

Persistent/Stable sulfur-based radical cations in organic chemistry

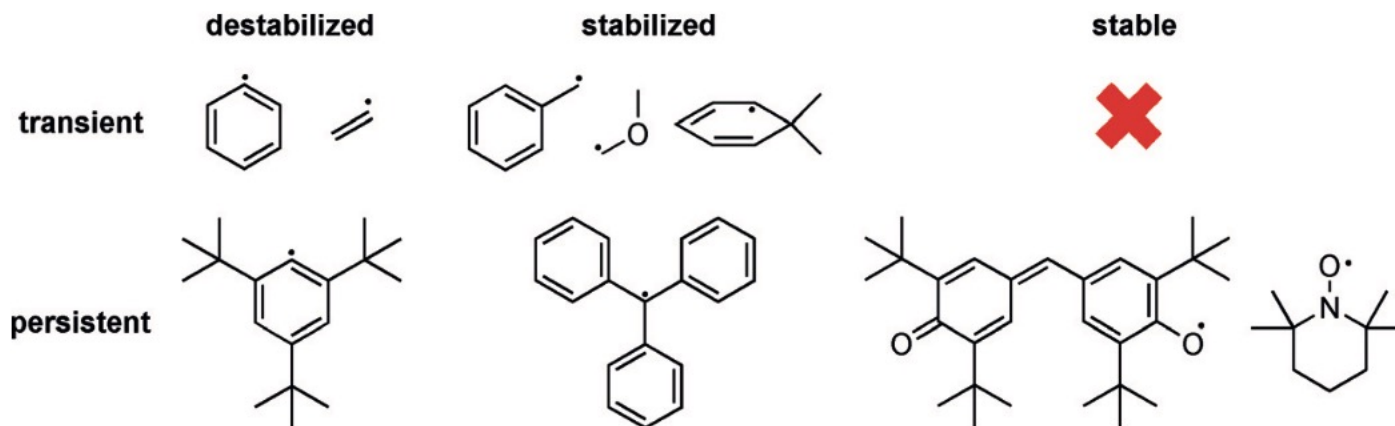
2022. 9. 29

M2 Yuri Katayama

Contents

1. Introduction of persistent radicals
2. Site-selective C-H functionalization by thianthrenation
 - I. Ritter's first work
 - II. Mechanistic insight into site-selectivity
3. PTH catalyzed C(sp³)-O formation
4. Summary & Perspective

What is a “persistent radical” ?



“Persistent” radical : lifetime is significantly longer than $\cdot\text{CH}_3$
 \leftrightarrow “transient” $< 10^{-3}$ s

Kinetic stability

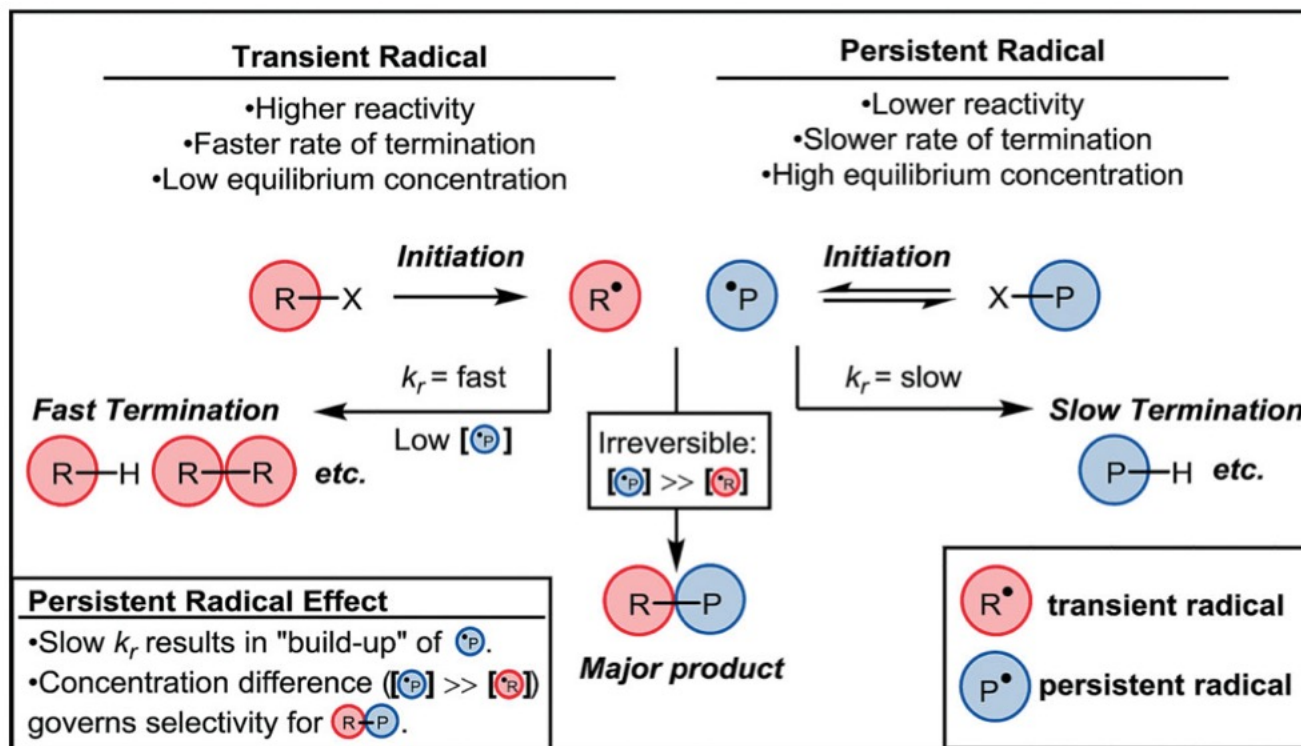
“Stabilized” radical : BDE (R-H) $<$ BDE of C-H alkanes
 \leftrightarrow “destabilized” > 104.9 kcal/mol (BDE for $\text{H}_3\text{C-H}$)

Thermodynamic stability

Defined by Griller and Ingold

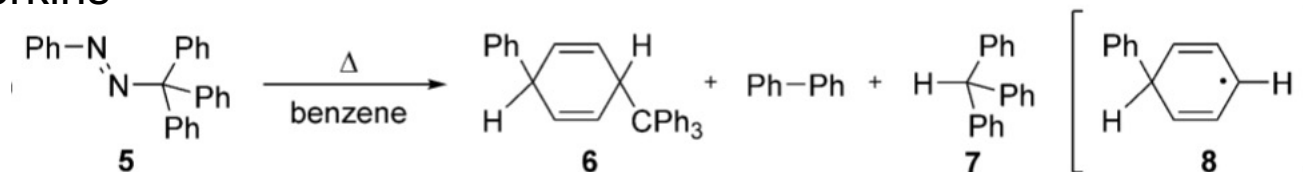
Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1976**, 9, 13.
Leifert, D.; Studer, A. *Angew. Chem. Int. Ed.* **2020**, 59, 74.

Persistent Radical Effect (PRE)



One example of PRE-mediated cross-coupling reactions

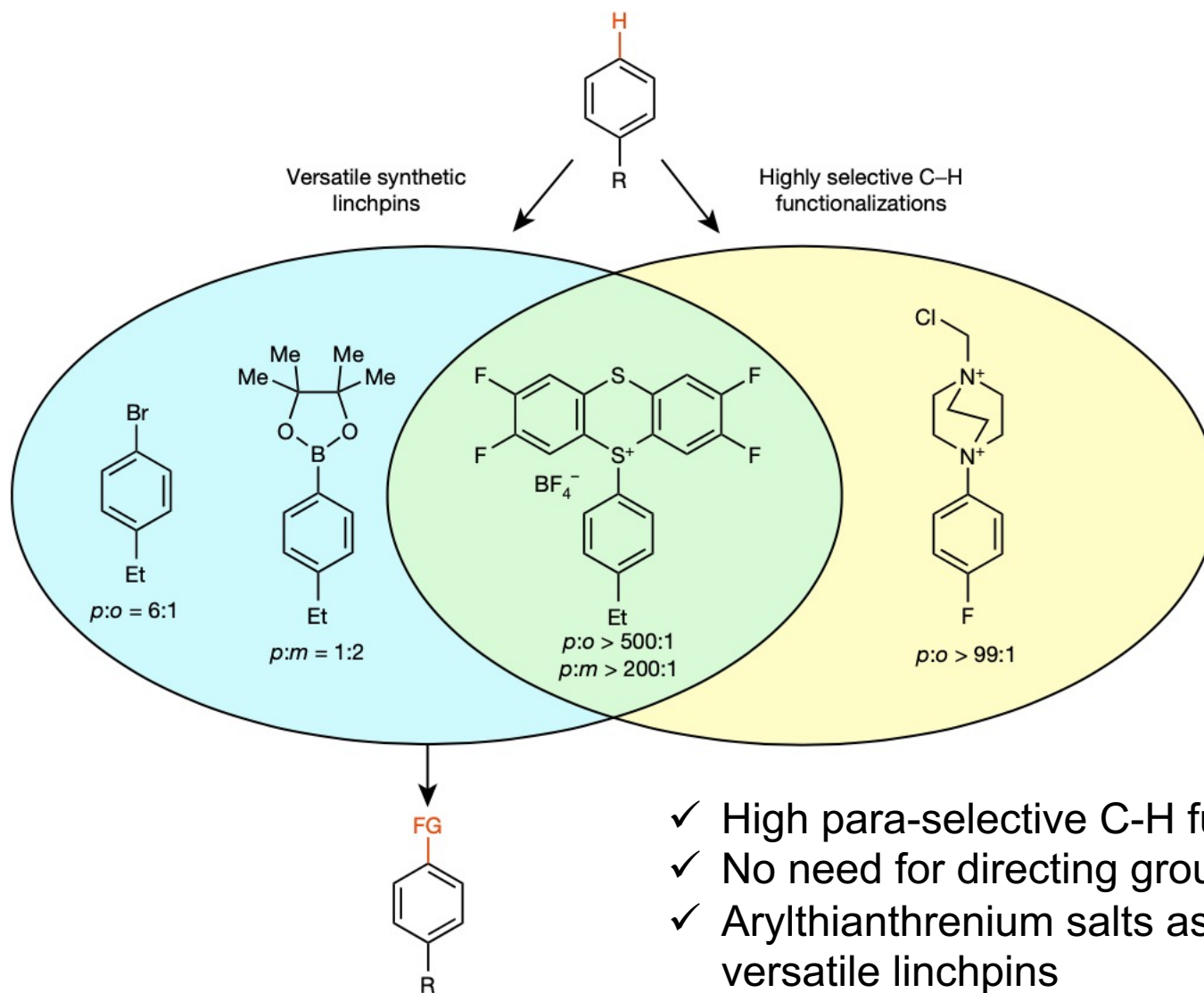
1963 Perkins



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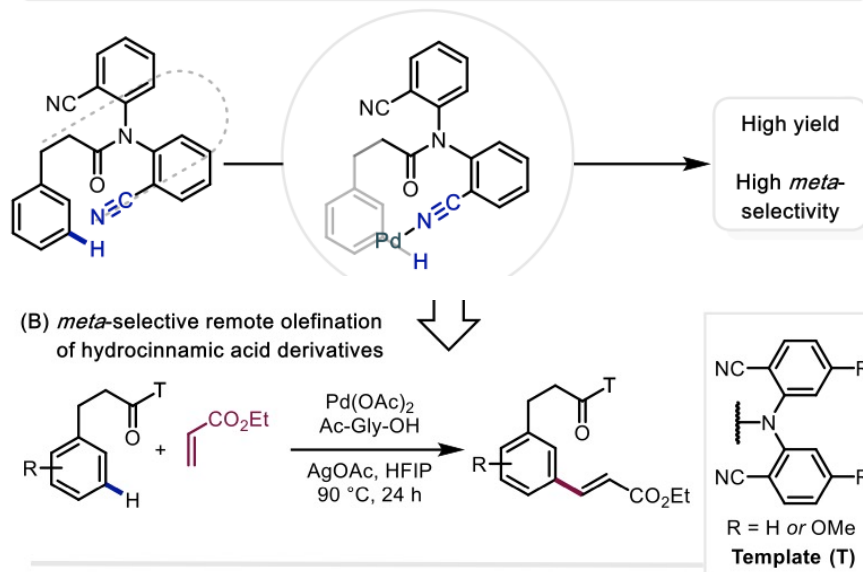
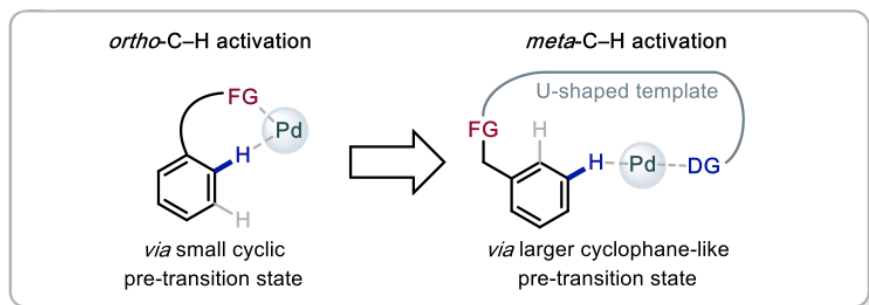
Ritter's work



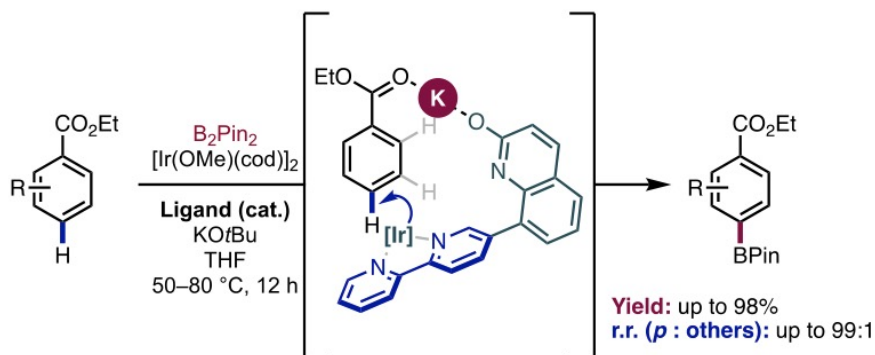
Background

Site-selective aromatic C-H functionalization

2012. Yu



2017. Chattopadhyay



J.-Q., Yu. *et al.*, *Nature* **2012**, 486, 518.

Chattopadhyay, B. *et al.*, *J. Am. Chem. Soc.* **2017**, 139, 7745.

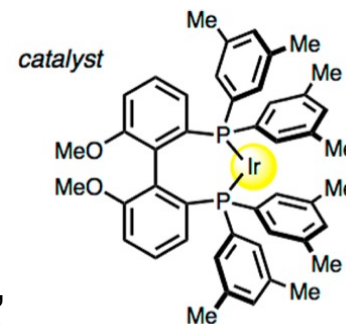
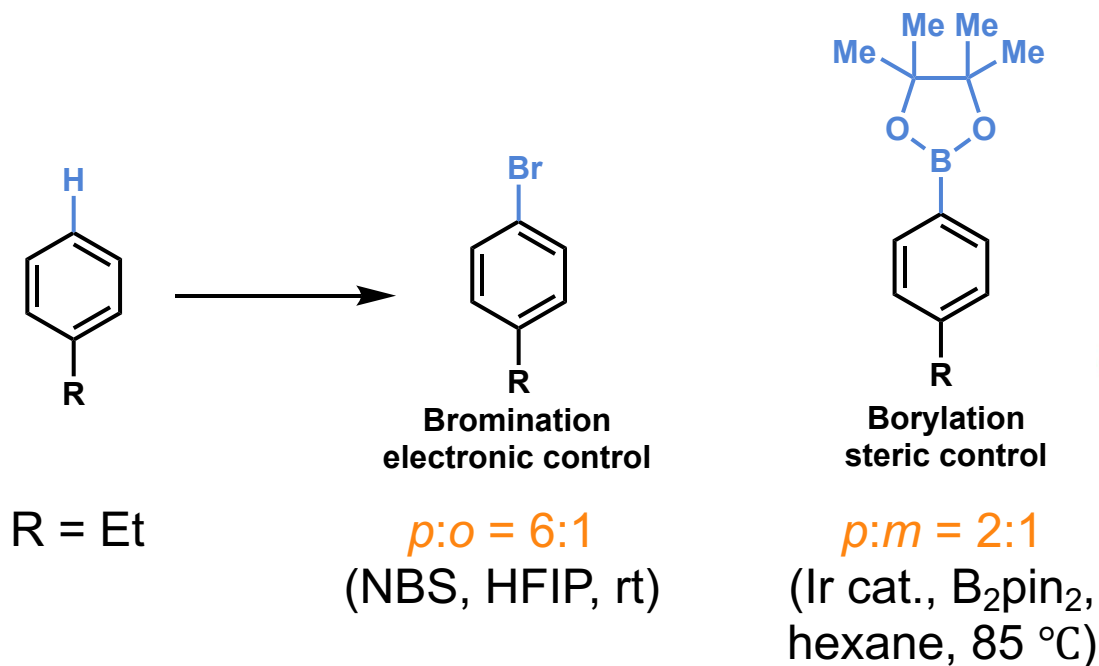
J.-Q., Yu. *et al.*, *J. Am. Chem. Soc.* **2020**, 142, 10571.

Chelation-assisted site-selectivity requires particular directing group or substitution patterns.

No report can introduce synthetically useful linchpins.

Background

Site-selective aromatic C-H functionalization

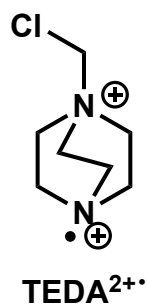
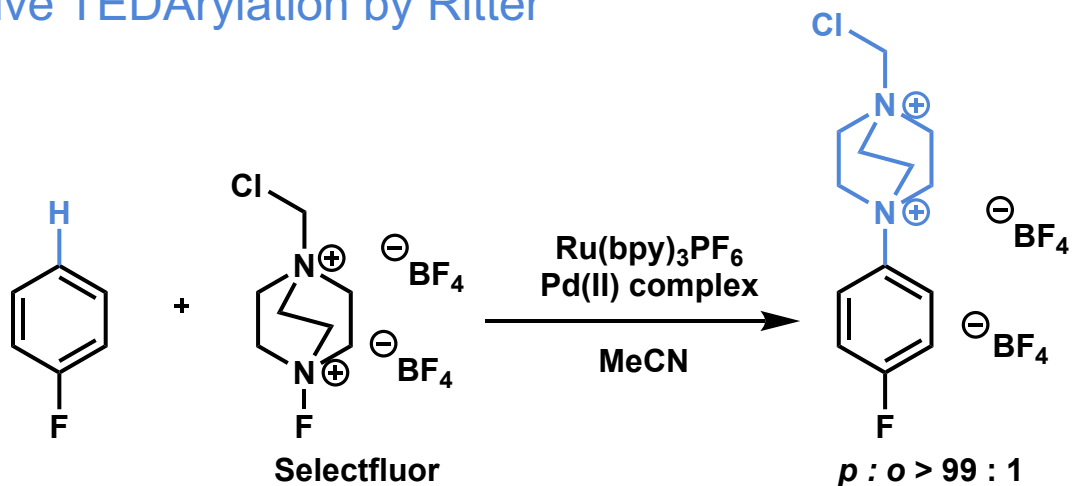


Site-selective bromination and borylation of undirected arenes is challenging.

Ritter, T. *et al.*, *Nature*. **2019**, 567, 223.
Itami, K. *et al.*, *J. Am. Chem. Soc.* **2015**, 137, 5193.

Background

Para-selective TEDArylation by Ritter

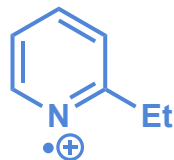


- TEDA dication with **high electron affinity**
- Arene-to-radical charge transfer in radical aromatic substitution

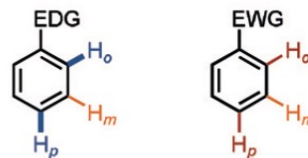
Highly site-selective but not synthetically useful

Background

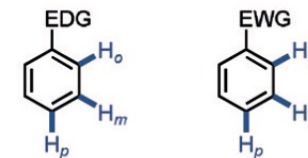
Pyridinium radical cation



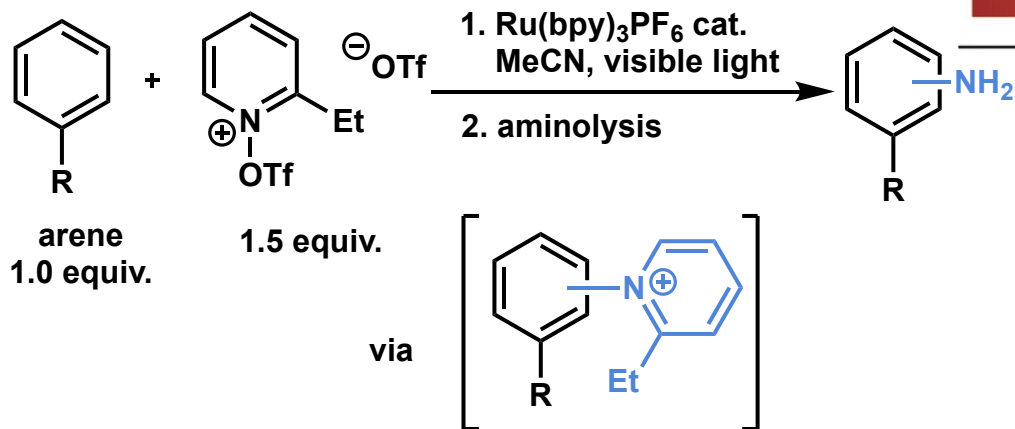
[late TS of bond formation][‡]
large polar effect



[early TS of bond formation][‡]
small polar effect

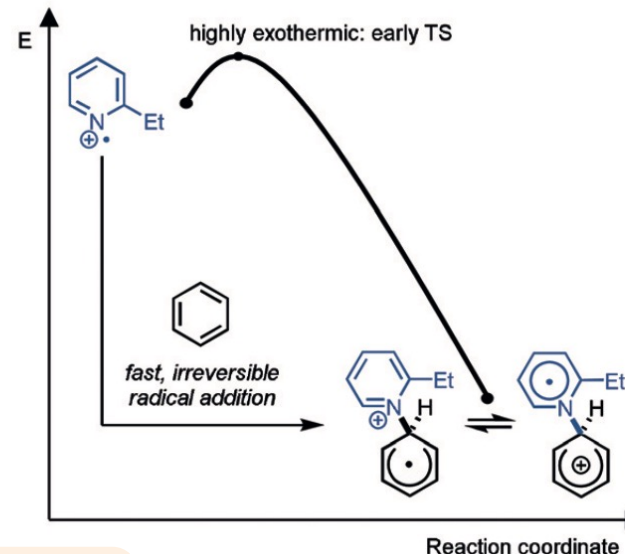


positional reactivity toward electrophilic species



electron-rich R = OAc o:m:p = 24 : 21 : 30

electron-poor R = NO₂ o:m:p = 23 : 49 : 19



Highly **exergonic** radical addition with an **early TS**
→ Small electronic bias leads to low site-selectivity.

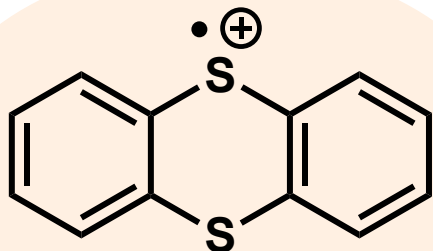
Hypothesis

- High **endergonic** radical addition with a **late** transition state
- Larger electronic difference leads to higher selectivity



Electrophilic persistent sulfur-based radicals

- ✓ No deleterious side reactions
- ✓ An endergonic radical addition with a late TS



Thianthrene radical cation

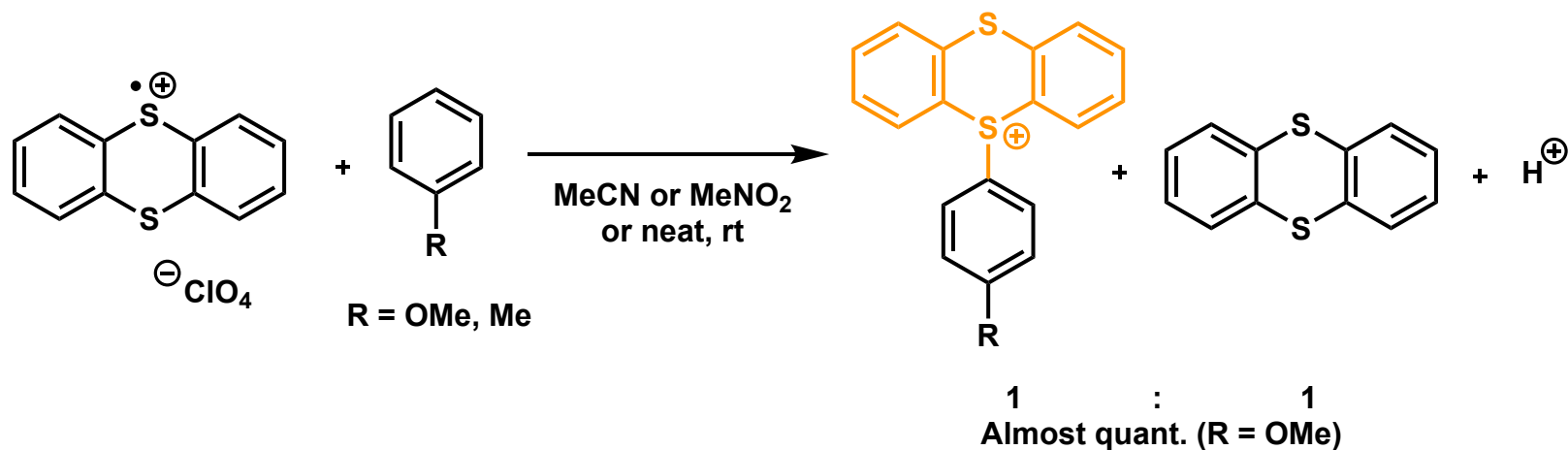
Studied from 1970s by Shine et al

- Persistent radical
- Sulfonium salts as versatile intermediates

Ritter, T. *et al.*, *Nature*. **2019**, 567, 223.

Previous study about thianthrene radical cations

Para-selective thianthrenation

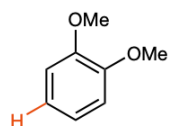
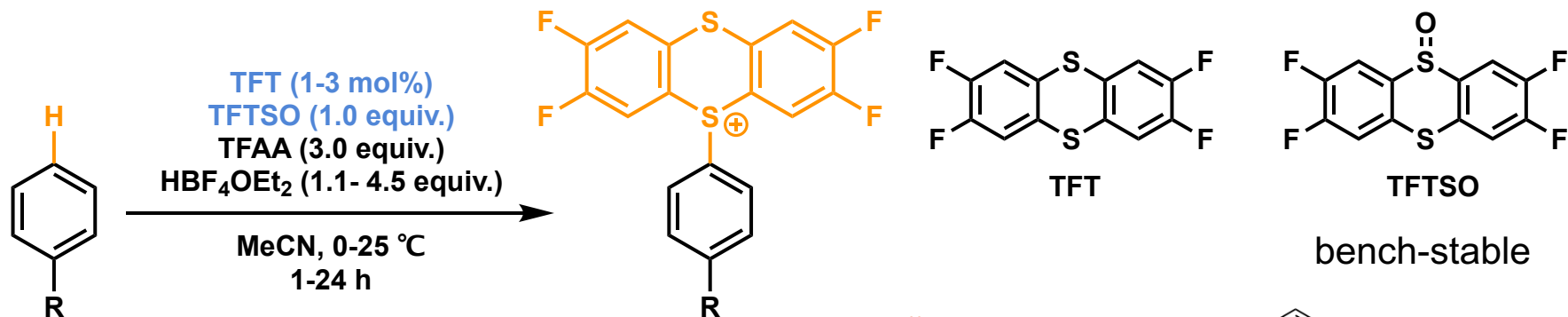


Electrophilic addition of thianthrene radical cation or dication

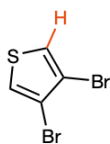
Shine, H. J. *et al.*, *J. Org. Chem.* **1971**, 36, 2923.

- × Limited to electron-rich arenes
- × Low functional group tolerance
- × No synthetic utility
- × No detailed investigation towards the selectivity

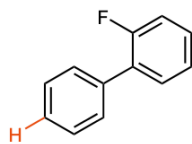
Reaction design



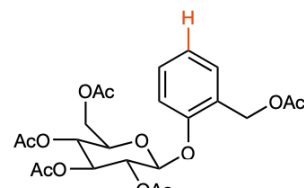
3
76%^a



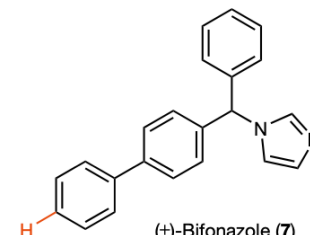
4
68%



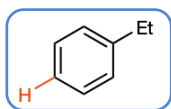
5
85%



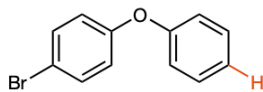
Salicin pentaacetate (**6**)
94%^b



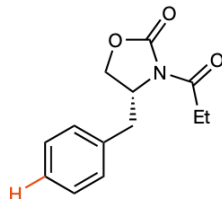
(±)-Bifonazole (**7**)
87%^c



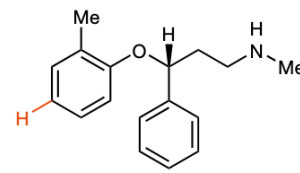
8
92%



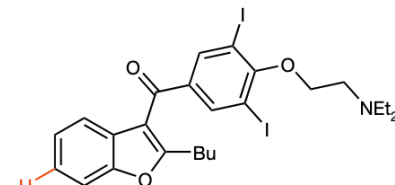
9
86%



10
87%

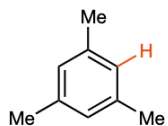


Atomoxetine (**11**)
58%^{a,d}

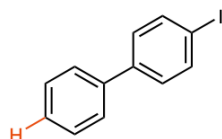


Amidarone (**12**)
92%

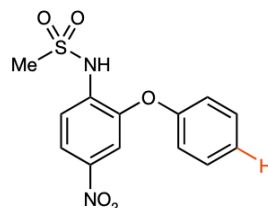
$p:o > 500:1$, $p:m > 200:1$



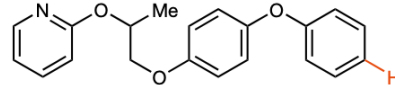
13
62%^a



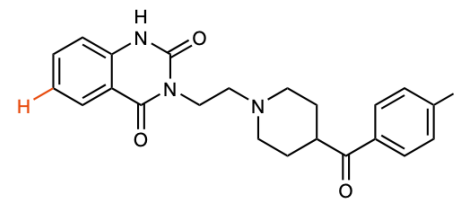
14
59%



Nimesulide (**15**)
93%



(±)-Pyriproxyphen (**16**)
92%



Ketanserin (**17**)
60%

Reaction design

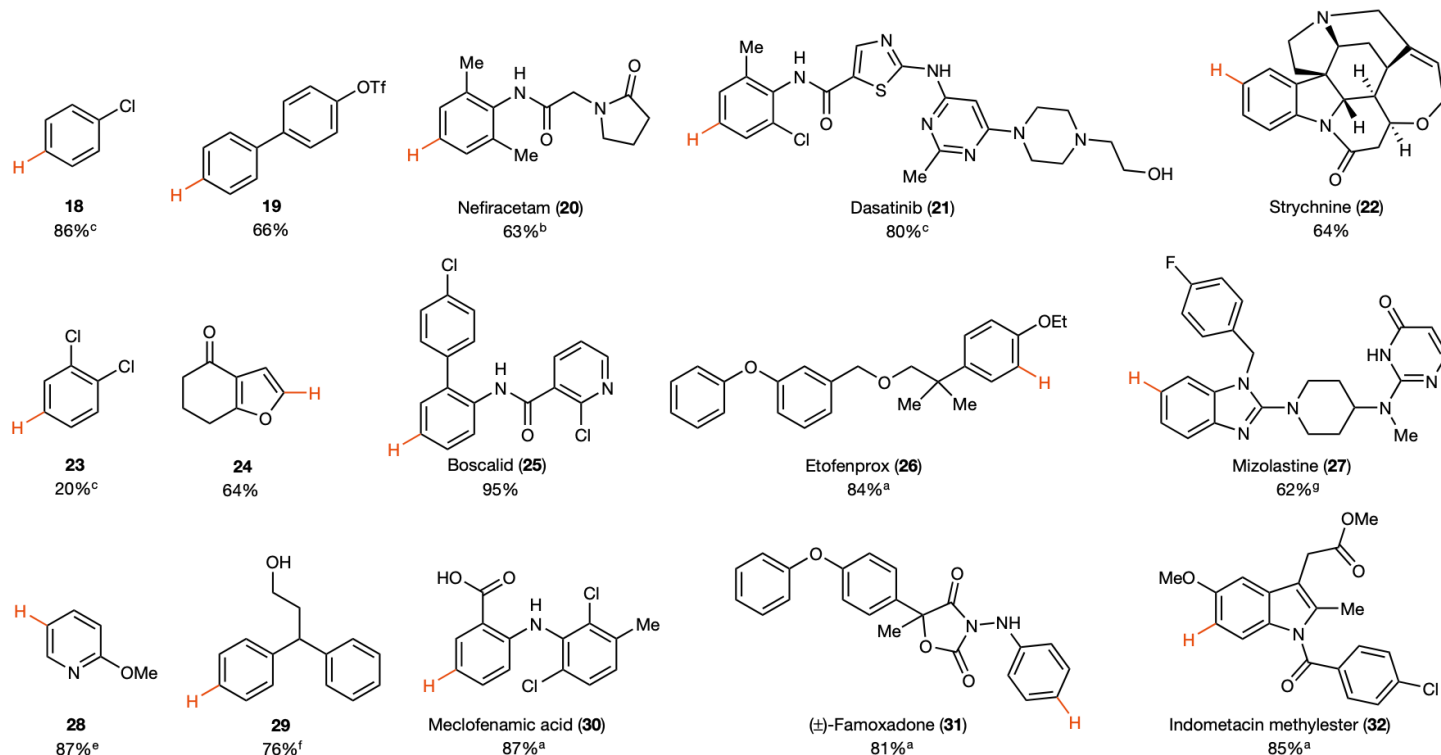


Fig. 2 | Substrate scope of thianthrenation. ^aNonfluorinated thianthrene S-oxide and nonfluorinated thianthrene were used instead of **1** and **2**; no additional acid was used. The reaction was initiated at -78°C . ^b BF_3OEt_2 was used instead of HBF_4OEt_2 . ^cTfOH was used instead of HBF_4OEt_2 .

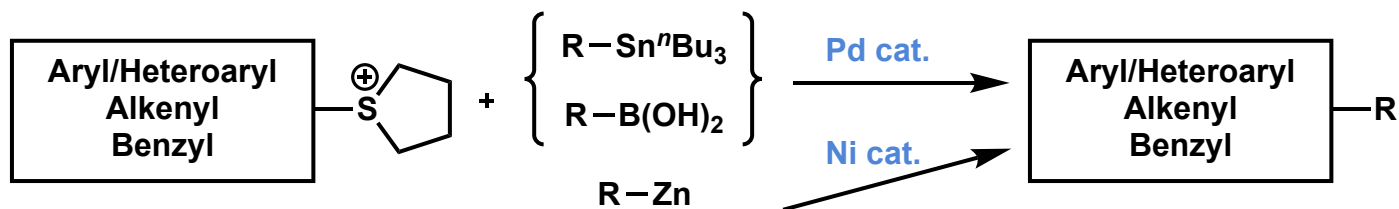
^dThe amino group was trifluoroacetylated. ^eTMSOTf was used instead of HBF_4OEt_2 and the reaction was carried out under an inert atmosphere with dry MeCN. ^f0.90 equiv. **1** was used. ^gSelectivity 16:1, isolated yield of major isomer. OTf, triflate; TMS, trimethylsilyl.

- ✓ A large substrate scope (electron-rich ~ electron-deficient arenes)
- ✓ High site-selectivity ($R = \text{Et}$, $p:o > 500:1$, $p:m > 200:1$)
- ✓ Monofunctionalization due to an electron-deficient sulfonium group
- ✓ Not sensitive to O_2 and traces of H_2O
- ✓ Stable thianthrenium salts

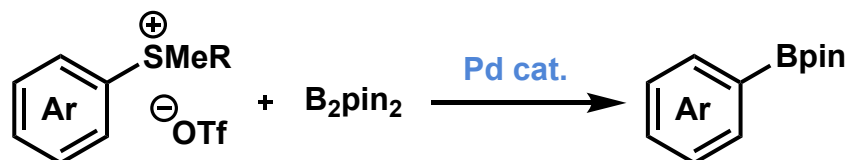
Application -1- cross-coupling

Previous cross-coupling :

Arylalkyl sulfonium salts were not tolerant of nucleophiles.

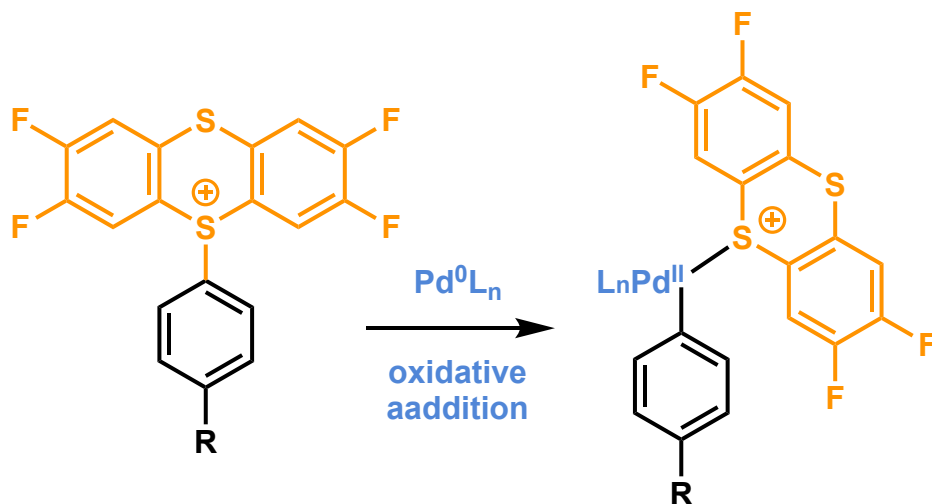


Liebeskind, L. S. *et al.*, *J. Am. Chem. Soc.* **1997**, *119*, 12376.



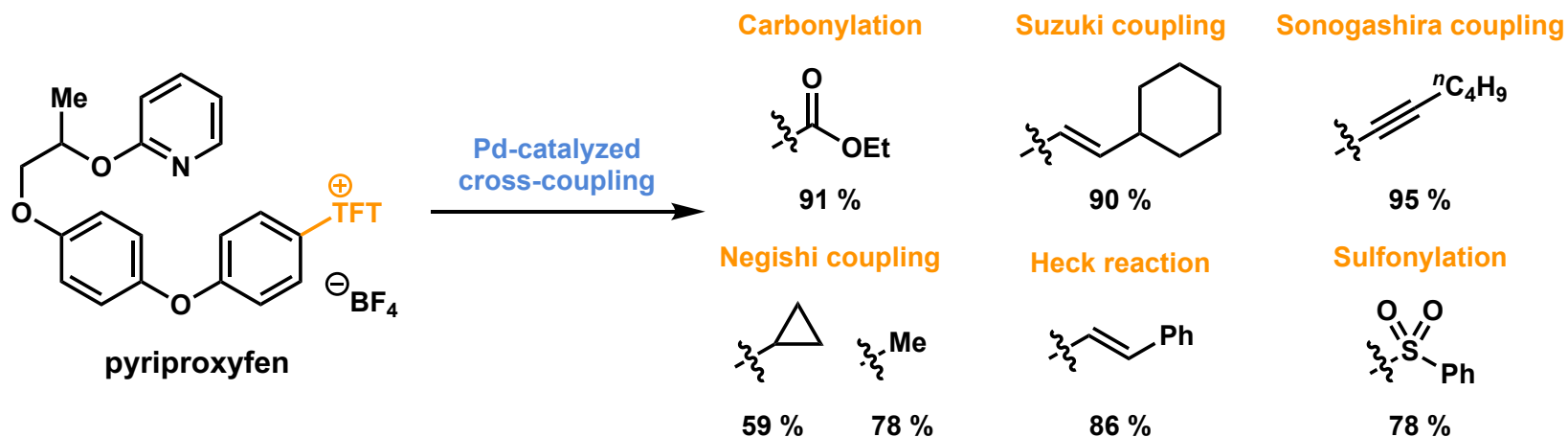
Yorimitsu, H. *et al.*, *ACS Catal.* **2018**, *8*, 579.

This work : Pd-catalyzed cross-coupling

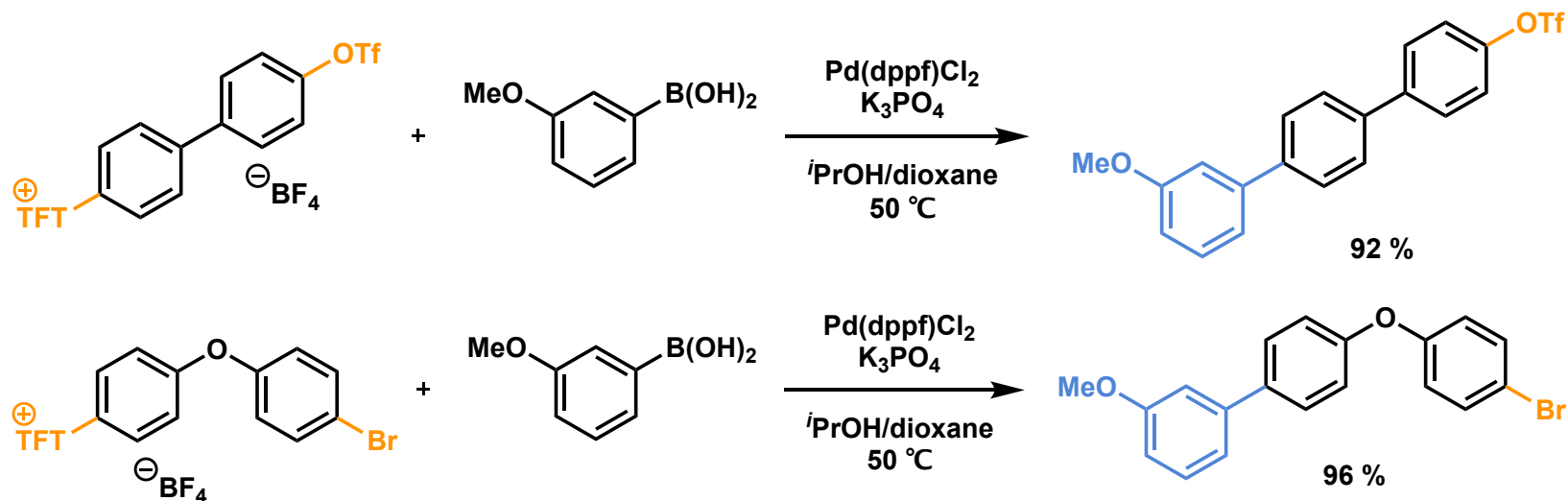


- ✓ More stable structure
- ✓ More resistant to nucleophiles
- ✓ Faster oxidative addition reactivity than ArBr and ArOTf → Chemoselectivity

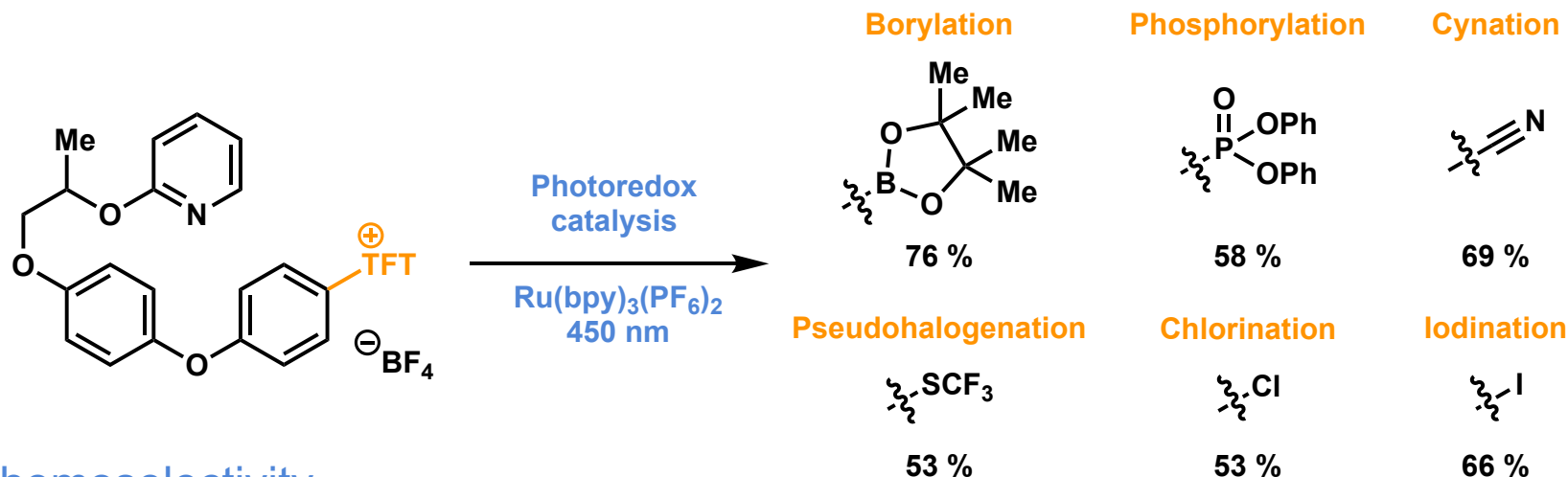
Application -1- cross-coupling



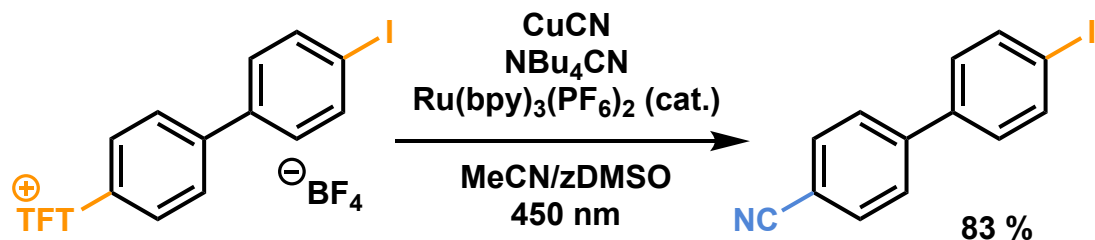
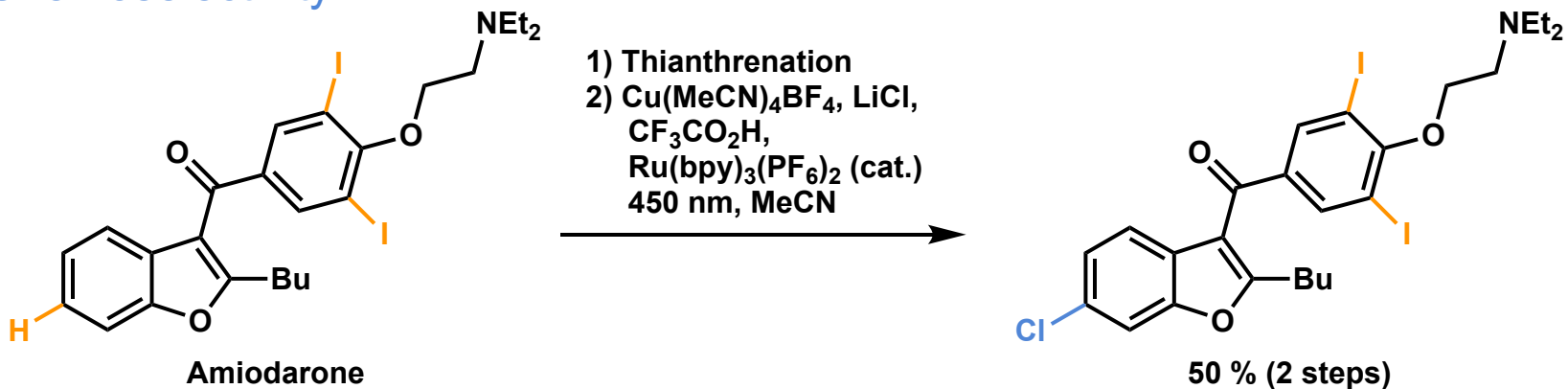
Chemoselectivity



Application -2- photoredox catalysis

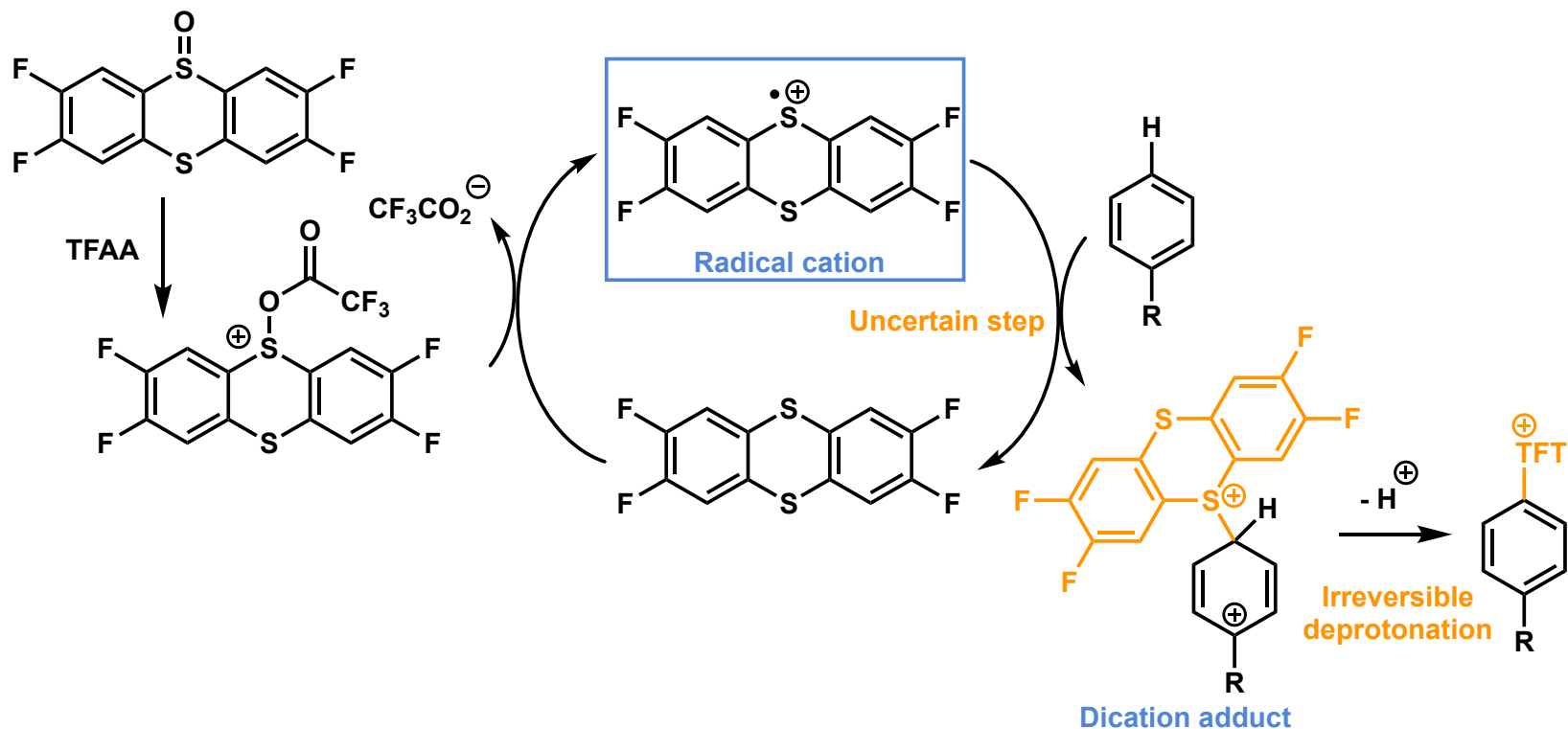


Chemoselectivity



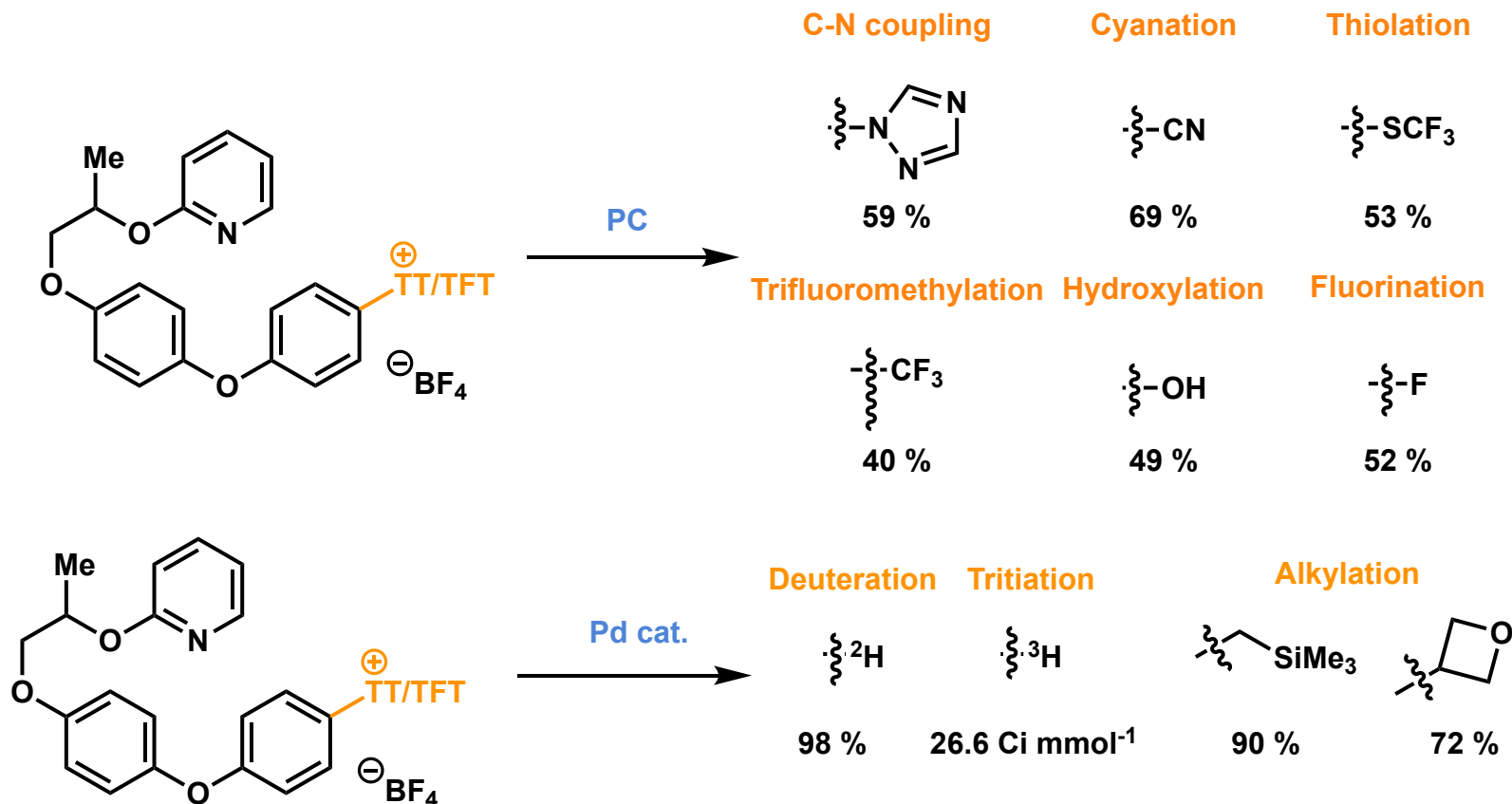
- ✓ Transformations with various nucleophiles
- ✓ Tolerant of arylhalides

Reaction mechanism



- Radical cations : supported by EPR
- Electrochemical oxidation gave the similar result.
- The Hammet analysis supports a cationic intermediate and $\rho = -11$ indicates a late TS.
- The step of dication adduct formation is uncertain.

Application – various functionalization



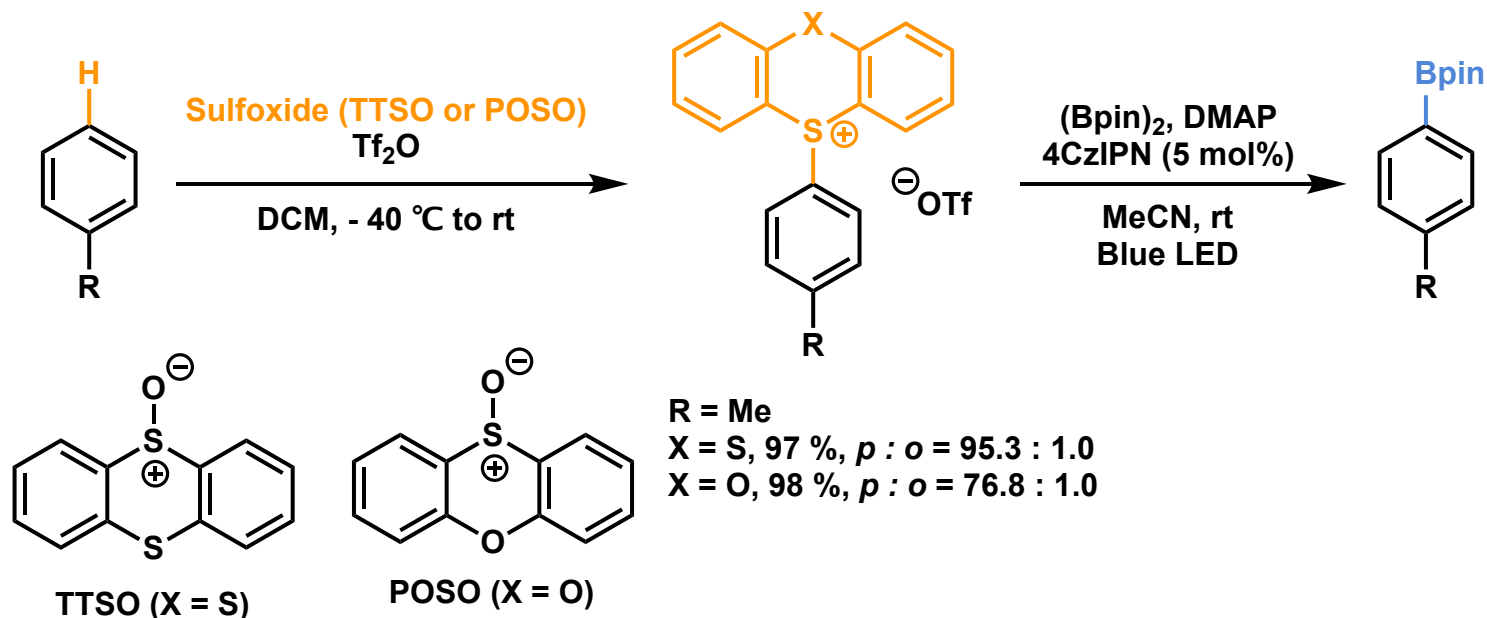
Ritter et al., *Nature*. **2019**, 567, 223.
Nature **2021**, 600, 444.
J. Am. Chem. Soc. **2021**, 143, 7909.
Synlett. **2022**, 33, 339.

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Wang's report

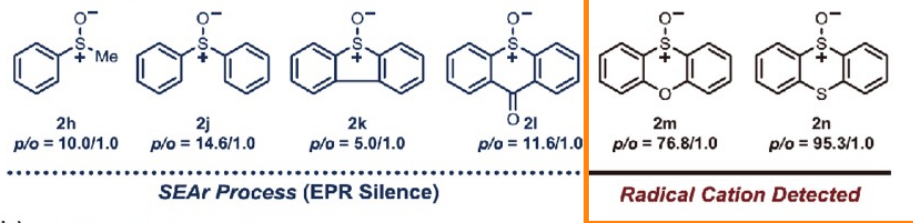
Wang's *para*-selective C-H functionalization using phenoxathiine or thianthrene just several months after Ritter's.



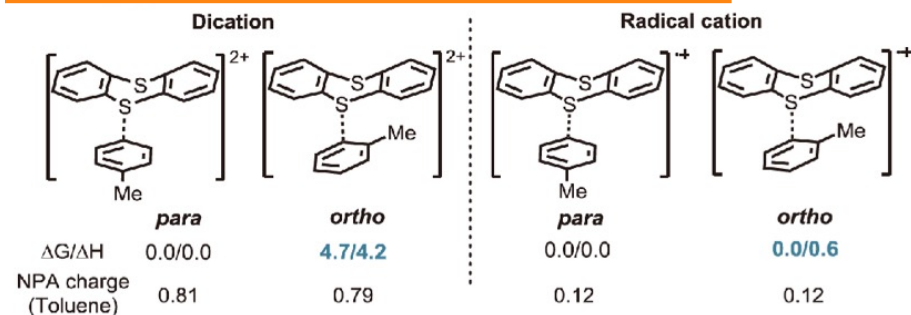
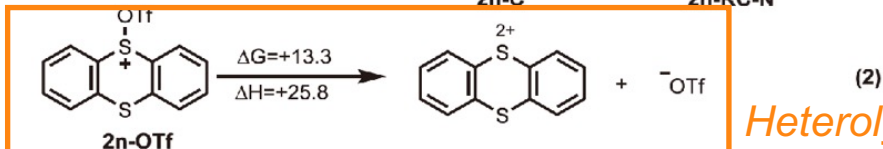
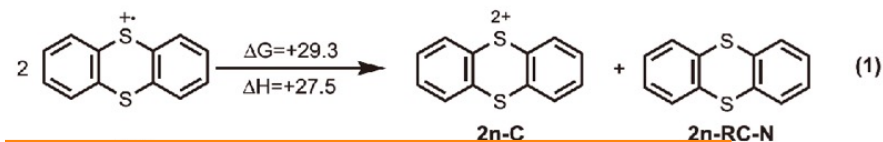
- ✓ High *para*-selective borylation by a transient mediator approach
- ✓ One-pot synthesis
- ✗ Electron-deficient arenes (X = Cl, Br, CO_2Me , COMe , CF_3)

Wang's mechanistic study

(a) EPR response for various sulfate ditriflates



(b) Computational study



What determines high site-selectivity ?

- Sulfoxide screening
→ Steric effect (partially)
- EPR experiment
→ Radical cation intermediates

However,
low concentration didn't afford TM.

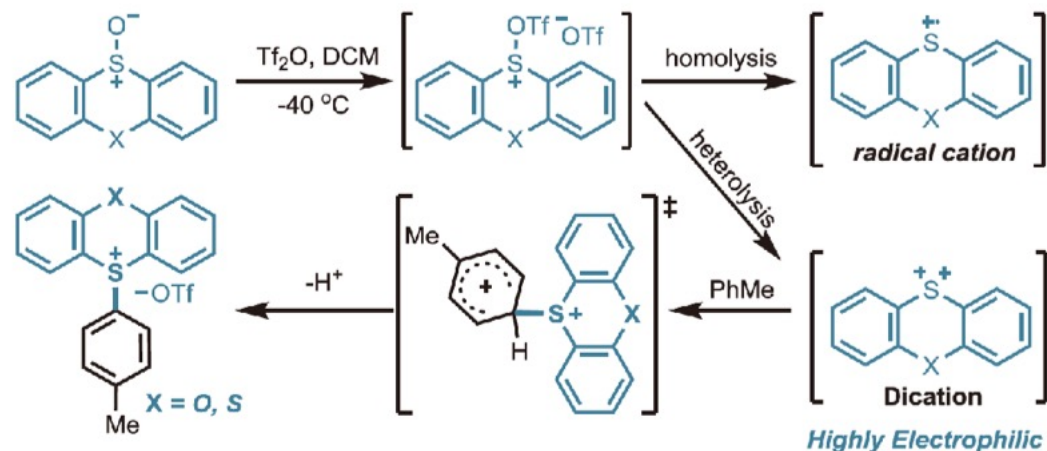
What is a real reactive species ?

DFT calculations

→ A larger free energy difference between *ortho* and *para* intermediates was detected in case of **dications**.

Wang's mechanistic study

(c) Proposed mechanism for *para*-selective sulfonium salts formation



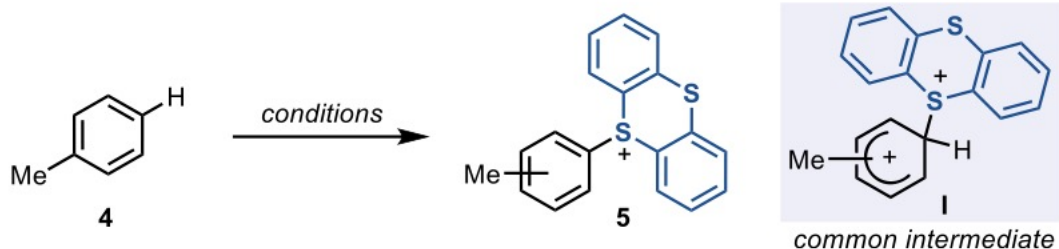
Mechanism

1. Heterolysis of sulfide ditriflate
2. Highly electrophilic dication reacts with toluene
3. Deprotonation

Para-selectivity

- High electrophilicity of the sulfide dications
- The favorable *para*-intermediate minimizes the electrostatic repulsions.

Different thianthrenation protocols



entry	conditions	proposed	<i>p/o</i>	<i>p/m</i>
1	TTO , TFAA, HBF ₄ ·OEt ₂ , MeCN	TT²⁺/TT⁺-TFA	106	132
2	TTO , neat H ₂ SO ₄	TT²⁺	122	132
3	[TT^{•+}]BF ₄ , MeCN	TT^{•+}	114	127
4	TTO , TFAOTf, K ₂ CO ₃ , MeCN	TT⁺-TFA	75	125

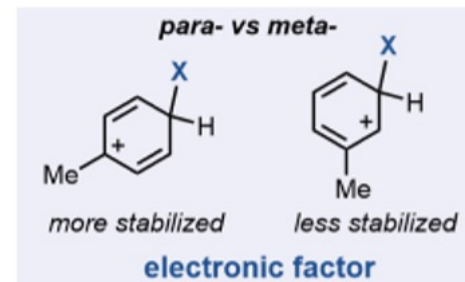
Different conditions gave the similar selectivity.

→ The selectivity is determined at the step after formation of a common Wheland intermediate.

Source of *p/m* & *p/o* selectivity

reaction	ρ	<i>p/m</i> in toluene	<i>p/o</i> in toluene
bromination	-12	220	2
thianthrenation ^b	-11	206	144
chlorination	-9	82	0.66
acetylation	-9	54	162
nitration	-6	17	0.54
electroiodination	-6	12	1
mercuration	-4	5	2
alkylation	-2	1.8	1.7

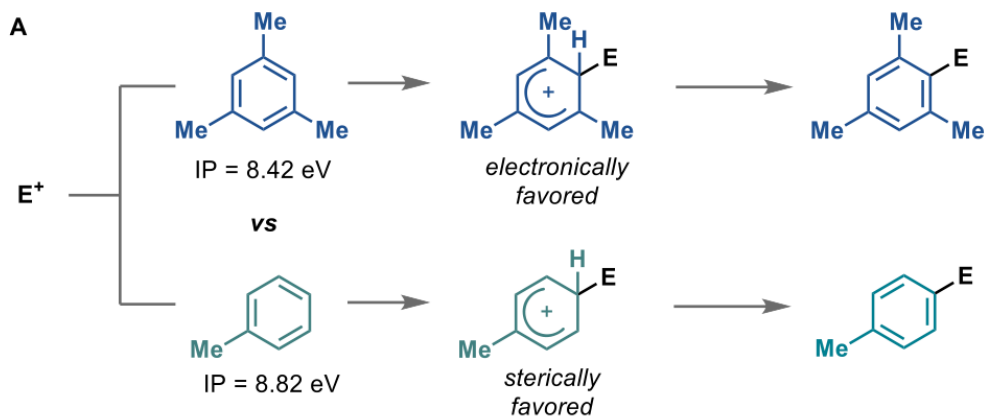
^aData obtained from refs 5 and 86–88. ^bData for reactions with TFTO.



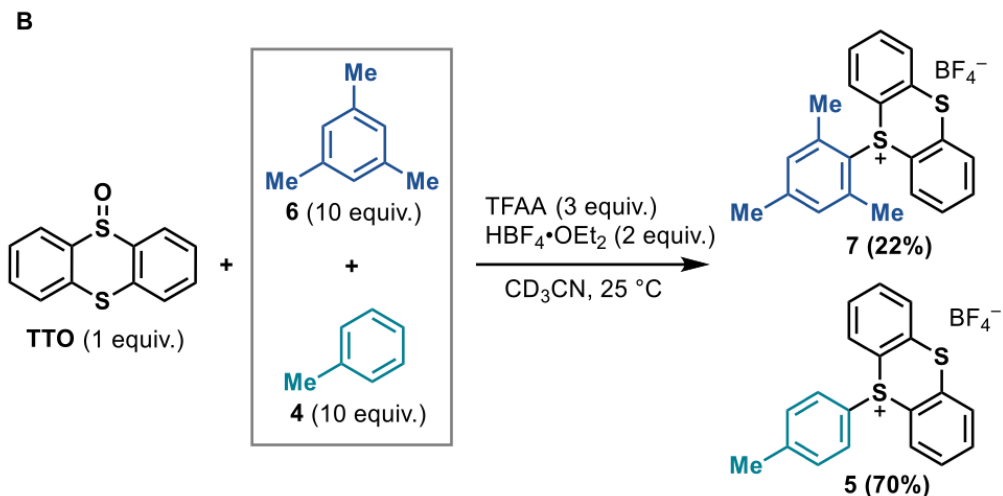
The ***p/m* selectivity** is determined by **the electronic effect** and predicted by the Hammett value ρ , but the *p/o* selectivity is not in the case.

Source of *p/m* & *p/o* selectivity

Different *p/o* selectivity between bromination and thianthrenation
→ The size of a substituent... **steric effect**



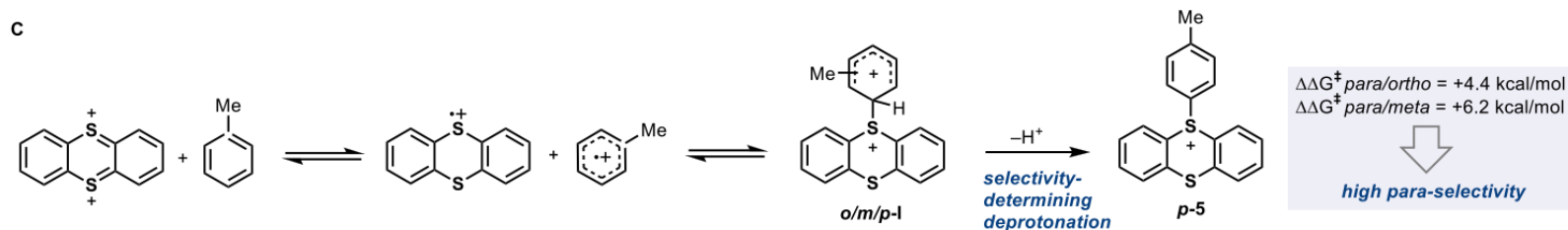
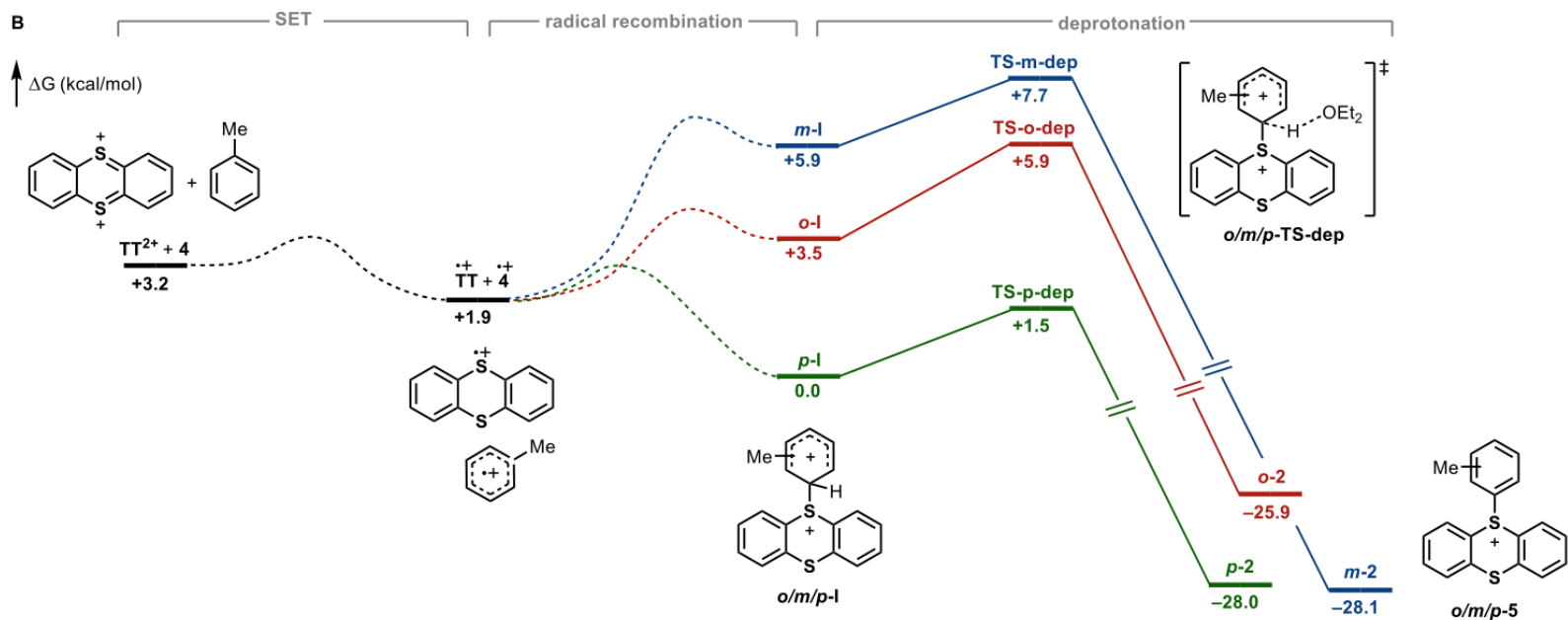
Intermolecular competition experiment



Selectivity of toluene over mesitylene
+ KIE > 1

→ Deprotonation is slower at the mesitylene-based Wheland intermediate.

Computational study



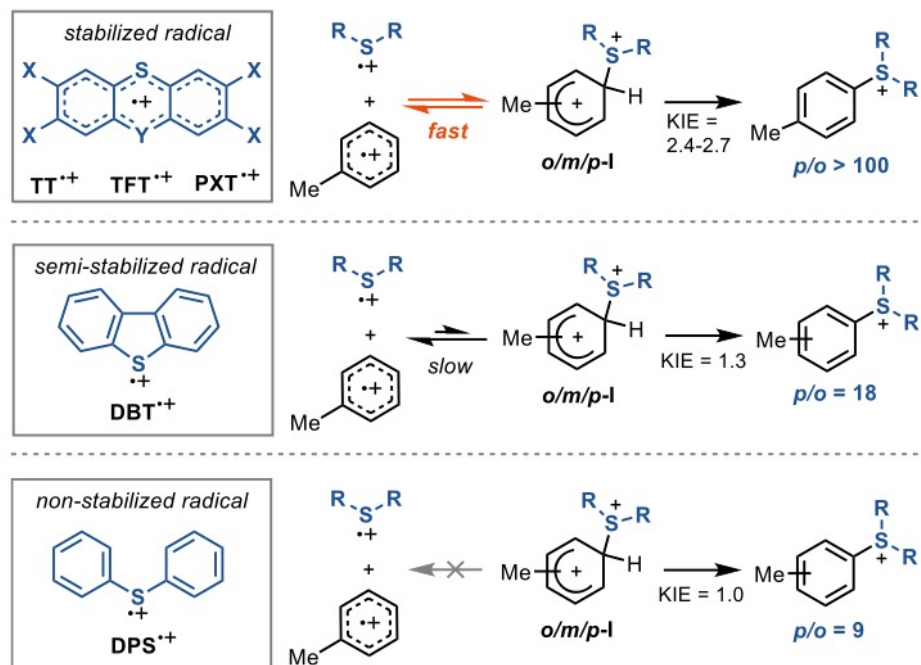
- The TSs of deprotonation are early TS, which are more SM-like.
- The high energy differences** rationalize the exquisite *para*-selectivity.
- The reversible interconversion enables all *o*, *m-l* to generate *p-l*.

Comparison of other sulfoxides



sulfoxide	p/o^a in 5	p/m^a in 5	k_H/k_D^b	$E(R_2S^{\bullet+}/R_2S)$ (V) vs SCE	reversible?
TTO	106	133	2.7	+1.24	Y
TFTO	144	206	2.4	+1.42	Y
PXTO	99	190	2.7	+1.20	Y
DBTO	18	114	1.3	+1.55	N
DPSO	9	86	1.0	+1.47	N

^aActivation method: TFAA + $HBf_4 \cdot OEt_2$. ^bFrom an intermolecular competition of 4/4- d_8 .

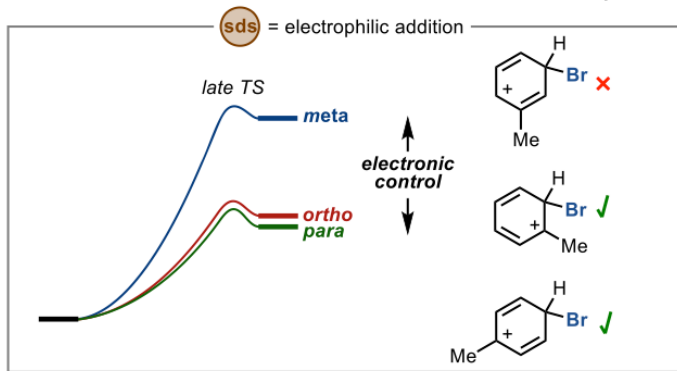
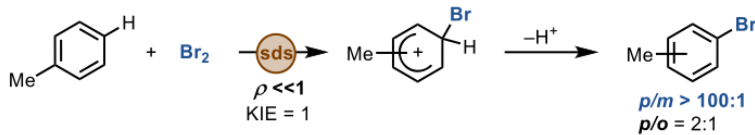


- The reversible homolysis can be explained by **the stability of the persistent thianthrene radical cation**.
- TFT, TT, and PXT shows **reversible 1e⁻ oxidation**, which means **persistent radical formation** and a **primary KIE**, which means **reversible Wheland int. formation**.

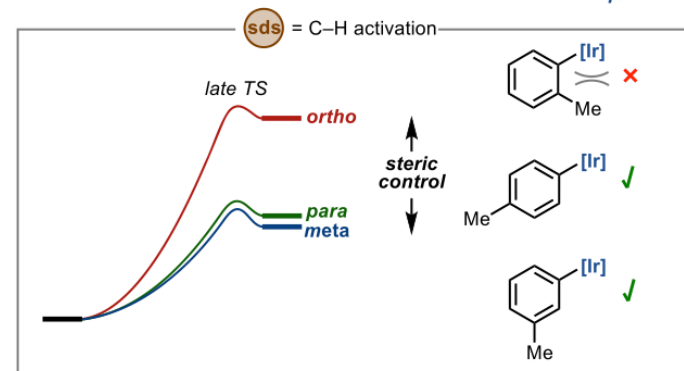
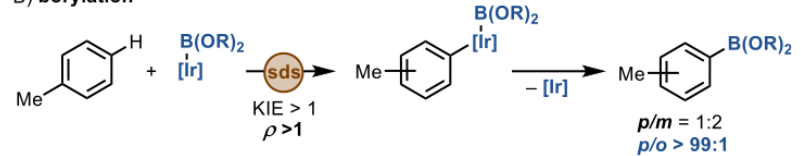
Guideline 1

The energy of Wheland intermediates

A) halogenation



B) borylation



Energy of Wheland intermediates

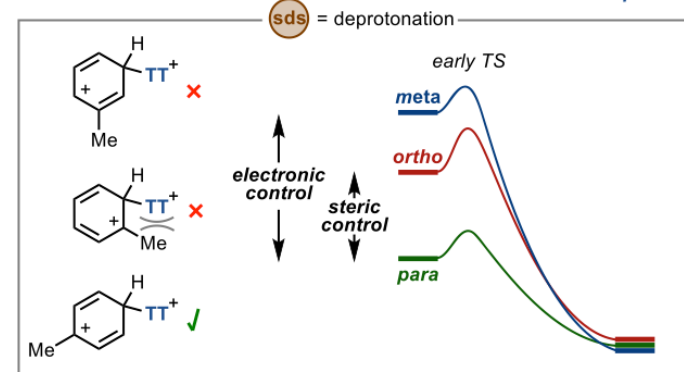
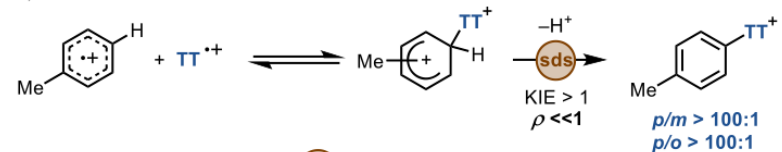
Halogenation : **electronic control**

Borylation : **steric control**

Thianthrenation : **electronic & steric control**

→ High *para*-selectivity

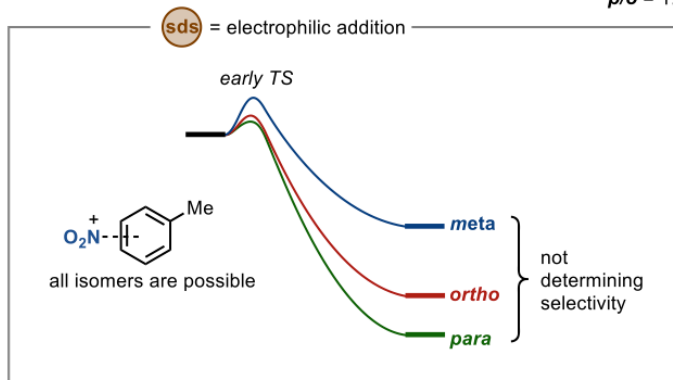
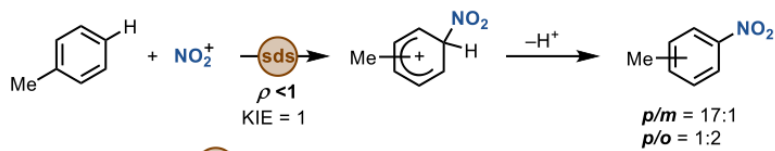
D) thianthrenation



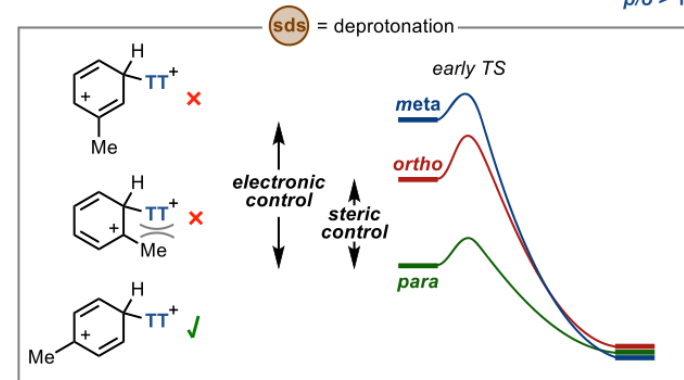
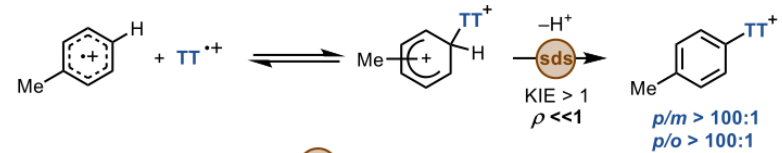
Guideline 2

TS resembles Wheland int. in the sds
 : Late TS for electrophilic addition or early TS for deprotonation

C) nitration



D) thianthrenation

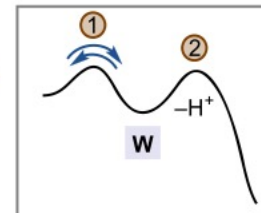
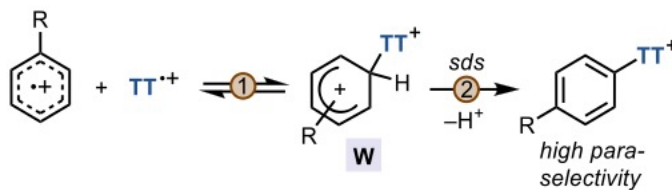


- Thianthrenation : The early TS in the selectivity-determining step resembles Wheland intermediates.
 → The energy difference in Wheland int. contributes to selectivity.

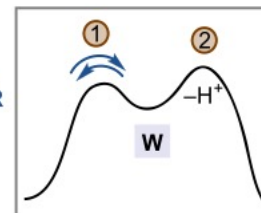
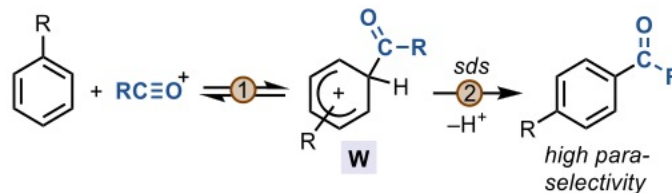
Guideline 3

Reversible electrophilic addition

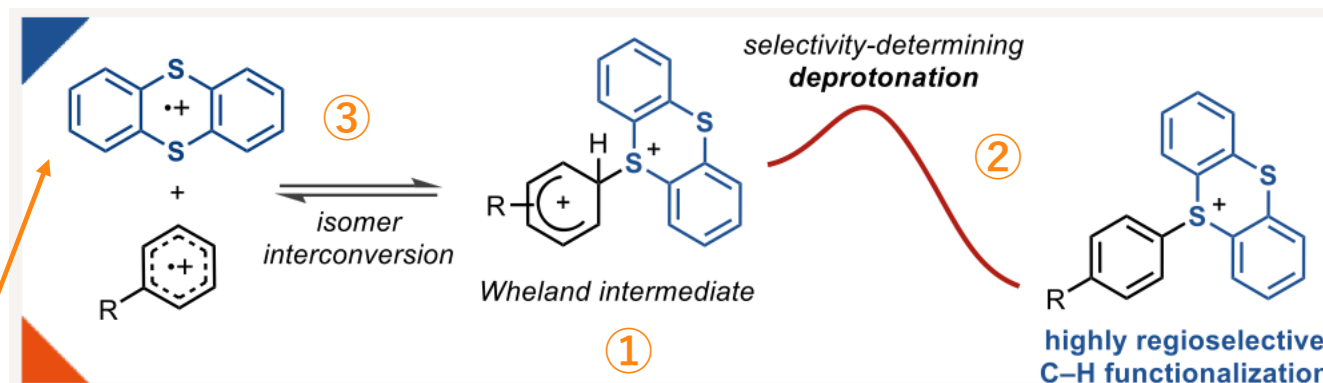
A) thianthrenation



B) acylation



$p/m = 54 : 1$
 $p/o = 162 : 1$

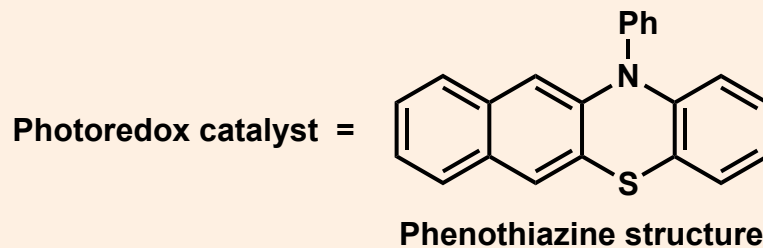
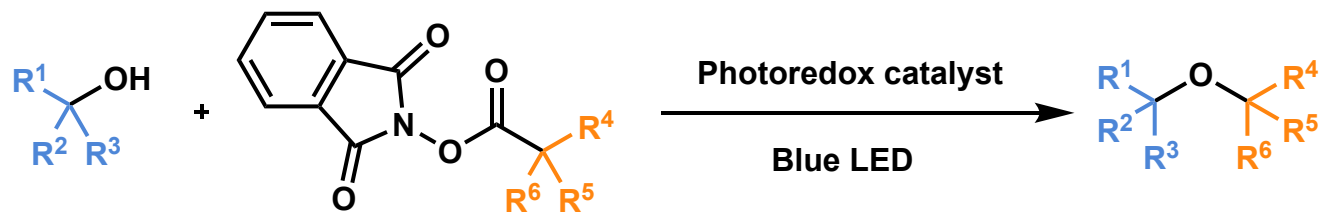


persistent radical

Contents

1. Introduction of persistent radicals
2. Site-selective C-H functionalization by thianthrenation
 - I. Ritter's first work
 - II. Mechanistic insight into site-selectivity
3. PTH catalyzed C(sp³)-O formation
4. Summary & Perspective

Photoredox-catalyzed C(sp³)-O formation



Ohmiya, H. *et al.*, *J. Am. Chem. Soc.* **2020**, *142*, 1211.

Background

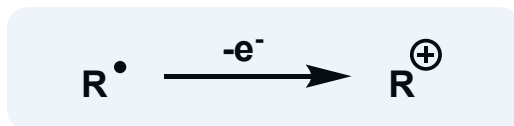
C(sp³)-X-C(sp³) formation

Conventional methods : Alkylheteroatom nucleophile & alkyl electrophile

- Nucleophilic substitution
 - × Functional group tolerance (S_N2, S_N1)
 - × Not tolerant of sterically demanding substrates (S_N2)
- Transition-metal catalysis
 - × Slow oxidative addition
 - × β-hydride elimination instead of reductive elimination

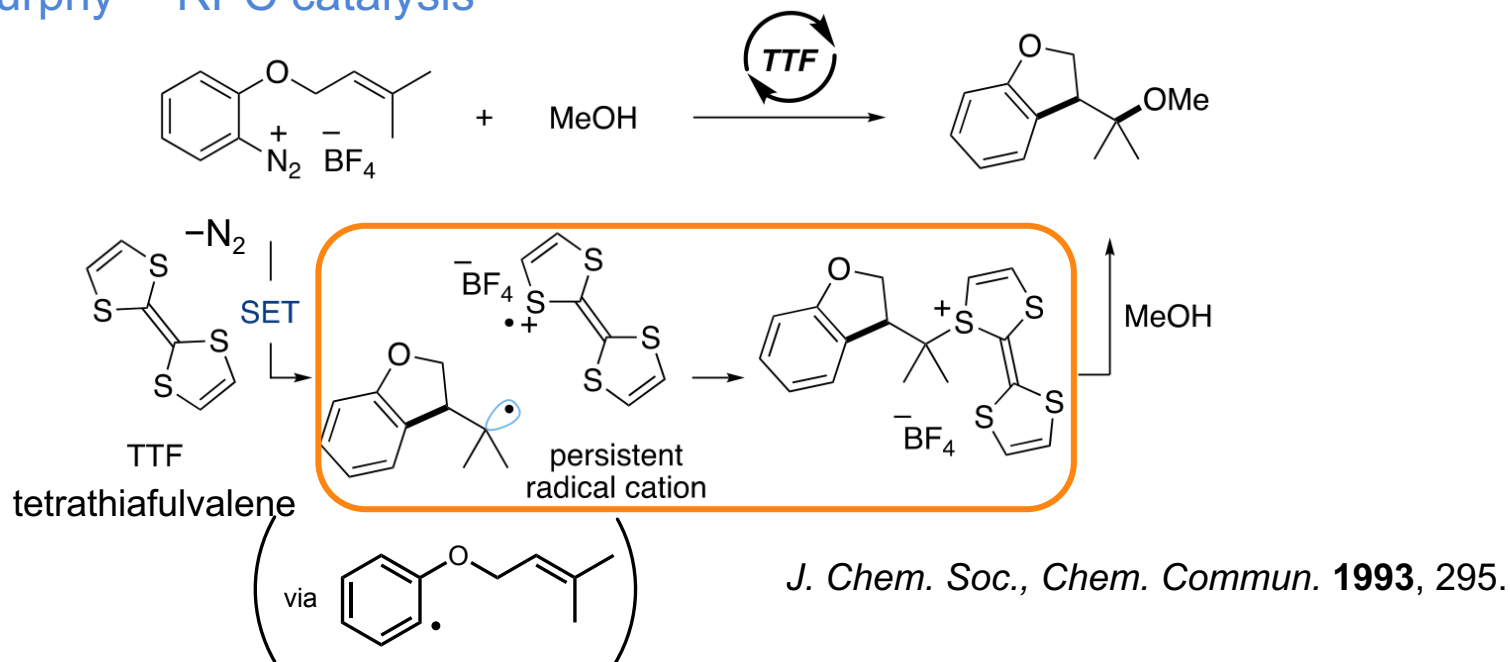
This work

- **Radical-polar crossover (RPC) reaction**



RPC reaction

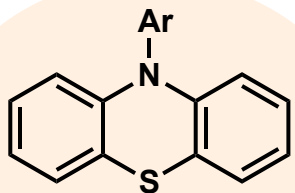
1993 Murphy RPC catalysis



- TTF as an RPC catalyst
- Radical to cation by trapping TTF \cdot^+
- Persistent radical effect

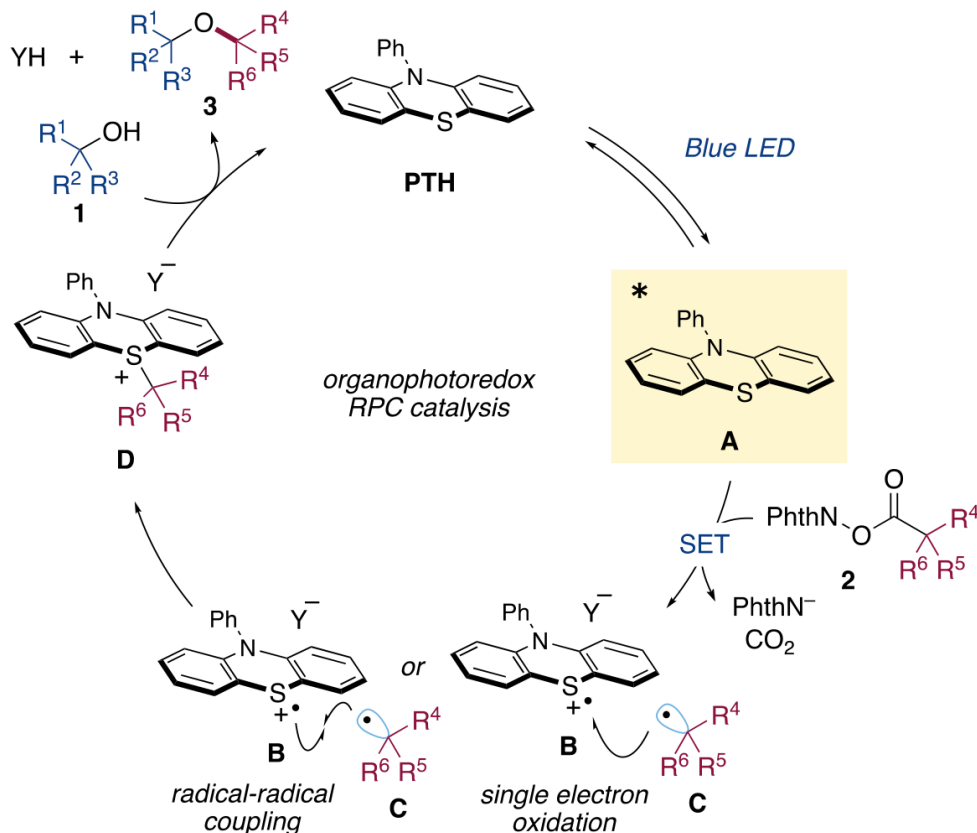
Towards C(sp³)-O-C(sp³) formation,
× Low reducing ability of TTF: $E^{\text{ox}} = -0.2 \text{ V}$ vs SCE in MeCN
→ **Strong redox property of organosulfide RPC catalyst by visible light excitation**

Hypothesis



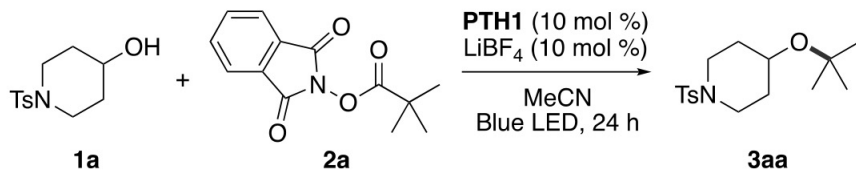
N-Ar-phenothiazine (PTH)

- Excitation in the UV-vis area ($\lambda_{\max} = 320 \text{ nm}$)
- High reduction potential (Ar = Ph, $E_{1/2}^* = -2.1 \text{ V vs SCE}$)
- Persistent radical cation

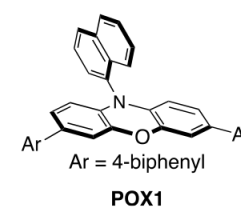
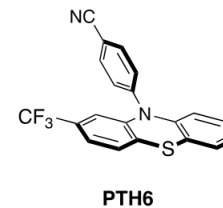
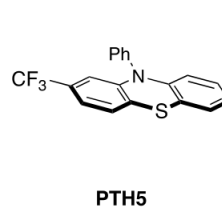
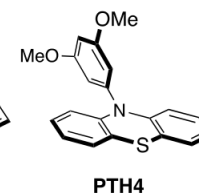
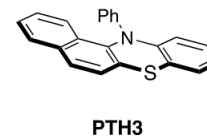
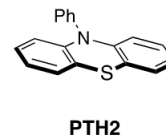
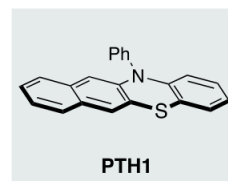


Alkylsulfonium salt is formed from alkyl radical and PTH radical cation.

Optimization



Entry	Change from standard conditions	Yield of 3aa (%) ^b
1	none	81
2	PTH2 instead of PTH1	26
3	PTH3 instead of PTH1	54
4	PTH4 instead of PTH1	40
5	PTH5 instead of PTH1	86
6	PTH6 instead of PTH1	19
7	POX1 instead of PTH1	40
8	Ir(ppy) ₃ (2 mol%) instead of PTH1	5
9	Ru(bpy) ₃ (PF ₆) ₂ (2 mol%) instead of PTH1 and LiBF ₄	8
10	Ir[dF(CF ₃)ppy] ₂ (dtbbpy)PF ₆ (2 mol%) instead of PTH1 and LiBF ₄	1

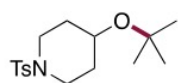


^aReaction was carried out with **1a** (0.6 mmol), **2a** (0.2 mmol), **PTH1** (0.02 mmol), and LiBF₄ (0.02 mmol) in MeCN (0.6 mL) under blue LED irradiation for 24 h. ^b¹H NMR yield based on **2a**.

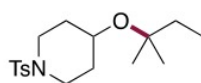
- The extension of π -conjugation or the introduction of an electron-deficient group
→ **PTH1** is the best photocatalyst.
- Ir or Ru photocatalyst gave lower yield.

Substrate scope

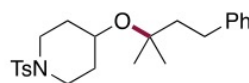
Scope of redox active ester with secondary alcohol **1a**



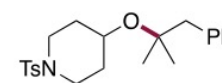
3aa, 79%



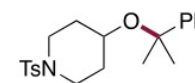
3ab, 65%



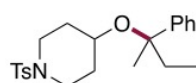
3ac, 48%



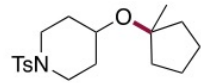
3ad, 28%



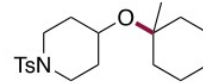
3ae, 74%



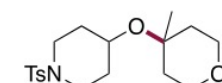
3af, 83%



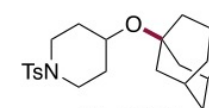
3ag, 47%^b



3ah, 44%^c



3ai, 41%^d

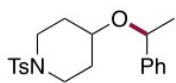


3aj, 53%^e

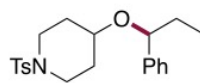
secondary benzylic

α-heteroatom

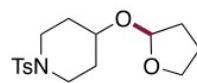
pharmaceutical drugs



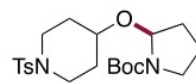
3ak, 50%^f



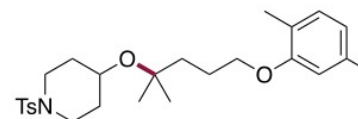
3al, 33%^f



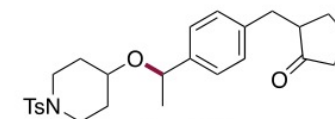
3am, 90%



3an, 50%



3ao, 44%

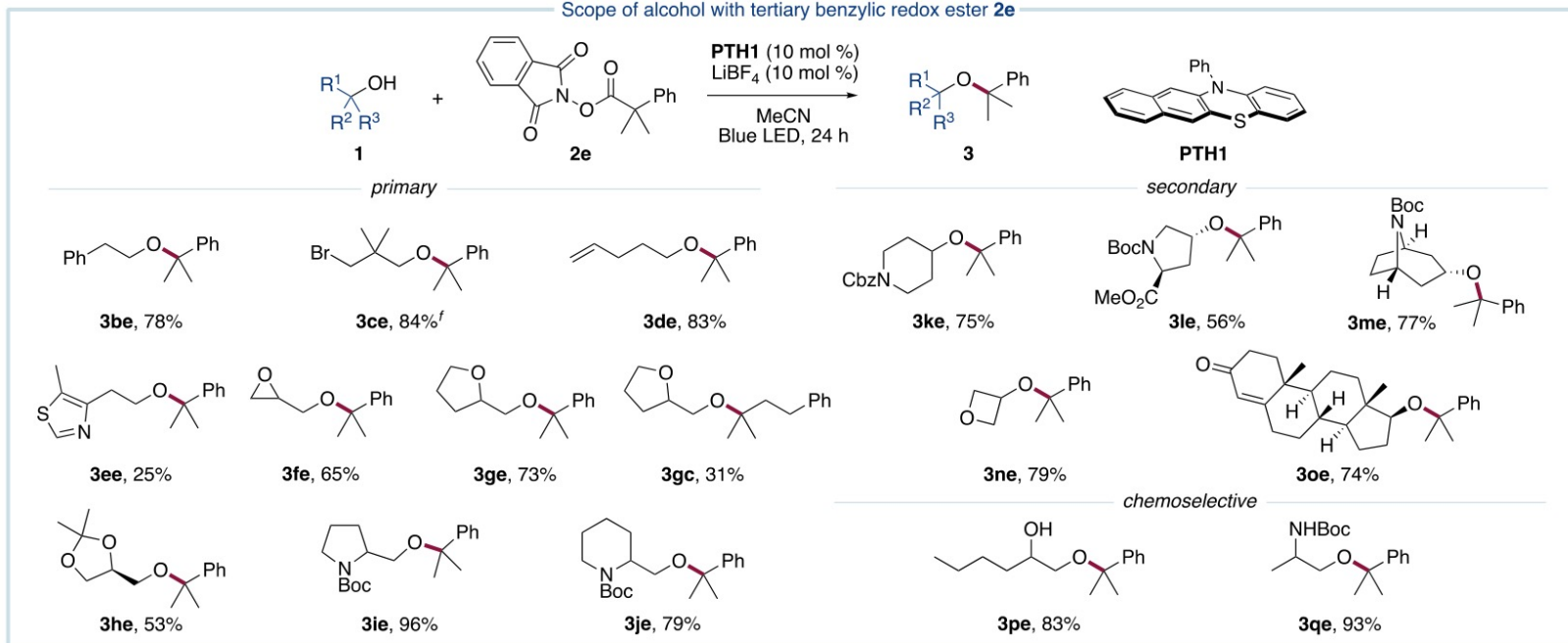


3ap, 91%

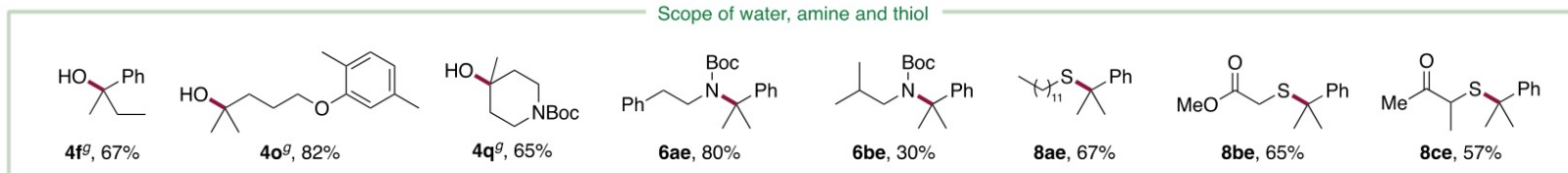
- ✓ Access to sterically hindered ether compounds
- ✓ Tertiary benzyl groups afforded high yield due to the stabilization of benzyl carbocations.

Substrate scope

Scope of alcohol with tertiary benzylic redox ester **2e**



Scope of water, amine and thiol



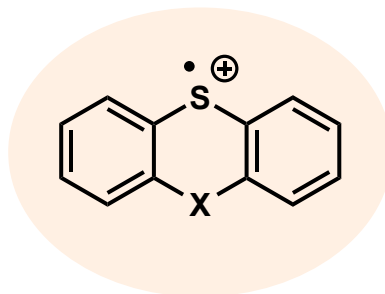
^gReaction was carried out with **1a** (0.6 mmol), **2a** (0.2 mmol), **PTH1** (0.02 mmol), and LiBF₄ (0.02 mmol) in MeCN (0.6 mL) under blue LED irradiation for 24 h. ^hThe color of light was changed. ^c**PTH6** (0.02 mmol) was used instead of **PTH1**. ^d**PTH3** (0.02 mmol) was used instead of **PTH1**. ^e**PTH4** (0.02 mmol) was used instead of **PTH1**. ^f12 h. ^gReaction was carried out with **2** (0.2 mmol), **PTH1** (0.02 mmol), water (10 μL), and LiBF₄ (0.02 mmol) in acetone (0.8 mL) under blue LED irradiation for 24 h.

- ✓ An alkyl halide and olefin were compatible.
- ✓ Acetonide- and Boc- protecting group were not removed.
- ✓ Chemoselectivity of the primary alcohol
- ✓ Water, amines, and thiol were also used as nucleophiles.

Contents

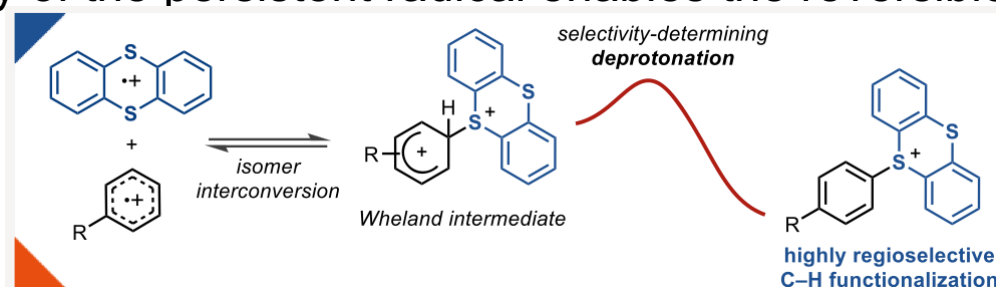
1. Introduction of persistent radicals
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 - I. Ritter's first work
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4. Summary

Summary

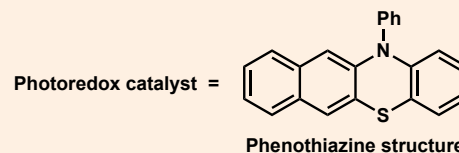
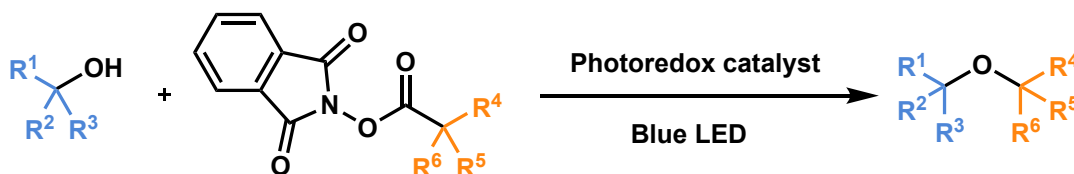


X = S, O, N

- Ritter's work : High site-selective C-H functionalization
 - ✓ Stability of the persistent radical enables the reversible interconversion.

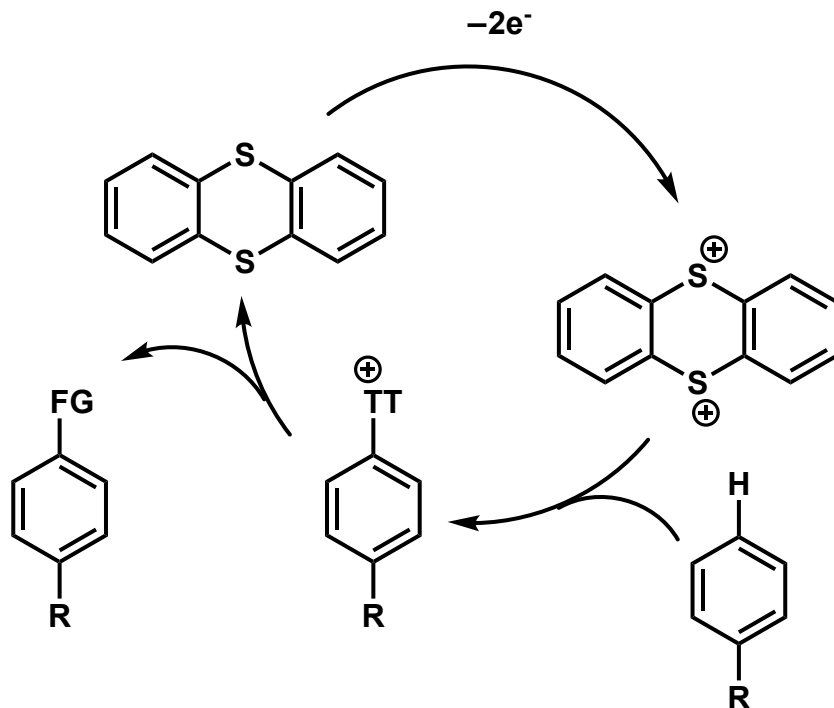


- Ohmiya's work : Photoredox-catalyzed C(sp³)-O formation
 - ✓ The persistent radical selectively oxidizes a transient alkyl radical.
 - ✓ Extended π -conjugation renders PTH a photoredox catalyst.



Perspective

In order to make C-H thianthrenation more convenient, it is important to realize the reactions. with **thianthrene catalysts**



TT to TT^{•+} = 1.21 V vs SCE
TT^{•+} to TT²⁺ = 1.74 V vs SCE

Ritter, T. *et al.*, *Angew. Chem. Int. Ed.* **2020**, 59, 5626.

Strategy

- $2e^-$ oxidation of thianthrene by external strong oxidants
- Thianthrene derivative itself as PC