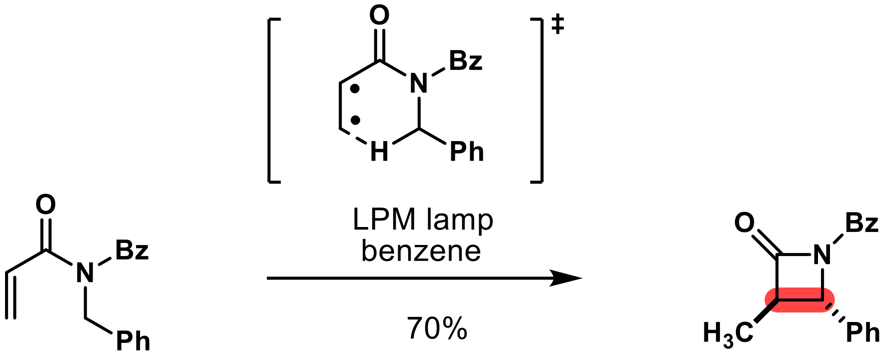
R. G. W. Norrish *et al.*, *J. Chem. Soc.* **1934**, 874; N. C. Yang *et al.*, *J. Am. Chem. Soc.***1958**, *80*, 2913.

1. Introduction

➢ Seminal Work of 1,5-HAT through Carbon Centered Radicals

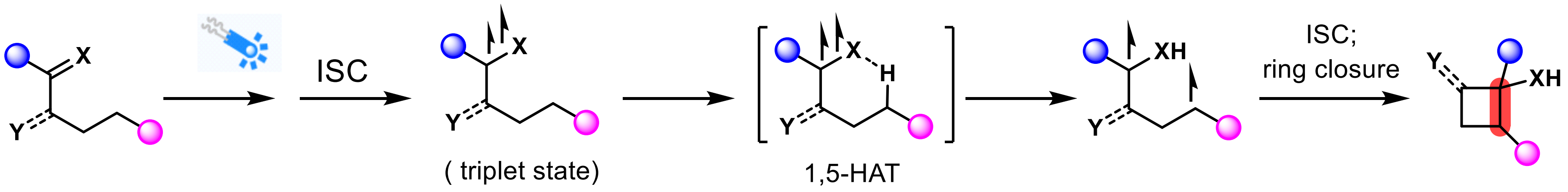


W. C. Agosta *et al.*, *J. Am. Chem. Soc.* **1972**, *94*, 5100.



H. Aoyama *et al.*, *Tetrahedron.* **1977**, *33*, 485.

➢ Outline of 1,5-HAT under Irradiation



■ **Carbon to oxygen 1,5-HAT:**

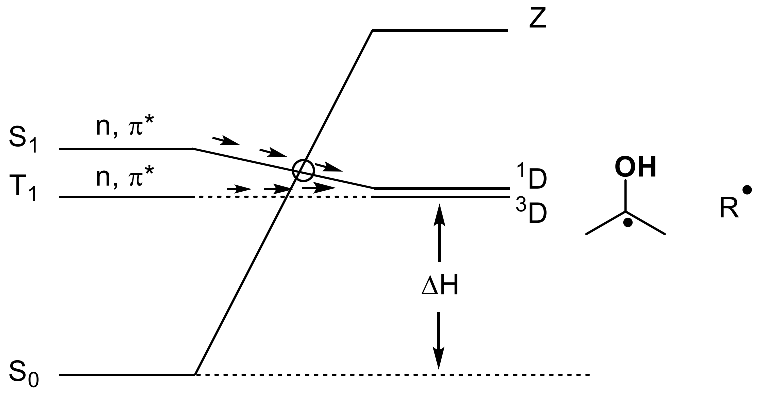
- **low HAT barrier** ● **irreversible**
- **favorable conformation**

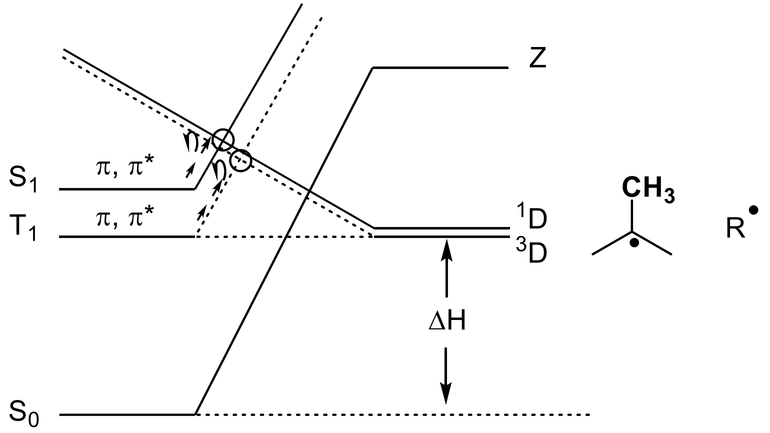
■ **Carbon to carbon 1,5-HAT:**

- **higher HAT barrier** ● **reversible**
- **unfavorable conformation**

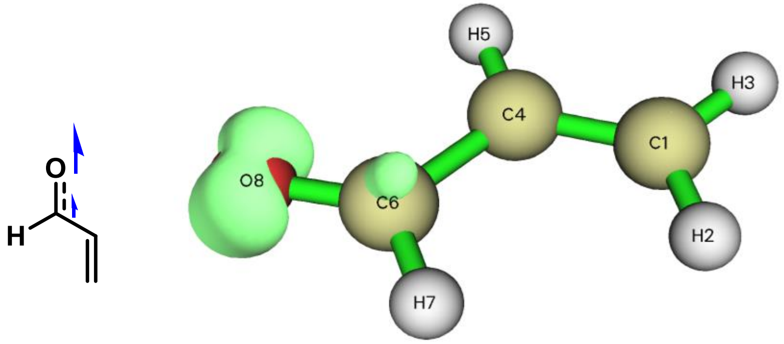
➢ O– C vs. C– C Centered Biradicals: HAT Reactivity

surface correlation diagram

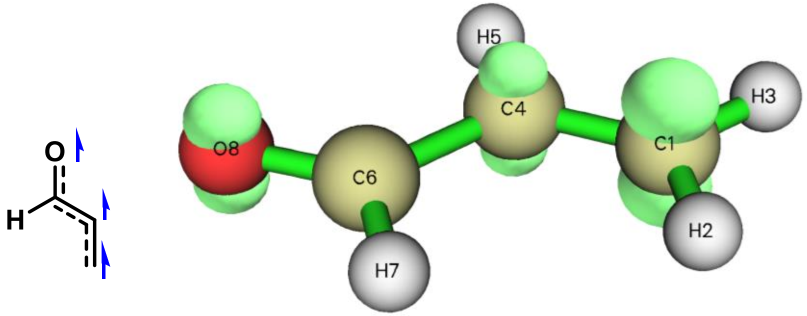




spin-density distribution of the acrolein



T_1 (n, π*)



T_2 (π, π*)

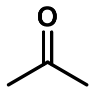
Part 2

1,5-HAT Promoted by C–O-Centered Biradical Species

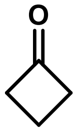
2. 1,5-HAT Promoted by C–O-Centered Biradical Species

➢ Introduction of Chromophore Activation Group: 1,2-Diketones

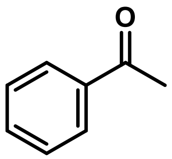
➢ Energetics of Carbonyl Compounds



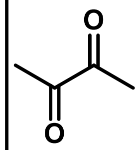
E_1 = 84 kcal/mol
E_T = 78 kcal/mol



E_1 = 84 kcal/mol
E_T = 78 kcal/mol

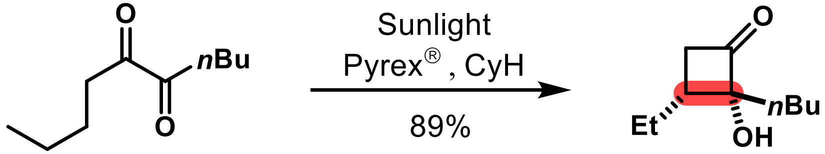


E_1 = 76 kcal/mol
E_T = 69 kcal/mol

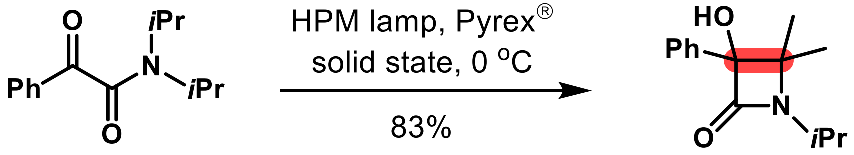


E_1 = 62 kcal/mol
E_T = 55 kcal/mol

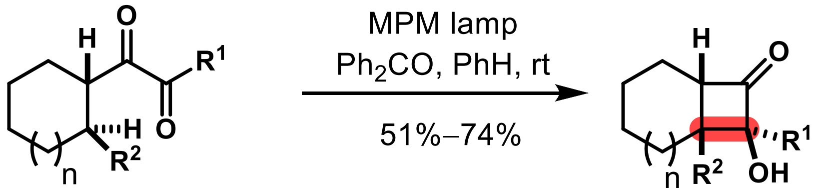
N. J. Turro, *Modern Molecular Photochemistry*, The Benjamin/Cummings Publishing Company, Inc., **1978**, pp. 290.



W. H. Urry *et al.*, *J. Am. Chem. Soc.* **1962**, *84*, 118.

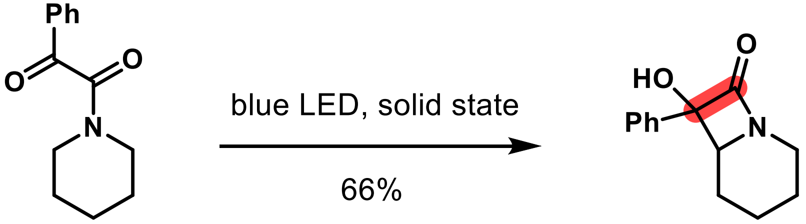


H. Aoyama *et al.*, *J. Am. Chem. Soc.* **1979**, *101*, 5343.



n = 0-2 R^1 = alkyl R^2 = H or OMe

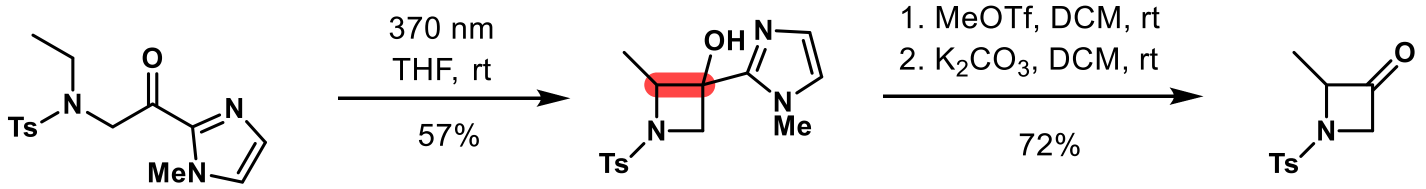
M. Inoue *et al.*, *Tetrahedron Lett.* **2010**, *51*, 872.



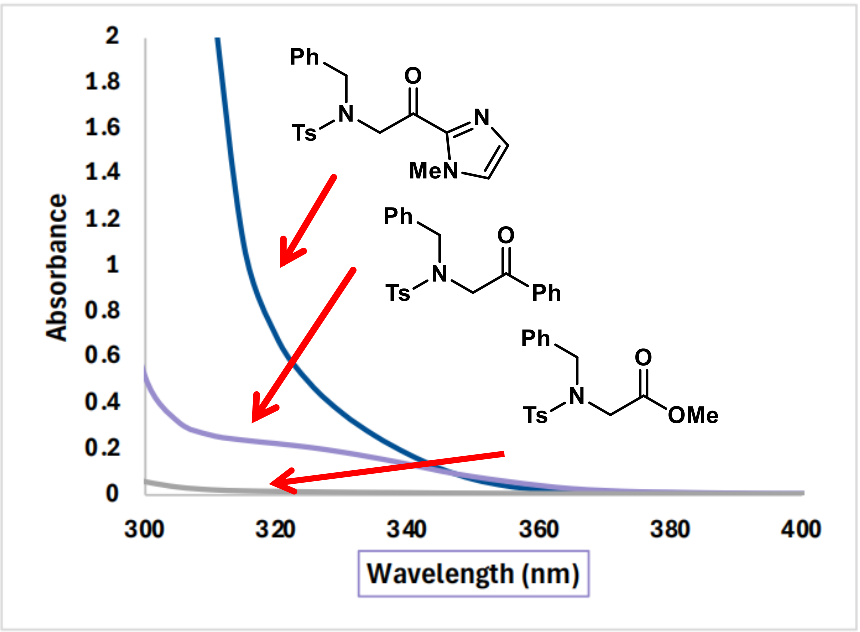
R. Sarpong *et al.*, *ACS Catal.* **2020**, *10*, 2929.

2. 1,5-HAT Promoted by C–O-Centered Biradical Species

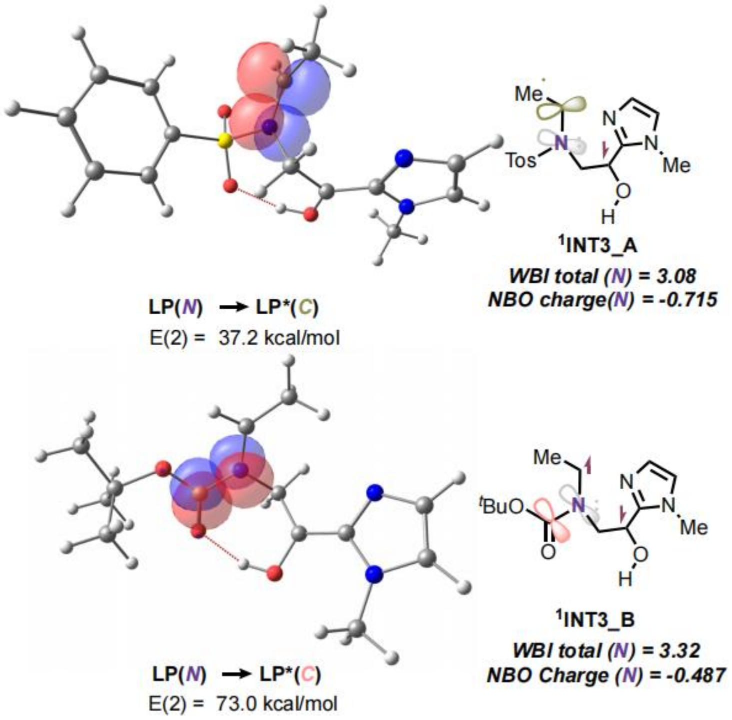
➢ Introduction of Chromophore Activation Group: Acyl Imidazole

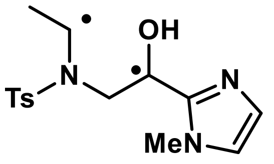


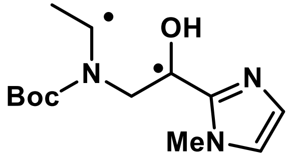
UV-visible absorption spectrum



NBO analysis of diradical intermediate

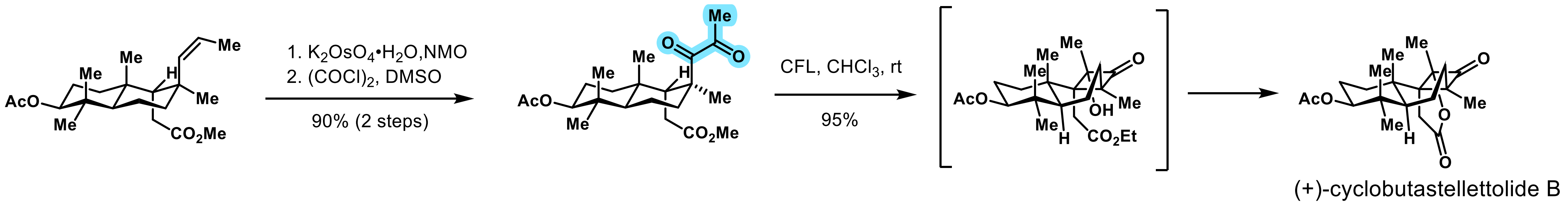




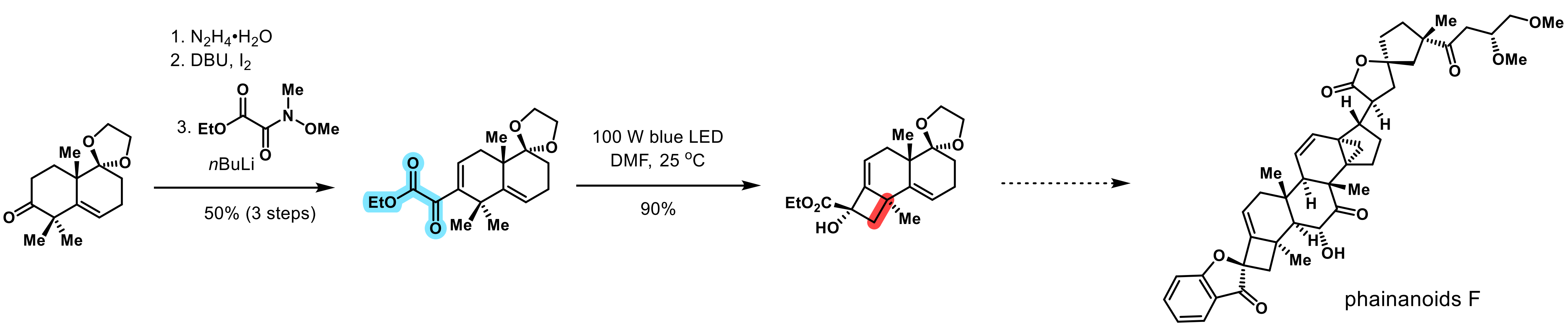


K. A. Scheidt *et al.*, *Chem. Sci.* **2026**, *17*, 6766.

Recent Applications in Natural Product Synthesis



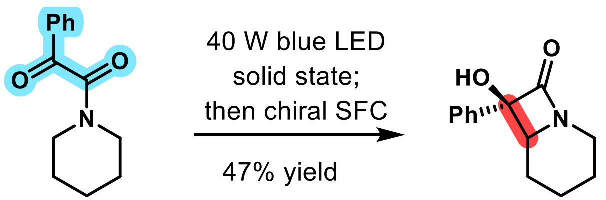
Z. Yang *et al.*, *J. Am. Chem. Soc.* **2021**, *143*, 18287.

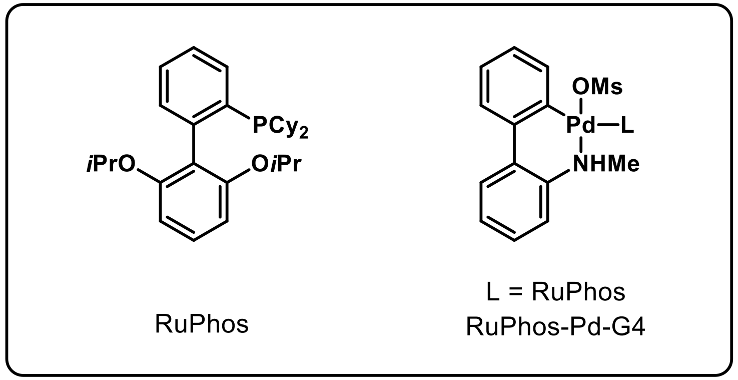


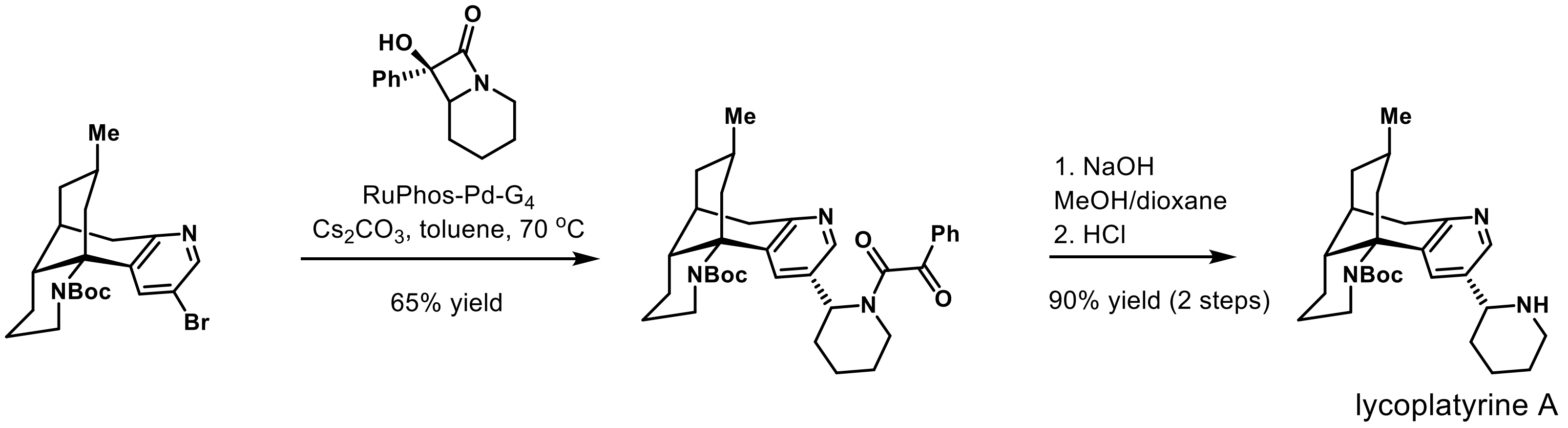
Z. Yang *et al.*, *Org. Lett.* **2024**, *26*, 8217.

2. 1,5-HAT Promoted by C–O-Centered Biradical Species

➢ Recent Applications in Natural Product Synthesis



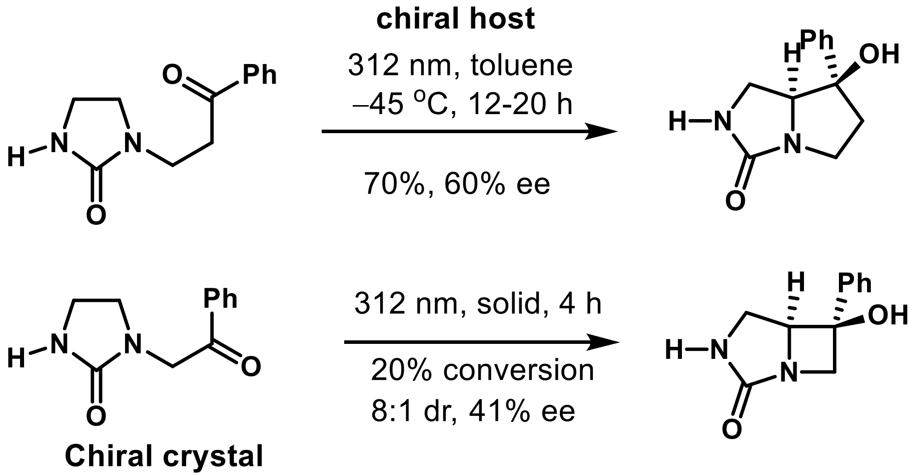


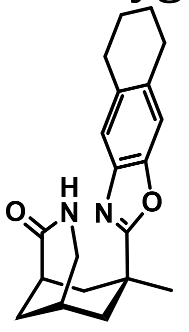


R. Sarpong *et al*., *J. Am. Chem. Soc.* **2021**, *143*, 4732.

2. 1,5-HAT Promoted by C–O-Centered Biradical Species

➢ Enantioselective and Enantiospecific Carbon to Oxygen 1,5-HAT

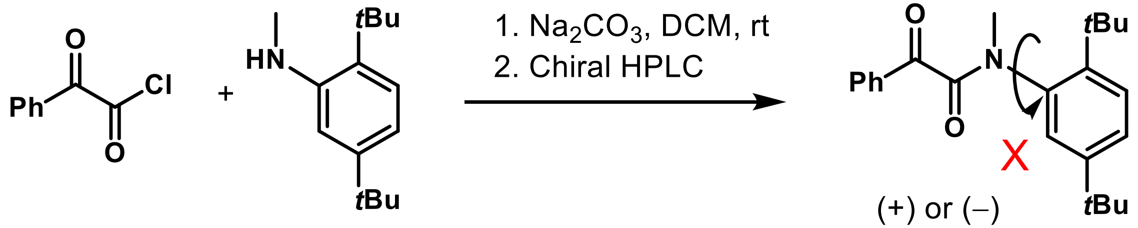


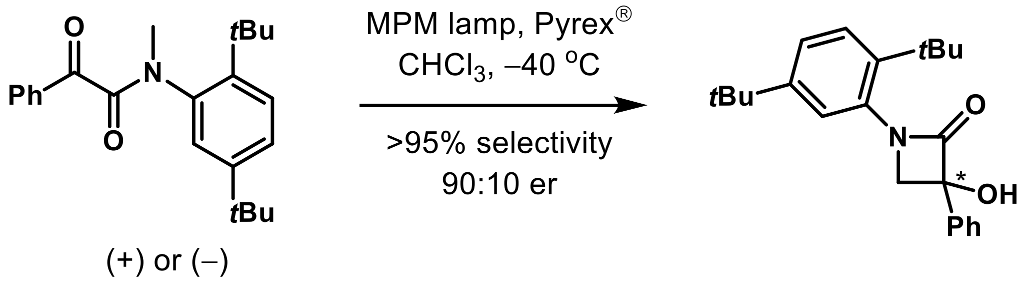


T. Bach *et al.*, *Chem. Eur. J.* **2002**, *8*, 2464.

■ Enantioselective 1,5-HAT controlled by chiral hosts was achieved with moderate ee.

■ No examples of four-membered rings were reported.





■ Products bearing central chirality were obtained from atripisomeric substrates.

■ Chiral resolution was needed to prepare atropisomic substrates.

J. Sivaguru *et al.*, *J. Am. Chem. Soc.* **2009**, *131*, 11314.

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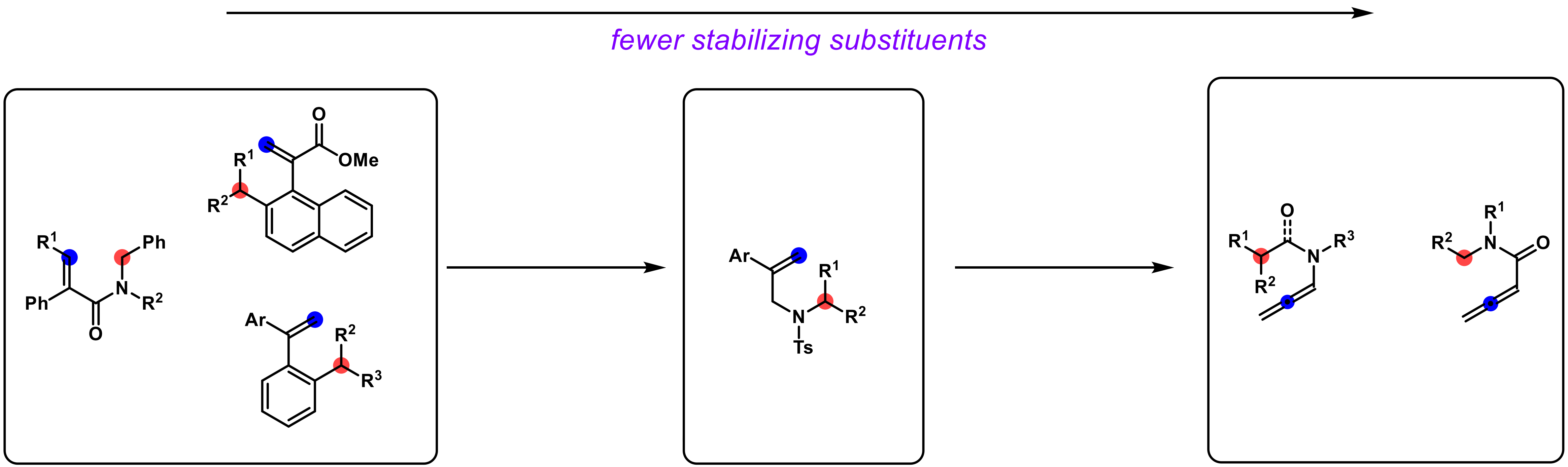
Part 3

1,5-HAT Promoted by C–C-Centered Biradical Species

3. 1,5-HAT Promoted by C–C-Centered Biradical Species



diaryl ethylenes or aryl acrylates

styrene derivatives

Challenge

instability of intermediates

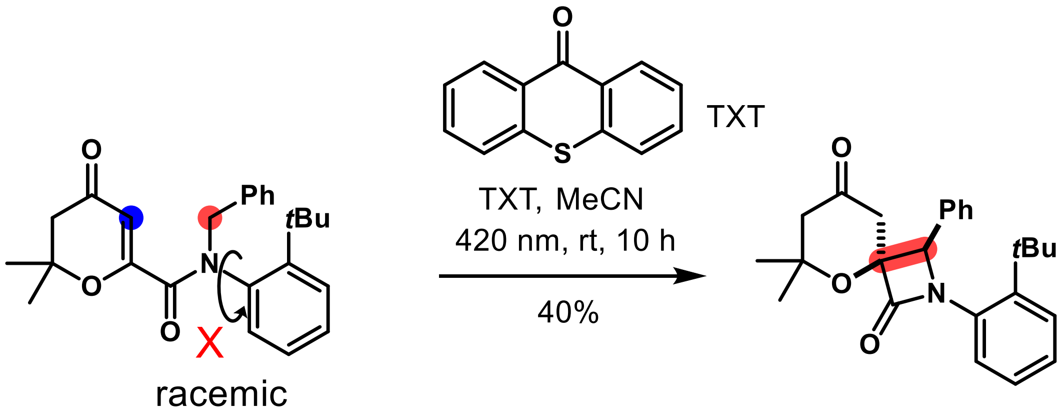
allene derivatives

Challenge

low efficiency of EnT

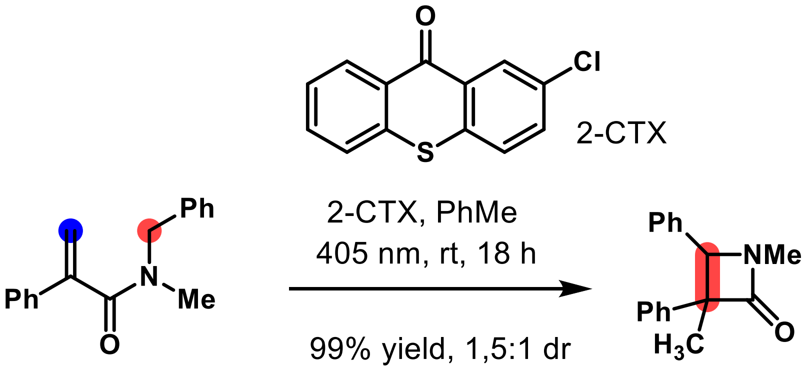
3. 1,5-HAT Promoted by C–C-Centered Biradical Species

➢ Activation of Conjugated Acrylate Derivatives

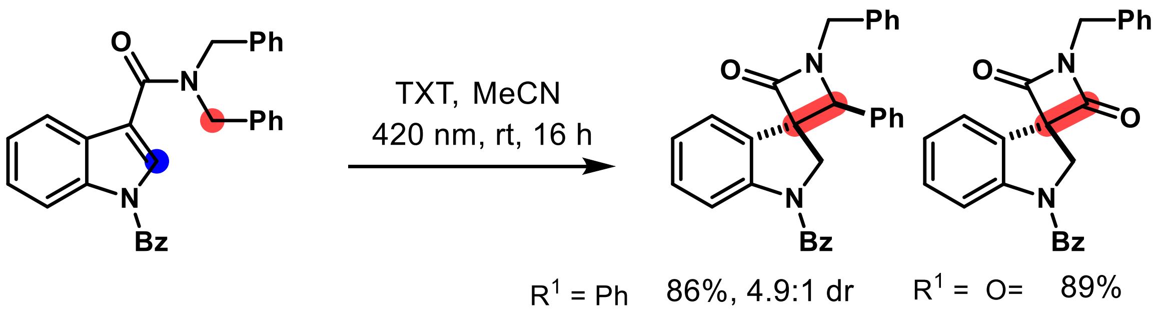


45%, 98% ee from (–)- substrate under 350 nm

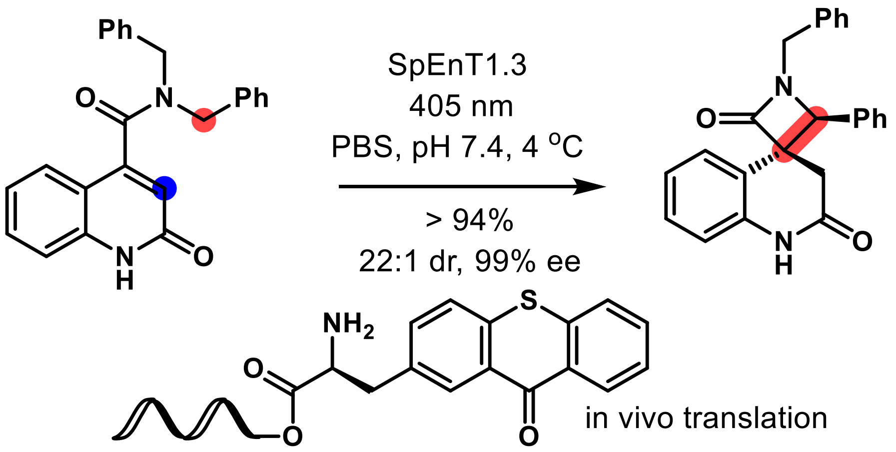
J. Sivaguru *et al.*, *Chem. Eur. J.* **2016**, *22*, 11339.



W. F. Peterson *et al.*, *Angew. Chem. Int. Ed.* **2022**, *61*, e202213086.



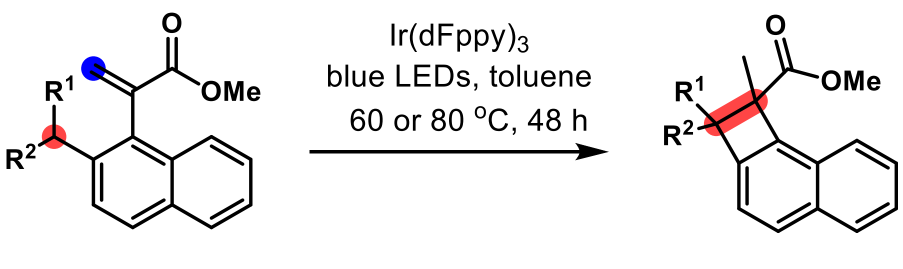
T. Bach *et al.*, *Angew. Chem. Int. Ed.* **2022**, *61*, e202200555.



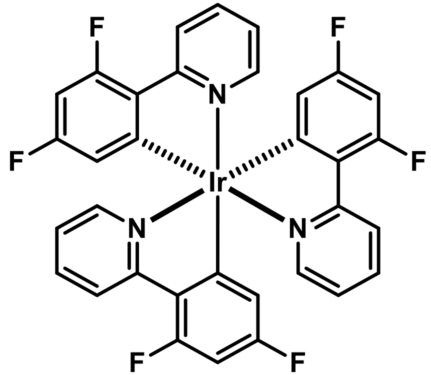
T. Bach, A. P. Green *et al.*, *Nat. Chem.* **2025**, *17*, 1083.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

➢ Activation of Diarylethylene Derivatives

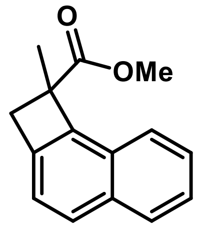


1 2

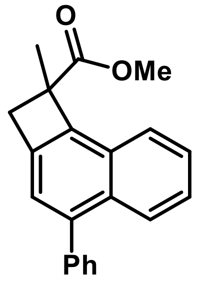


Ir(dFppy)$_3$

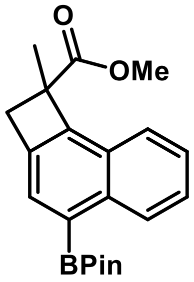
Selected substrates



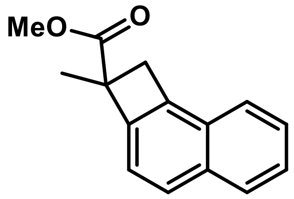
2a, 95%



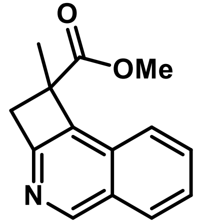
2b, 93%



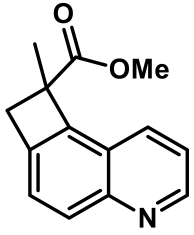
2c, 72%



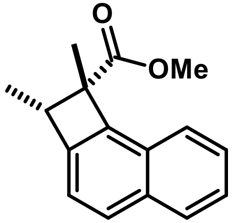
2d, 75%



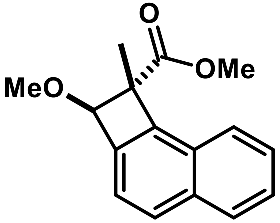
2e, 85%



2f, 76%

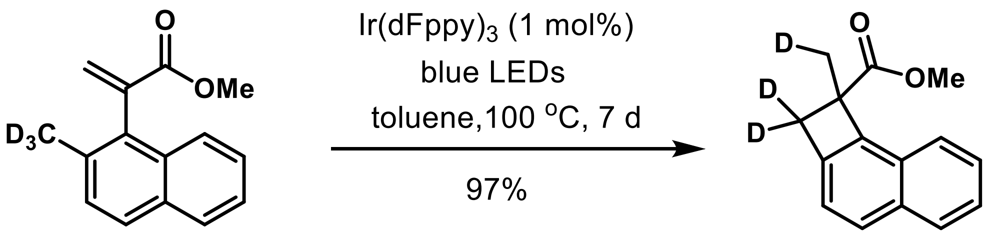


2g, 81%, dr > 20:1



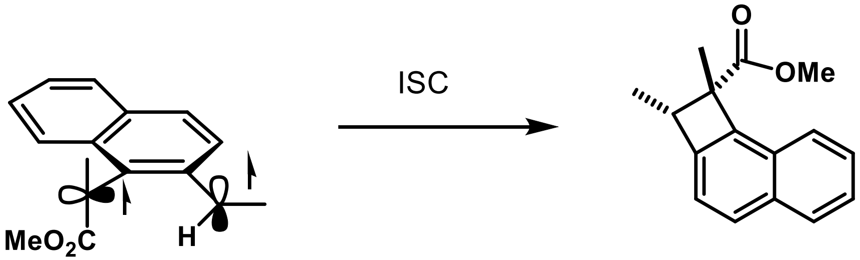
2h, 95%, dr > 20:1

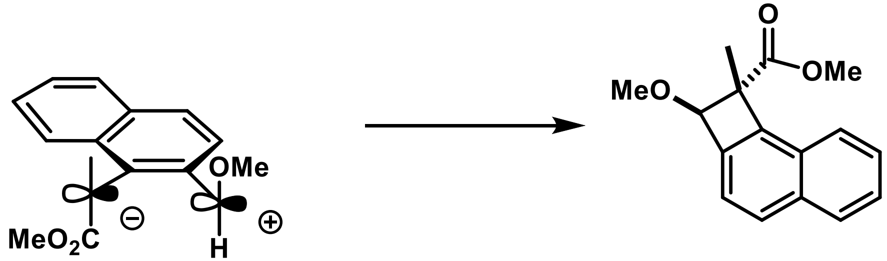
KIE experiment



$k_H/k_D = 4.23$

Stereochemical outcome

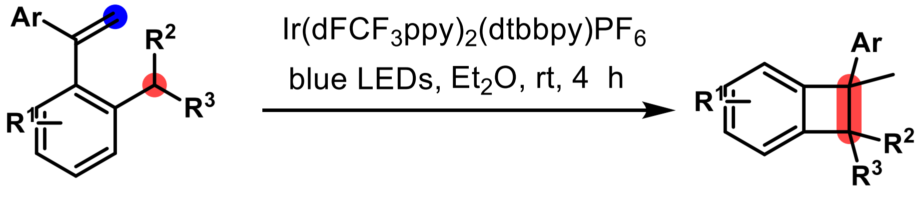




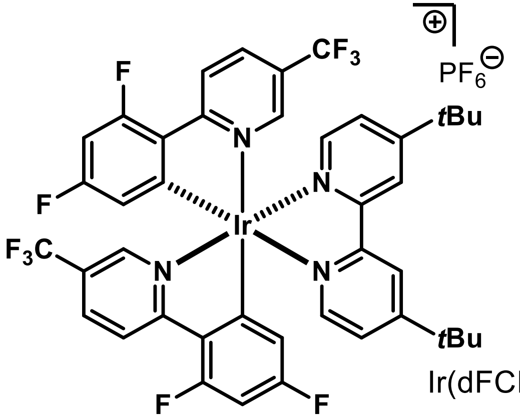
U. Koert *et al*., *Org. Lett.* **2019**, *21*, 4365.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

➢ Activation of Diarylethylene Derivatives

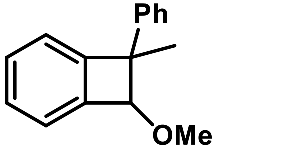


3 → 4

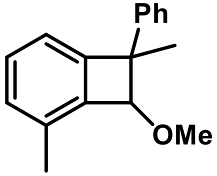


Ir(dFCF3ppy)2(dtbbpy)PF6

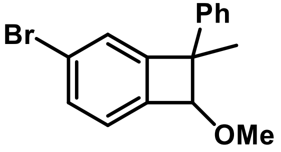
Selected substrates



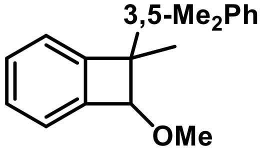
4a, 95%, dr = 2.4:1



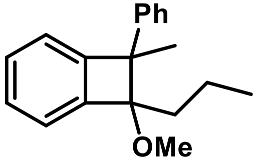
4b, 89%, dr = 1.3:1



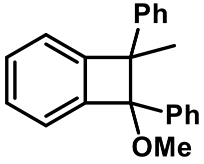
4c, 87%, dr = 3:1



4d, 88%, dr = 2.8:1

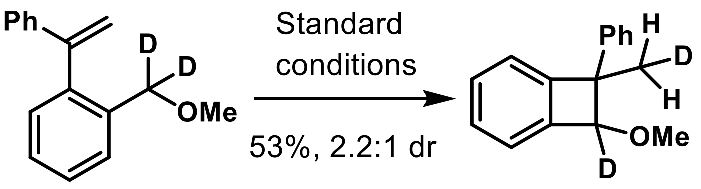


4e, 91%, dr = 1.6:1



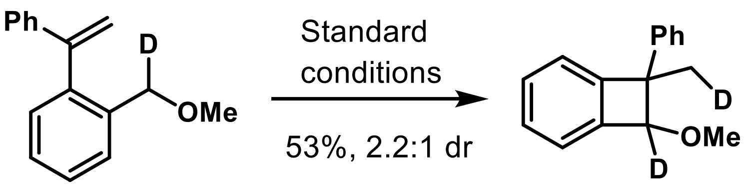
4f, 87%, dr = 1.6:1

Deuterium experiment



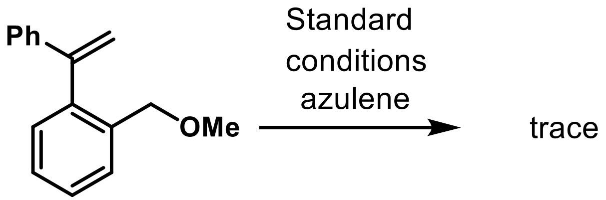
[D2]-**3a** → [D$_2$]-**4a** >95% D

KIE experiment



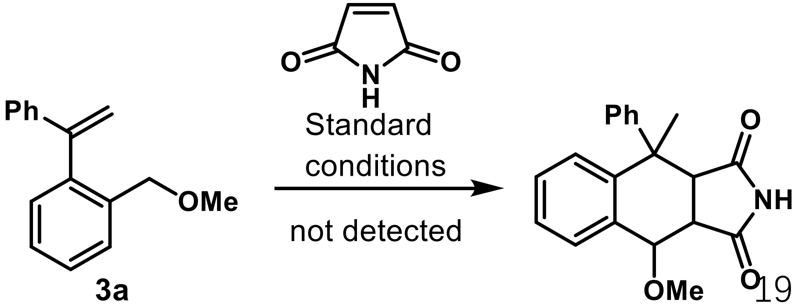
[D1]-**3a** k_H/k_D = 4.6 [D]-**4a** 18% H

Triplet state quenching experiment



3a

Diene capturing experiment

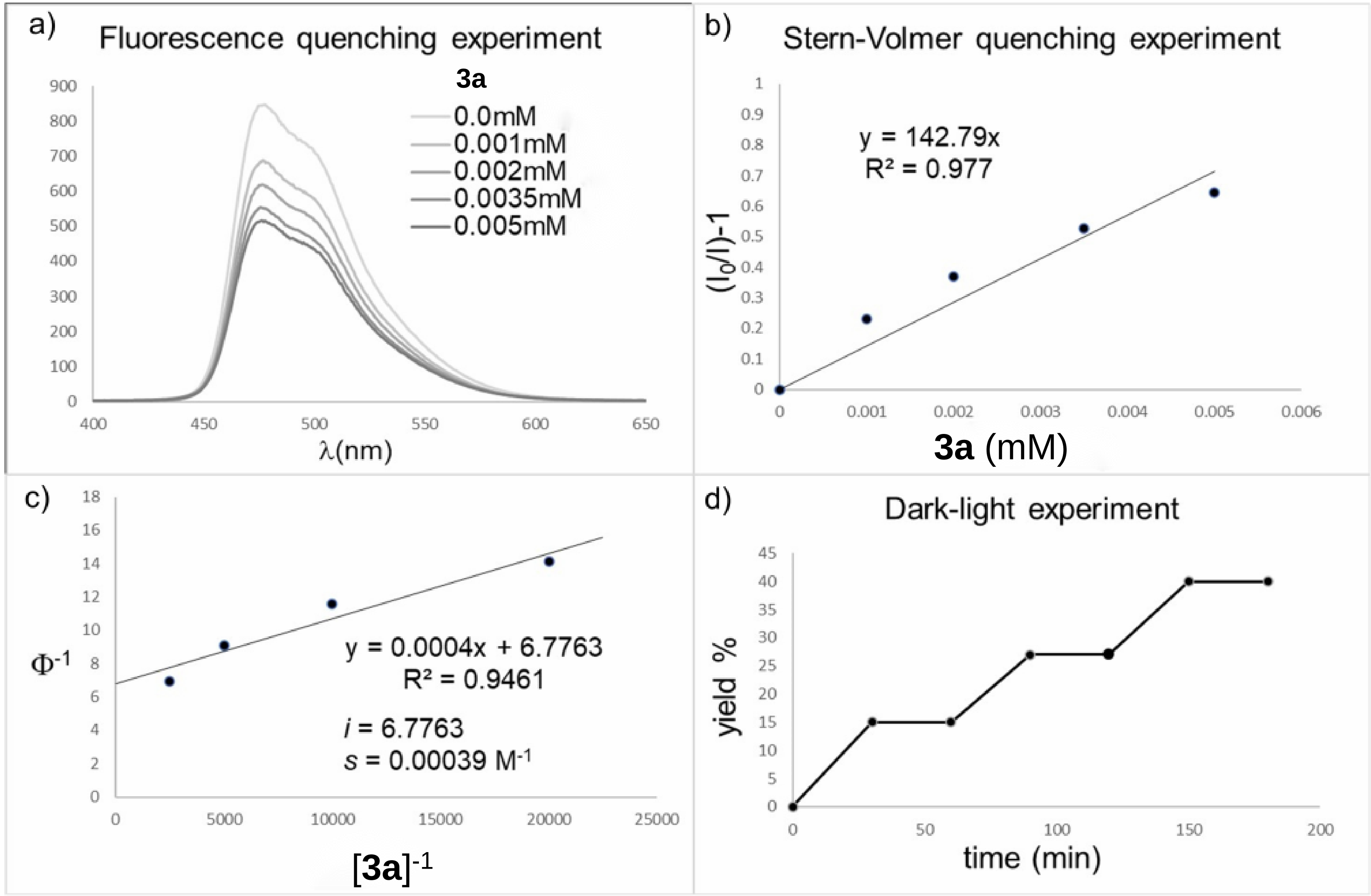


3a

M. Shi, Y. Wei *et al*., *Angew.Chem. Int. Ed.* **2022**, *61*, e202204515.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

➢ Activation of Diarylethylene Derivatives

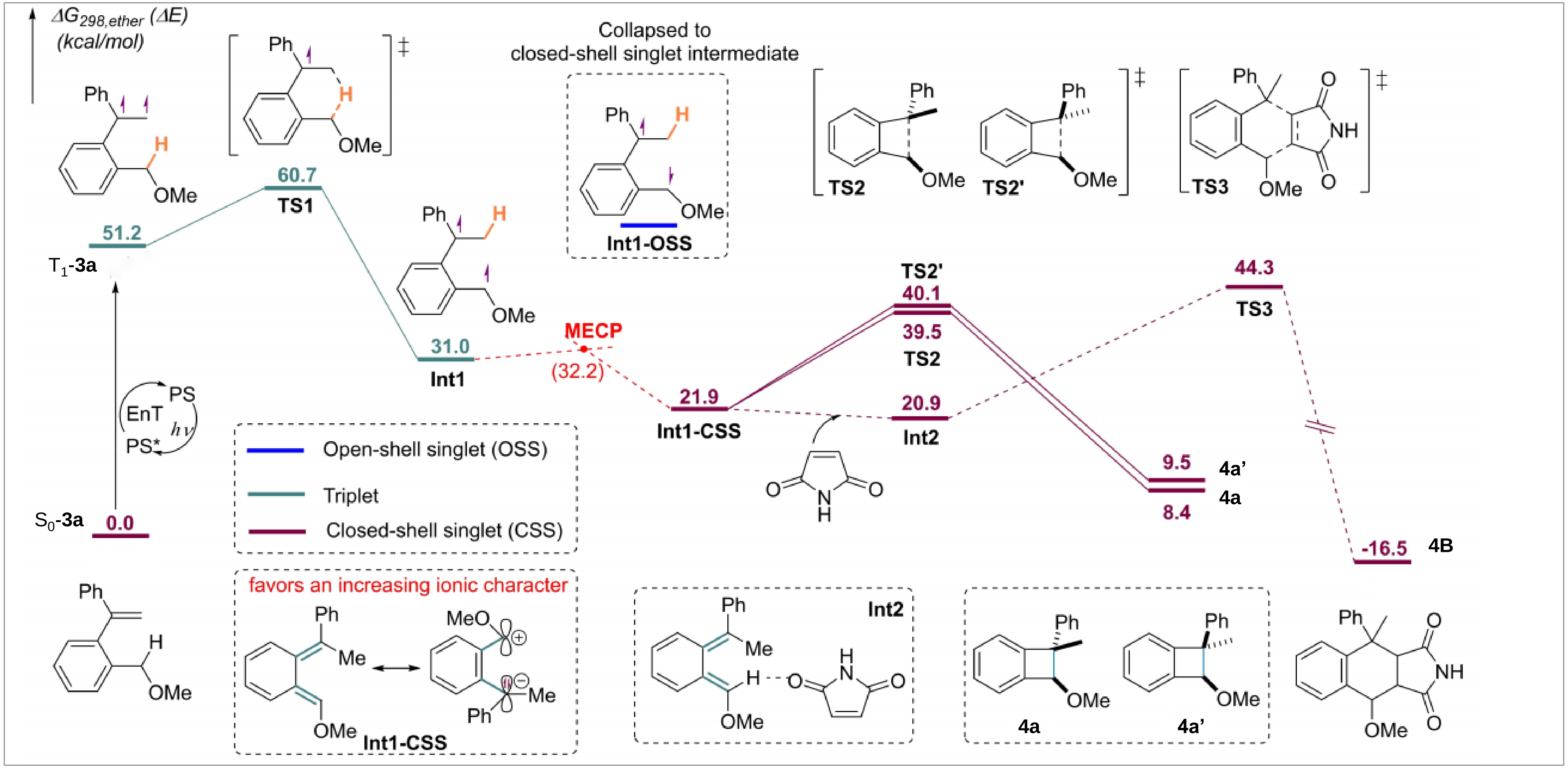


■ $k_q\tau$ (1.43×10^5 M^{-1}) vs i/s (1.74×10^4 M^{-1})

■ EnT induced cyclization process

M. Shi, Y. Wei *et al.*, *Angew.Chem. Int. Ed.* **2022**, *61*, e202204515.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

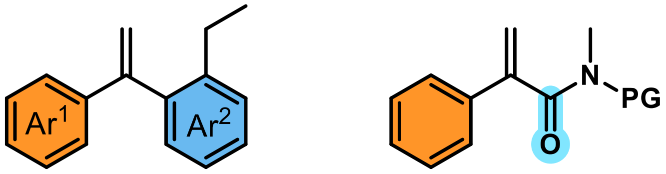


M. Shi, Y. Wei *et al.*, *Angew. Chem. Int. Ed.* **2022**, *61*, e202204515.

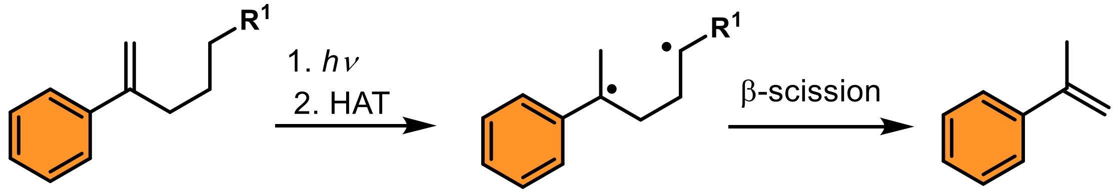
3. 1,5-HAT Promoted by C–C-Centered Biradical Species

➢ Activation of Styrene Derivatives via Introducing Heteroatoms

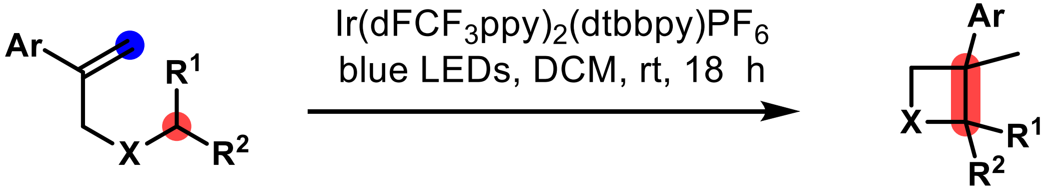
The role of diaryl or carbonyl motif



The challenges for styrene derivatives

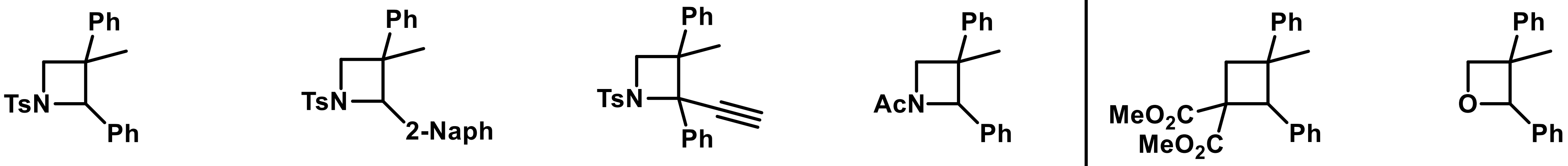


• stablize 1,4-biradical • preorganize the substrate to favorable conformation



5 → **6**

Selected substrates



6a, 85%, dr = 1.4:1

6b, 32%, dr = 1.6:1

6c, 65%, dr = 1:1

6d, 64%, dr = 1.1:1

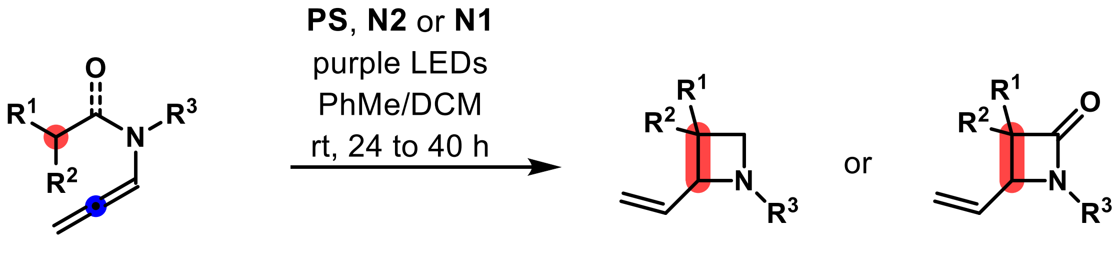
6e, not detected
71% elimination product

6f, 38%, dr = 2:1

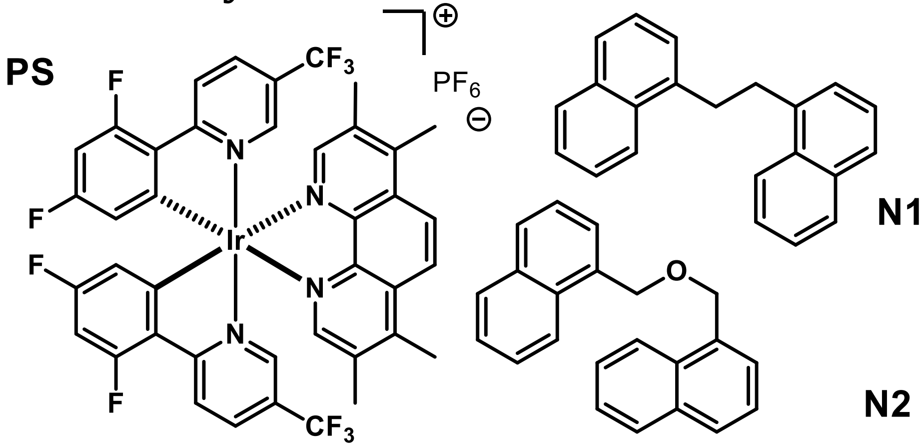
M. Shi, Y. Wei *et al.*, *Angew.Chem. Int. Ed.* **2024**, *63*, e202409463.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

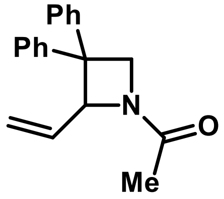
➢ Activation of the Cumulated π-System via Energy-Transfer Relay



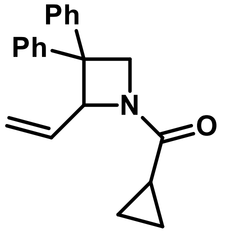
7 8 9



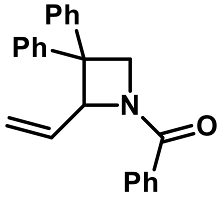
Selected substrates **2** (**N2** was used)



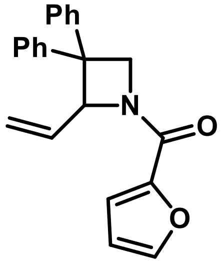
8a, 75%



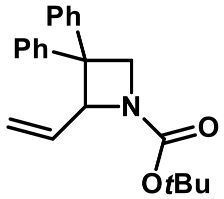
8b, 75%



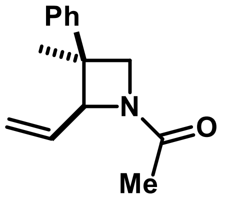
8c, 73%



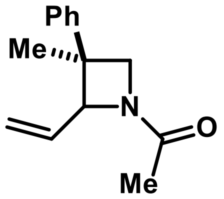
8d, 74%



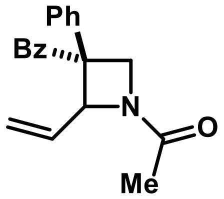
8e, 51%



8f, 72%

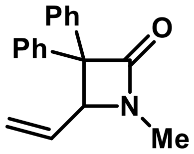


8g, 45%

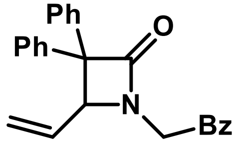


8h, 52%

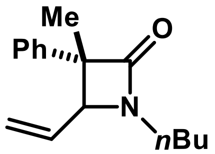
Selected substrates **3** (**N1** was used)



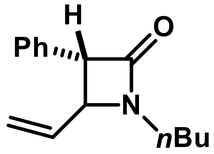
9i, 61%



9j, 76%



9k, 61%, 1.6:1 dr

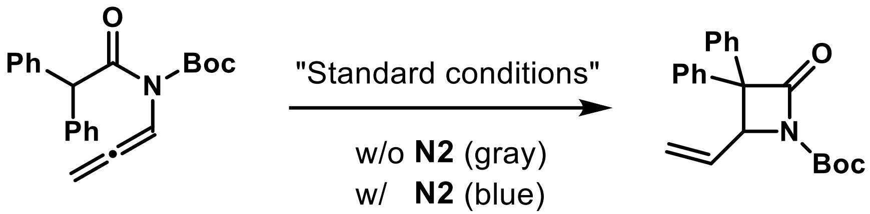


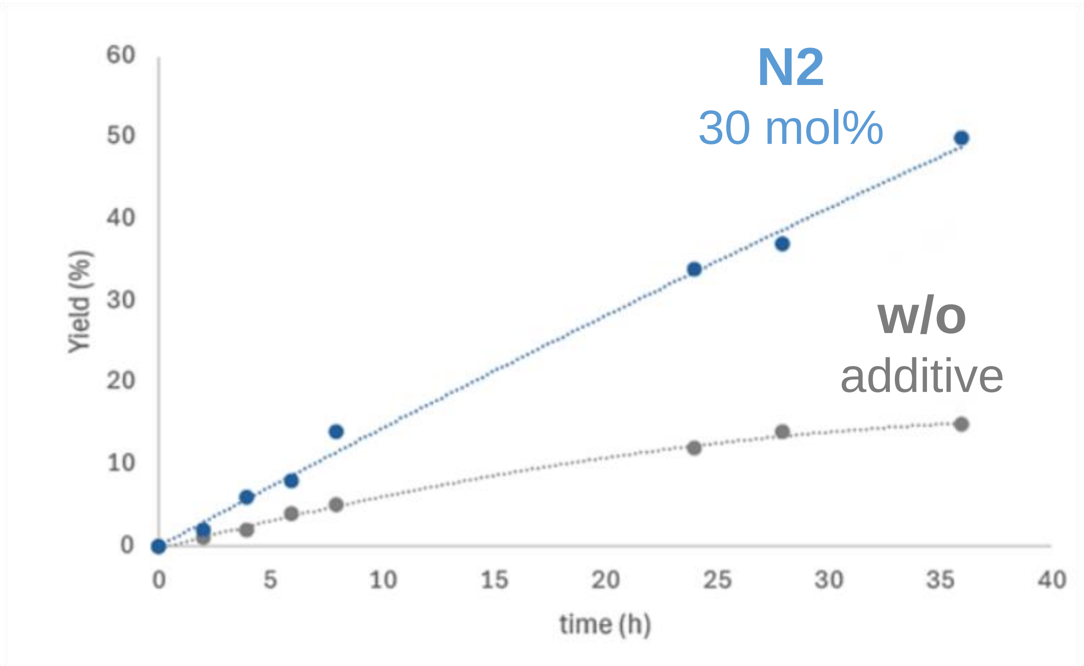
9l, 61%, 20:1 dr

G. Maestri *et al.*, *ACS Catal*. **2025**, *15*, 13799.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

a. Monitoring experiment

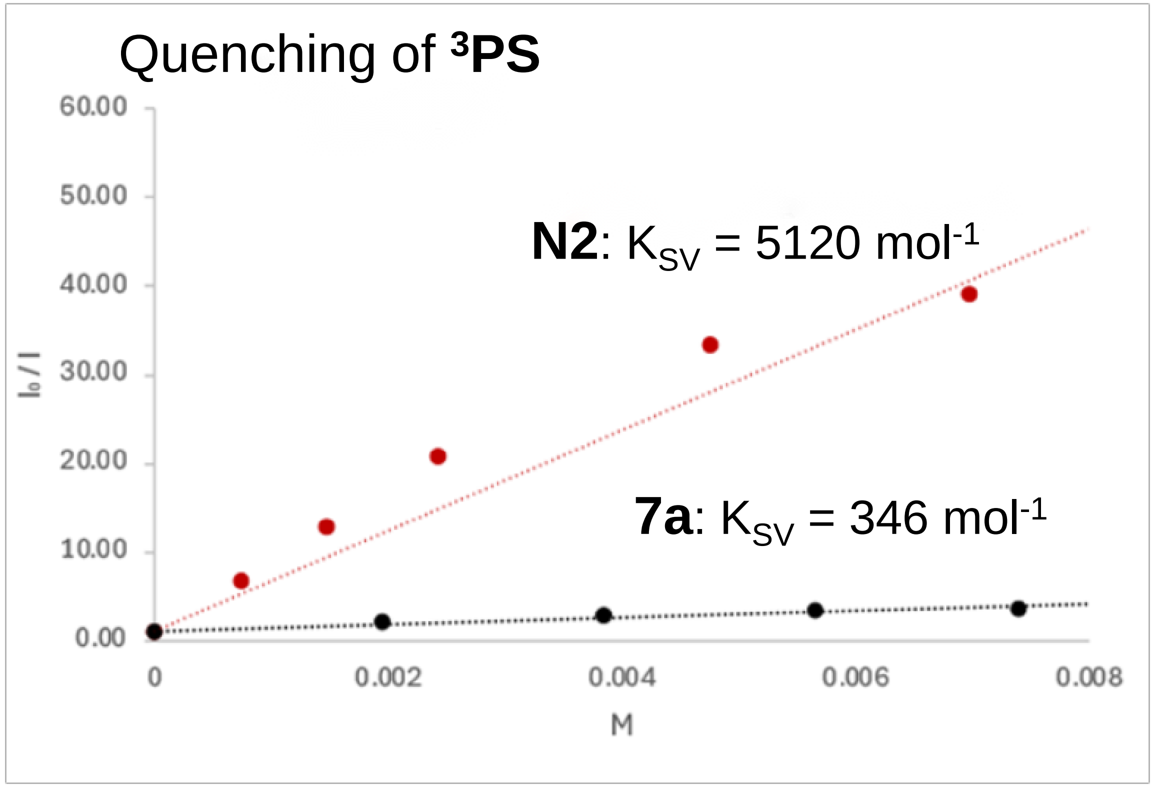




b. Stern-Volmer quenching experiment

k_q **PS-7a** 2.2×10^{8} L mol^{-1}s^{-1}

PS-N2 3.2×10^{9} L mol^{-1}s^{-1}

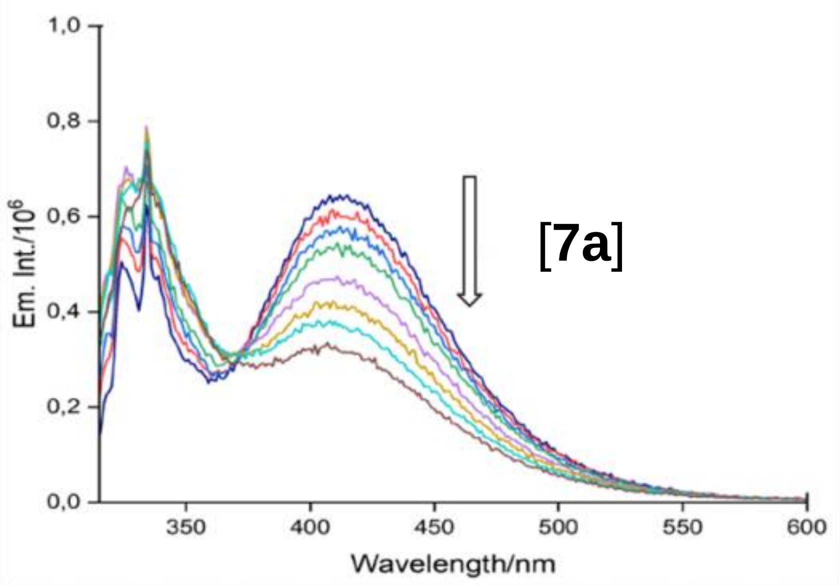


G. Maestri *et al.*, *ACS Catal.* **2025**, *15*, 13799.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

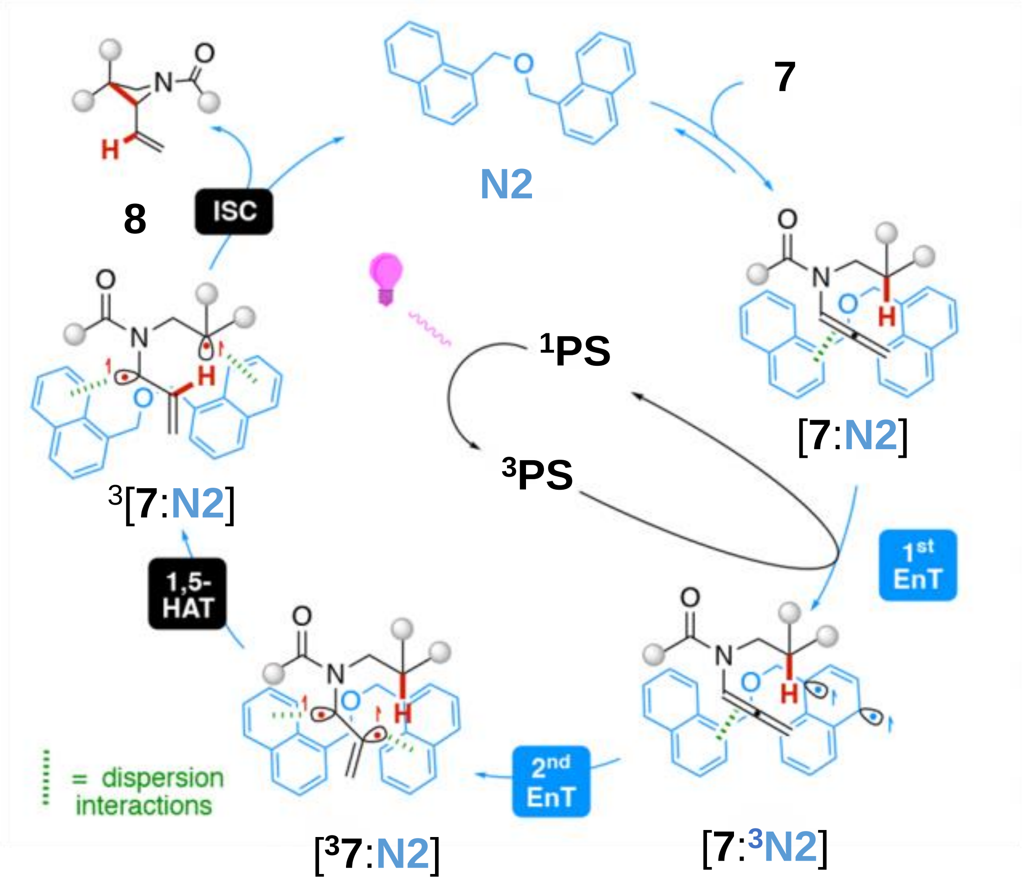
c. Transient absorption experiment

Quenching of *N2 by **7a**



k_q **N2-7a** > 1.6×10^{10} L mol^{-1}s^{-1}

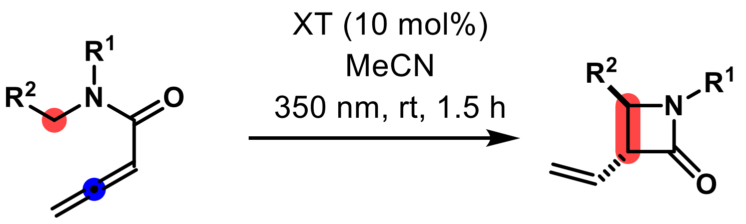
d. Proposed mechanism



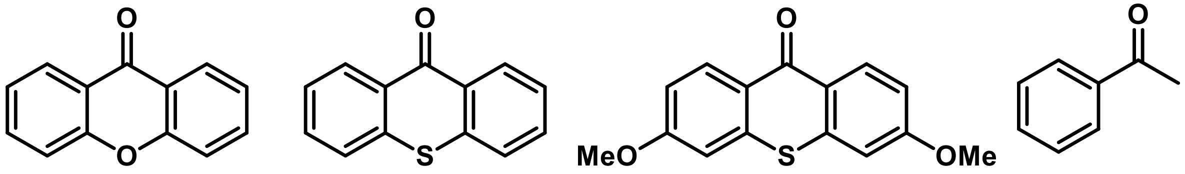
G. Maestri *et al.*, *ACS Catal*. **2025**, *15*, 13799.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species

➢ Activation of the Cumulated π-System with Higher Triplet State Energy



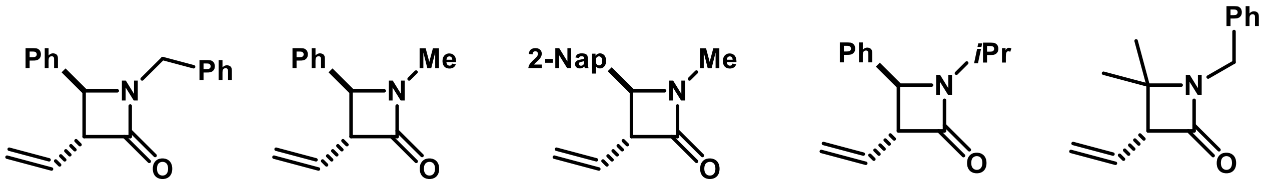
10 **11**



E_T kcal/mol	XT	TXT	TXT''	ACP
	74.1	65.5	71.2	73.6

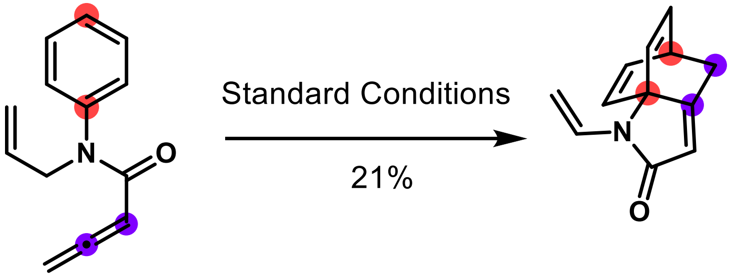
Entry	Sensitizer	$h\nu$[nm]	solvent	Yield[%]
1	TXT (20 mol%)	420	DCM	0
2	XT (20 mol%)	366	DCM	50
3	XT (10 mol%)	350	MeCN	73
4	TXT'' (10 mol%)	350	MeCN	64
5	ACP (10 mol%)	350	MeCN	41

selected substrates



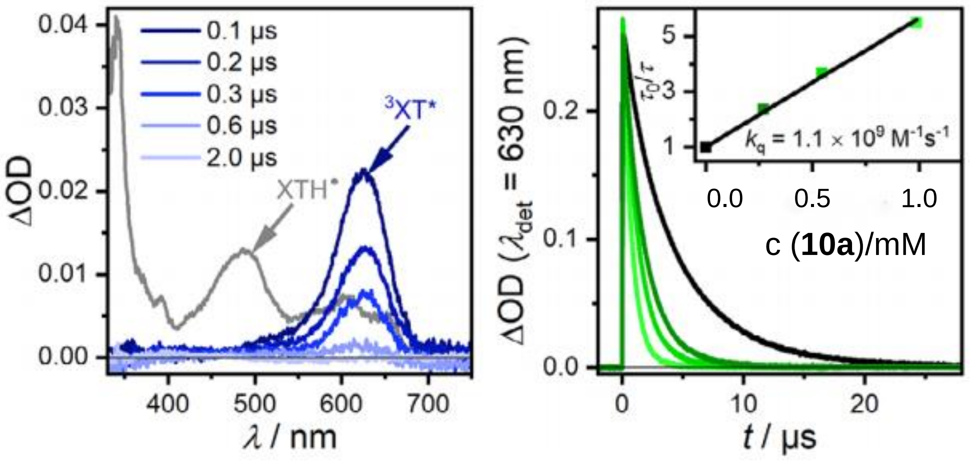
11a, 73% **11b**, 51% **11c**, 44% **11d**, 19% + **11d'**, 14%

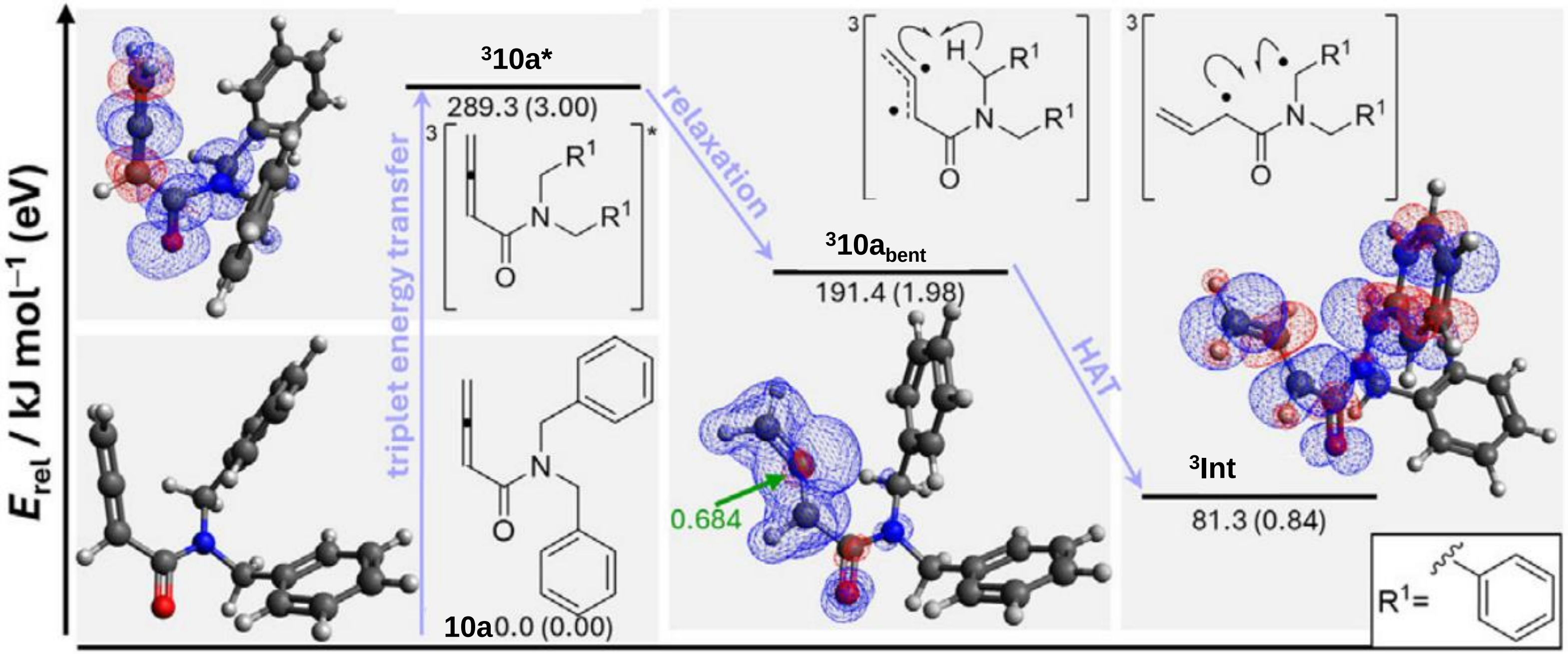
[4+2]-dearomative cycloaddition



T. Bach *et al.*, *Angew. Chem. Int. Ed.* **2026**, *45*, e25347.

3. 1,5-HAT Promoted by C–C-Centered Biradical Species





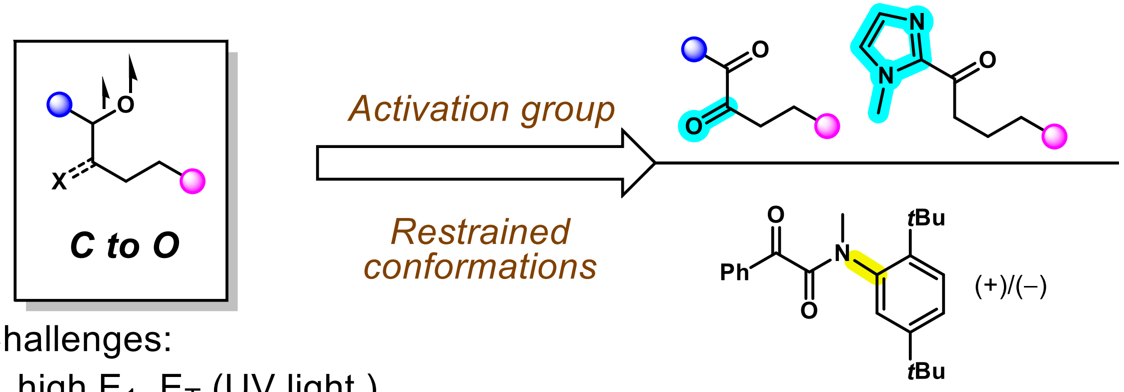
T. Bach *et al.*, *Angew. Chem. Int. Ed.* **2026**, *45*, e25347.

Part 4

Summary and Outlook

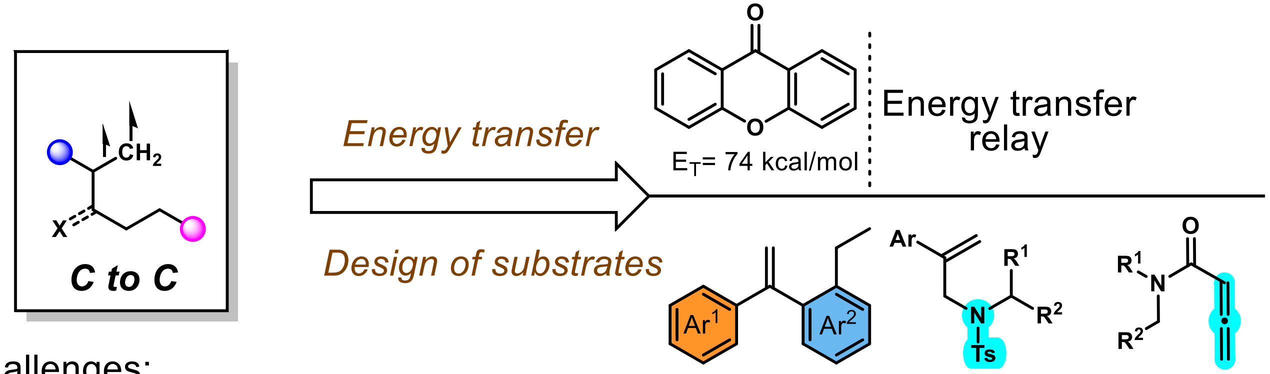
4. Summary and Outlook

Photochemical 1,5-HAT



Challenges:

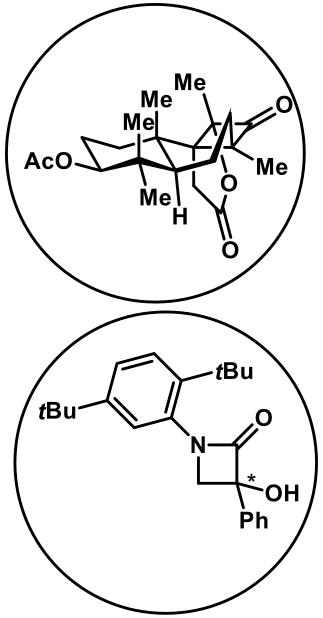
1. high E_1, E_T (UV light)
2. selectivity issues



Challenges:

1. low reactivity (π,π*)
2. instability of intermediates

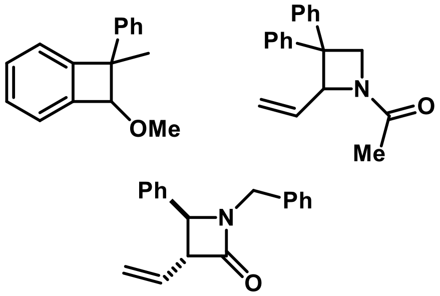
Four-Menbered Rings



☑ Regio-, stereoselectivity

☑ Late-stage elaboration

☑ Enantioselective transformation



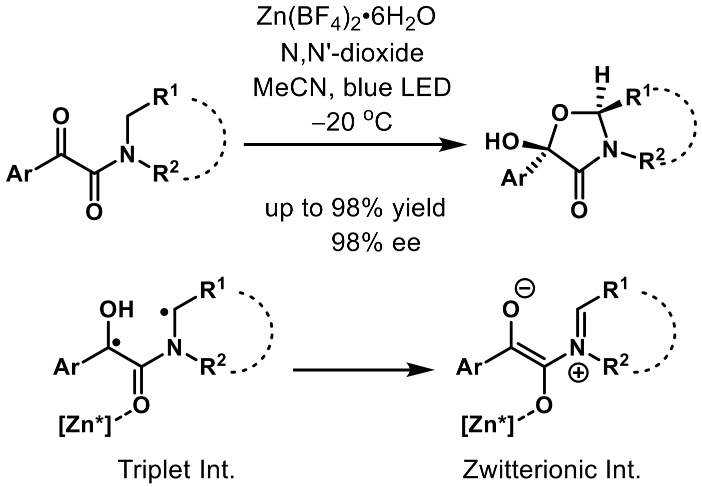
☑ Visible light photocatalysis

☑ Synthetically useful skeletons

4. Summary and Outlook

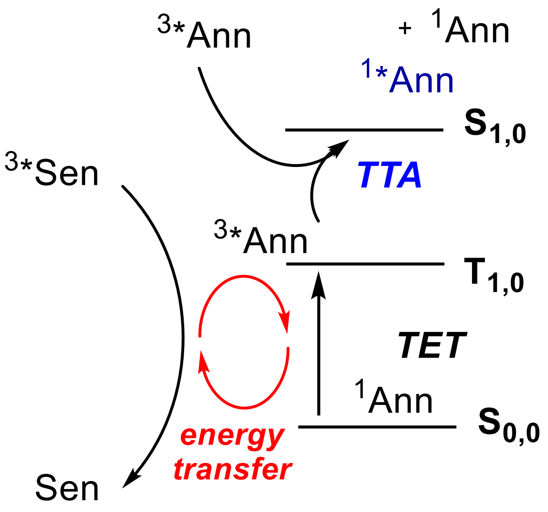
1. enantioselective pattern

X. Feng *et al.* 2023



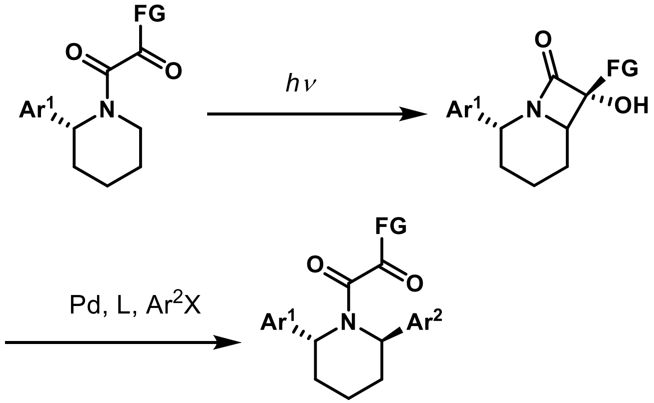
develop asymmetric catalysis methods forming chiral four-membered rings

2. upconversion



activate inert substrates using triplet-triplet annihilation upconversion

3. sequential transformation



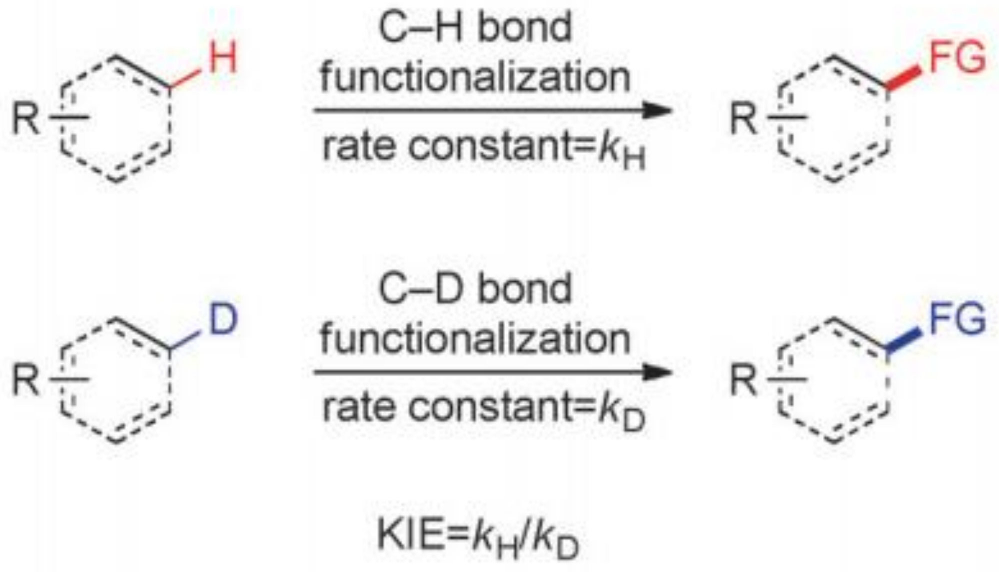
realize milti C(sp3)-H functionalization via sequential 1,5-HAT

X. Feng *et al.*, *CCS Chem.* ***2023***, *5*, 2101.

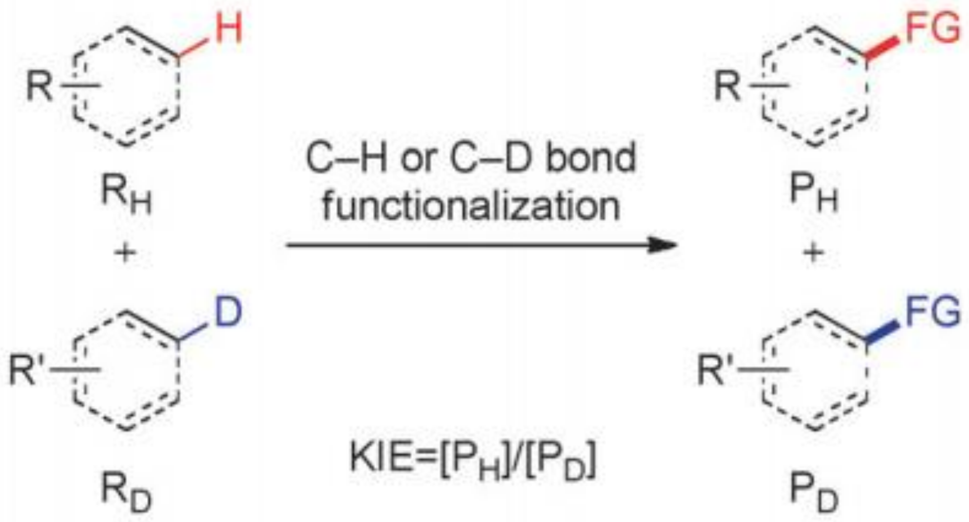
Thank you for your kind attention!

Appendix

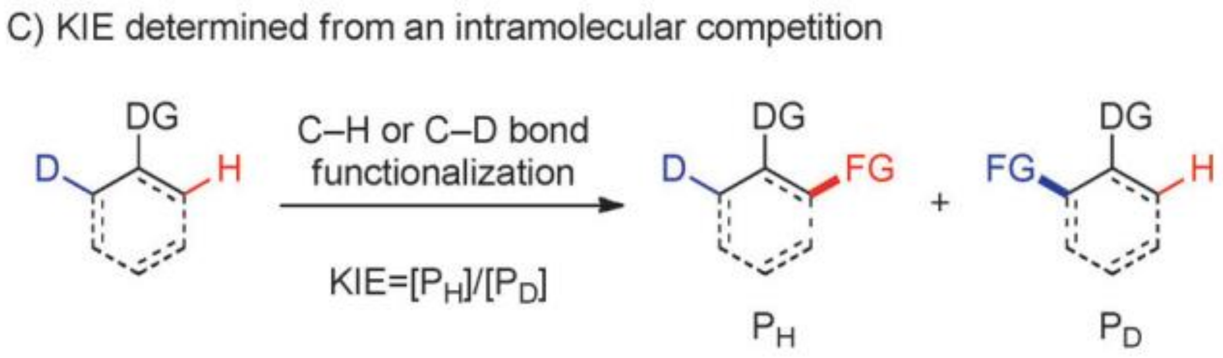
A) KIE determined from two parallel reactions



B) KIE determined from an intermolecular competition



Appendix



实际上，从 $\Phi_0/\Phi = 1 + K_{SV}[Q]$ 出发，两边取倒数：

$$\frac{\Phi}{\Phi_0} = \frac{1}{1 + K_{SV}[Q]}$$

然后两边取倒数并整理成 $1/\Phi$ 对 $1/[Q]$ 的形式：

$$\frac{1}{\Phi} = \frac{1}{\Phi_0} + \frac{K_{SV}}{\Phi_0} \cdot \frac{1}{[Q]}$$

这里 $K_{SV} = k_q \tau_0$。