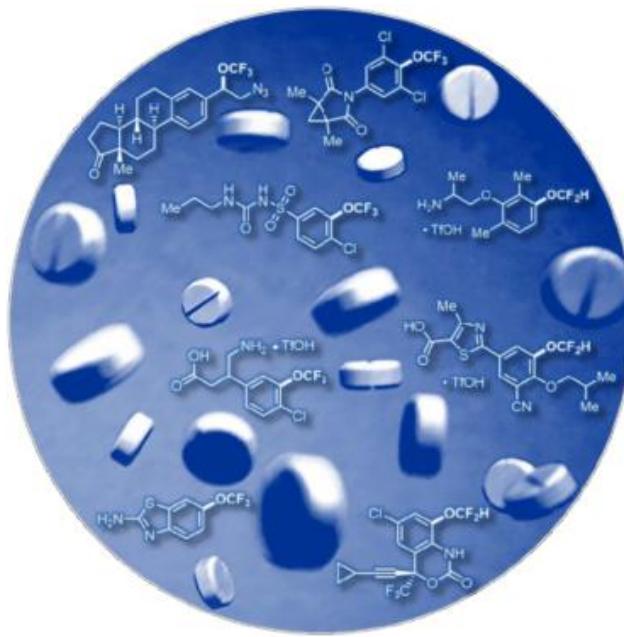


Synthesis of Tri- and Difluoromethoxylated Compounds via Visible Light Photoredox Catalysis



Reporter: Jinglei Yang
Supervisor: Prof. Huang

Date: 04. 22. 2019

Outline

1. Introduction

2. Synthesis of Trifluoromethoxylated Compounds

 2.1 Anionic Trifluoromethylation

 2.2 Radical Trifluoromethylation

3. Synthesis of Difluoromethoxylated Compounds

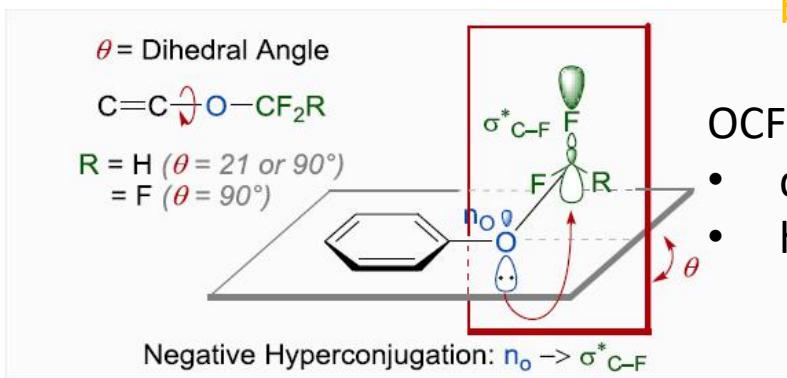
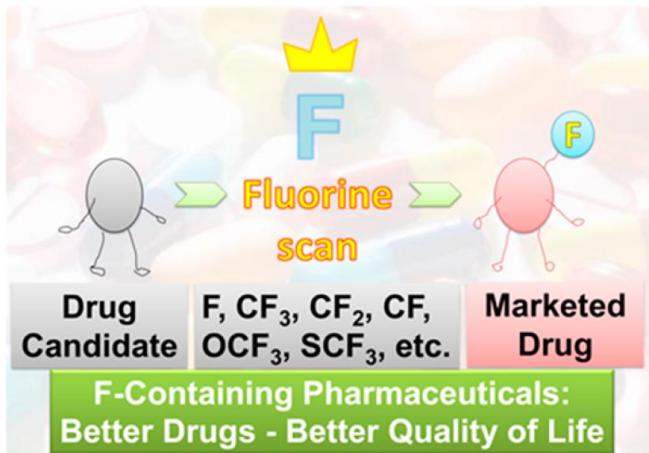
 3.1 Photocatalytic Difluorocarbene Protocol

 3.2 Radical Difluoromethylation

4. Conclusion

1. Introduction

Unique properties of OCF_3 and OCF_2H :



OCF_3 :

- high electronegativity: 3.7 (Pauling's electronegativity scale) → improved molecular metabolic stability
- excellent lipophilicity ($\pi_x = +1.04$) → enhanced membrane permeability
- orthogonal conformation → additional binding affinity to biological targets

OCF_2H :

- dynamic lipophilicity ($\pi_x = +0.2\text{--}0.6$)
- hydrogen bond donor

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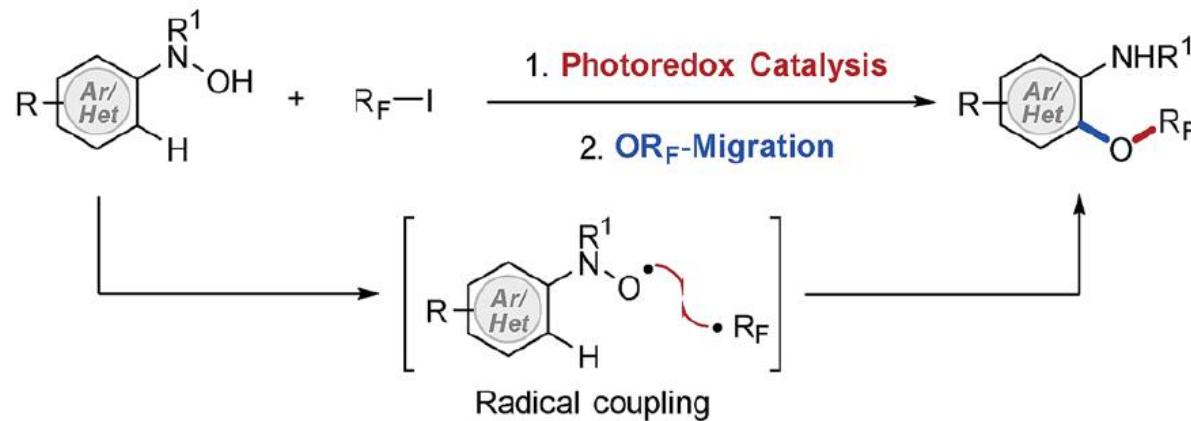
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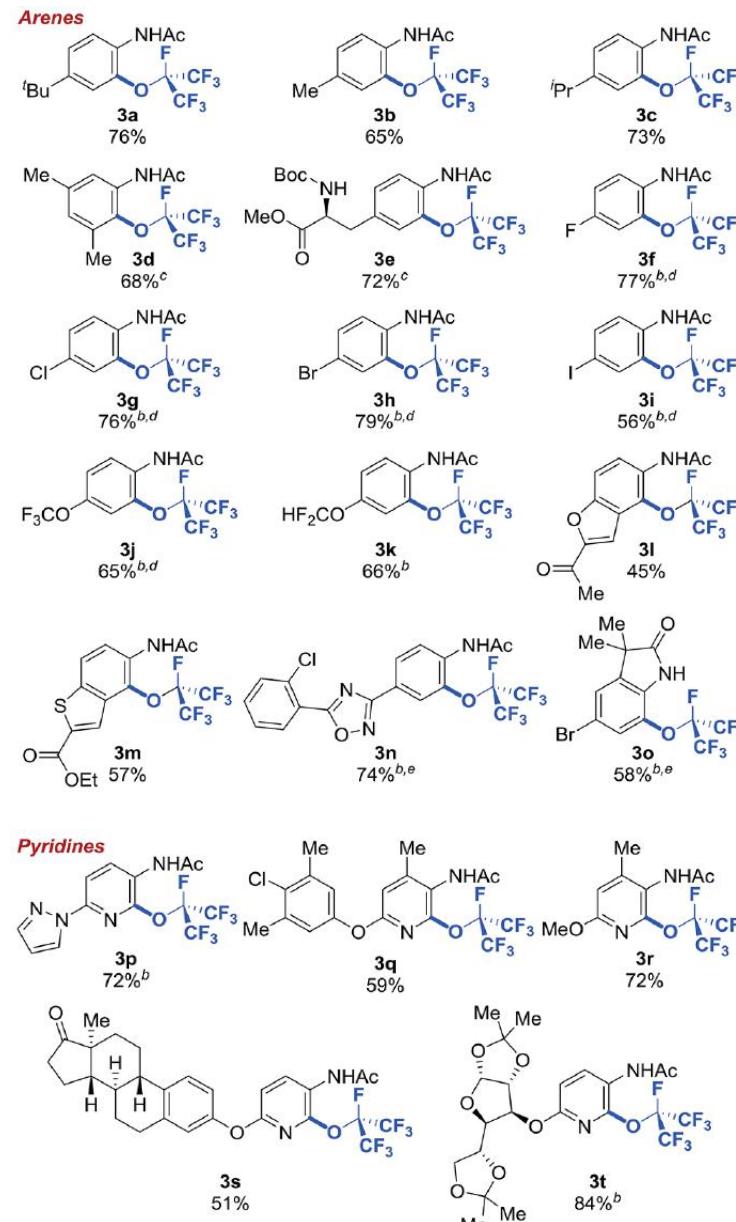
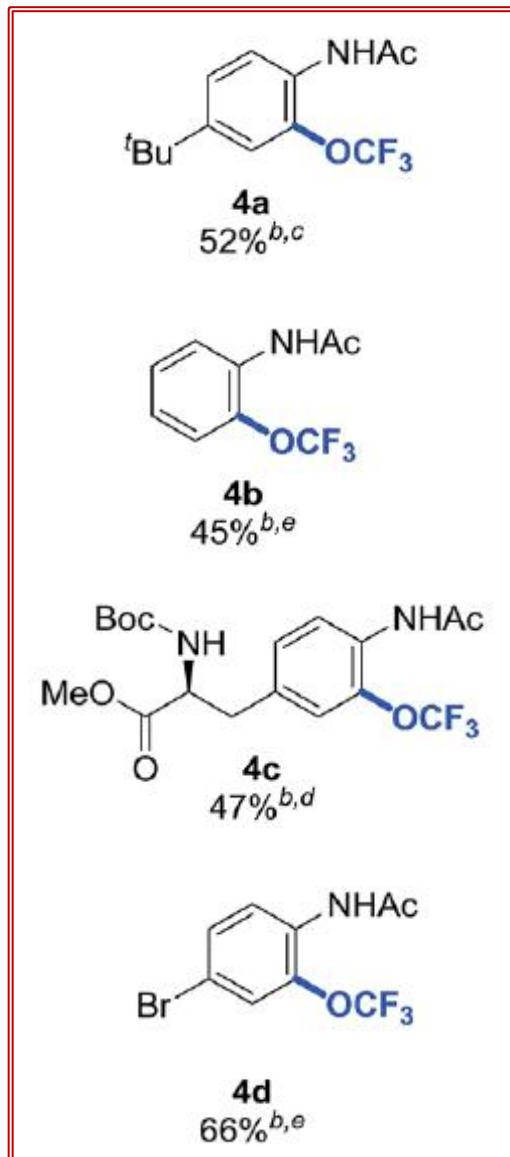
2.1 Anionic Trifluoromethoxylation



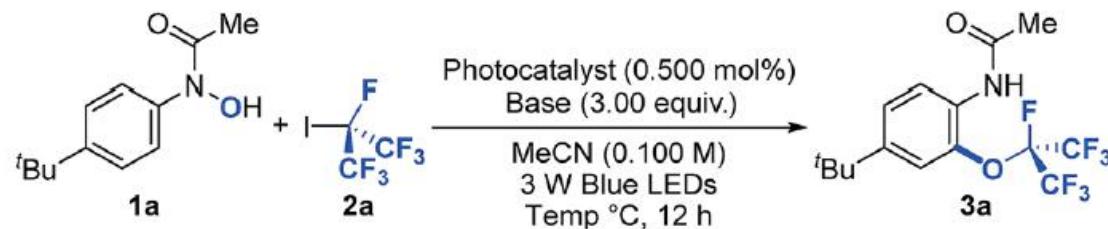
Prof. Dr. Ming-Yu Ngai

- Born in Fuching, China.
- B.Sc. degree from the University of Hong Kong in 2003
- Ph.D. degree from the University of Texas at Austin (2004–2008).
- Croucher postdoctoral fellow (2009–2011) at Stanford University apostdoctoral associate at Harvard University (2011–2013).
- In 2013, appointed as an Assistant Professor in the Department of Chemistry at Stony Brook University.
- His research focuses on photoredox catalysis and creating new functional molecules with a specific interest in fluorinated compounds and exploring their properties as well as applications in the fields of chemistry, biology, and materials science.

2.1 Anionic Trifluoromethoxylation



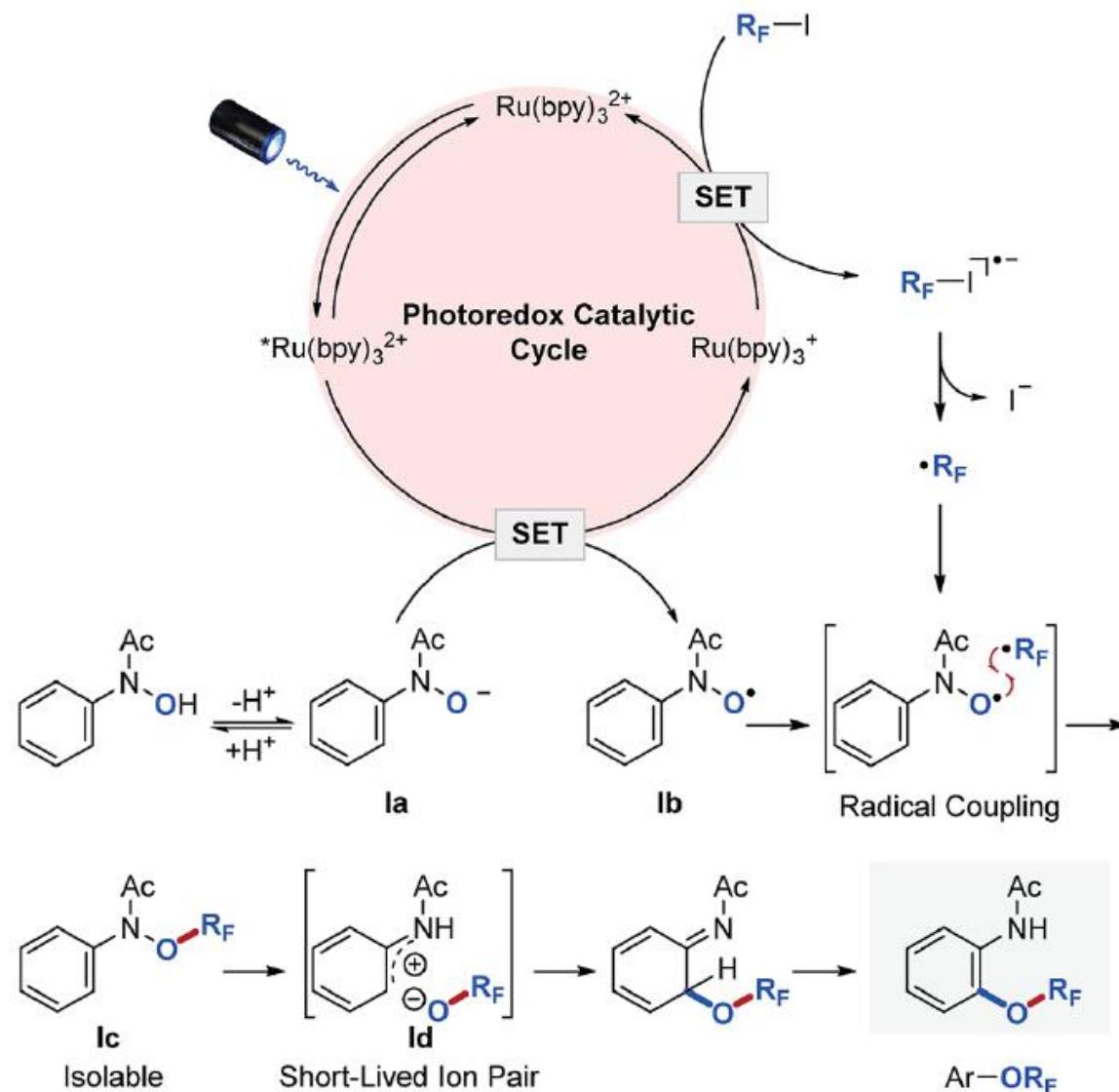
2.1 Anionic Trifluoromethoxylation



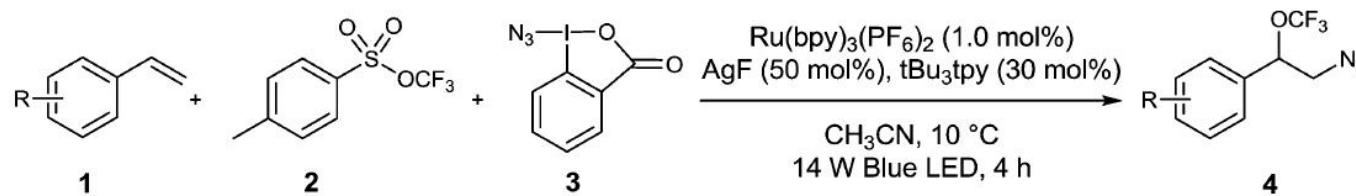
Entry	Photocatalyst	Base	Temp (°C)	Yield ^a (%)
1	Ru(bpy) ₃ (PF ₆) ₂	K ₂ CO ₃	23	38
2	Rhodamine 6-G	K ₂ CO ₃	23	<5
3	<i>fac</i> -Ir(ppy) ₃	K ₂ CO ₃	23	17
4	Ru(bpy) ₃ (PF ₆) ₂	K ₃ PO ₄	23	12
5	Ru(bpy) ₃ (PF ₆) ₂	2,6-Lutidine	23	12
6	Ru(bpy) ₃ (PF ₆) ₂	K ₂ CO ₃	0	80
7	—	K ₂ CO ₃	0	<5
8	Ru(bpy) ₃ (PF ₆) ₂	—	0	<5
9	Ru(bpy) ₃ (PF ₆) ₂	K ₂ CO ₃	0	<5 ^b
10	Ru(bpy) ₃ (PF ₆) ₂	K ₂ CO ₃	0	<5 ^c

^a Reaction conditions: **1a** (1.00 equiv.), **2a** (8.00 equiv.), photocatalyst (0.500 mol%) and base (3.00 equiv.) in MeCN (0.100 M) for 12 h. Yields were determined by ¹⁹F NMR using trifluorotoluene as the internal standard. ^b No light. ^c Exposed to air.

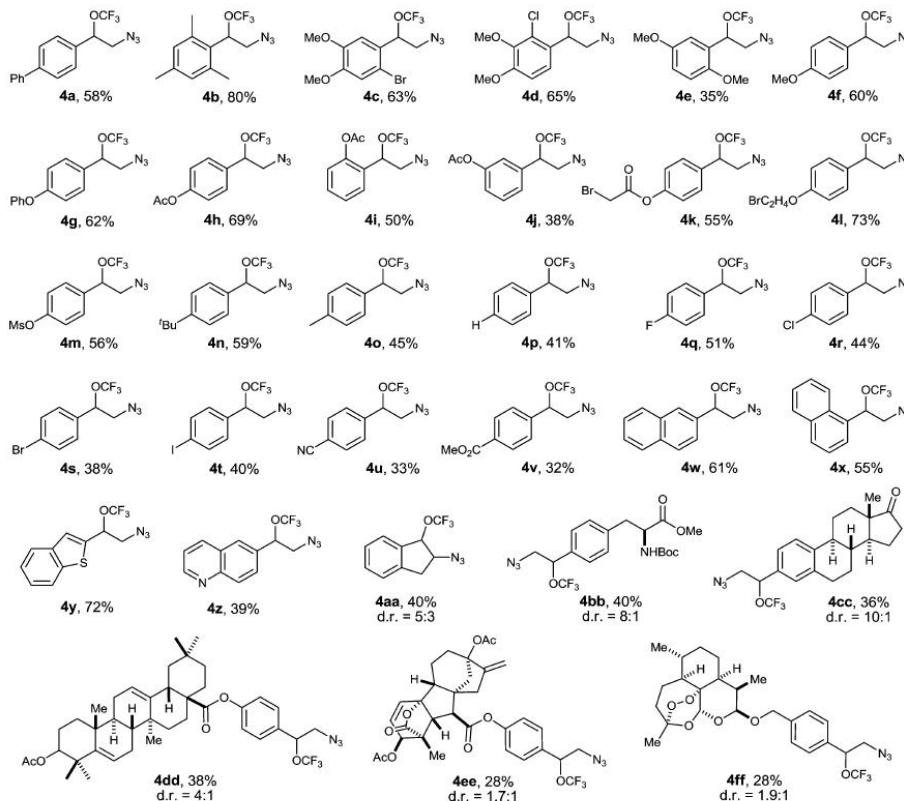
2.1 Anionic Trifluoromethoxylation



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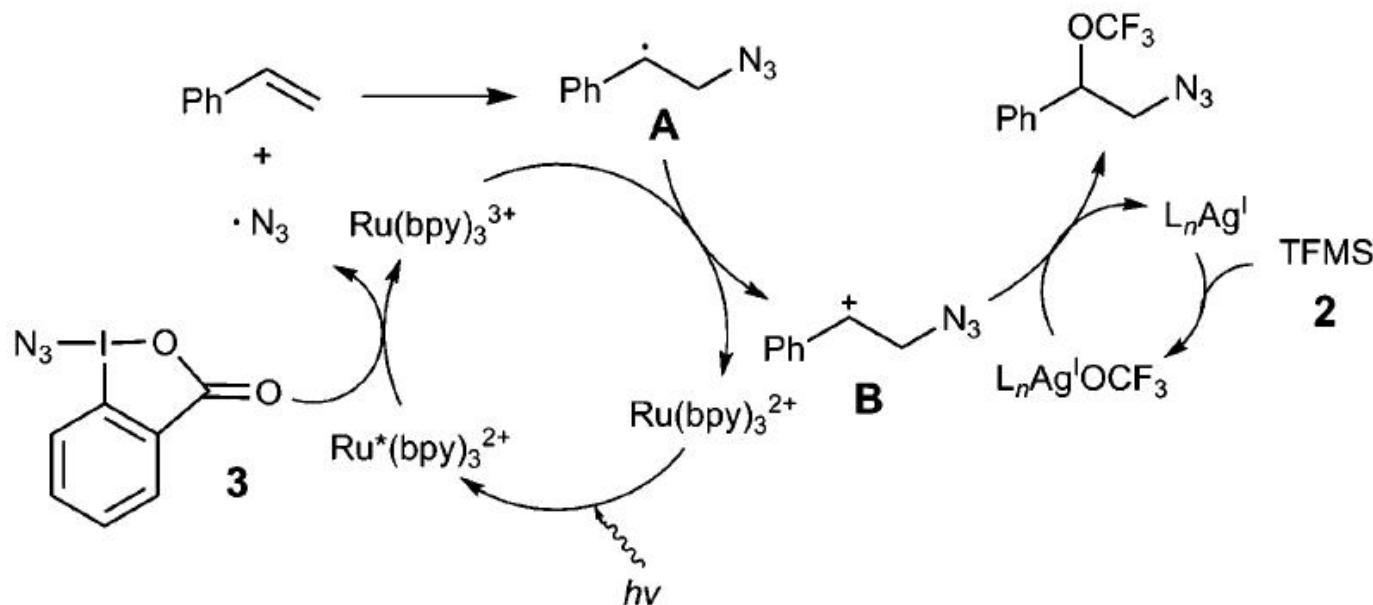
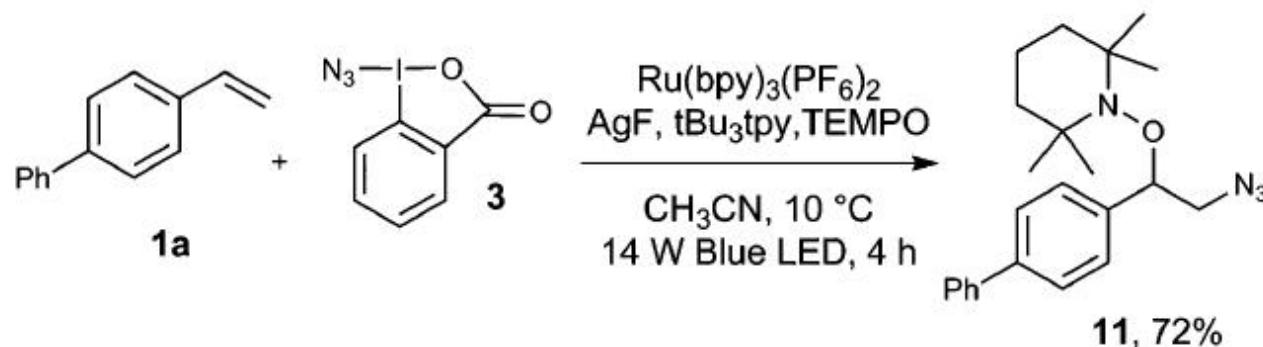


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^a Reaction conditions: 1 (1.0 equiv.), 2 (2.0 equiv.), 3 (5.0 equiv.), [Ru(bpy)₃](PF₆)₂ (1 mol%), AgF (50 mol%), tBu₃tpy (30 mol%), CH₃CN, N₂ atmosphere, 10 °C, 4 h, 14 W blue LED. Yields of isolated products are given. tBu₃tpy = 4,4',4"-tri-*tert*-butyl-2,2':6'2"-terpyridine.

2.1 Anionic Trifluoromethoxylation



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2.2 Radical Trifluoromethoxylation

Recent developments in direct trifluoromethylation reagents

Reactive Gases

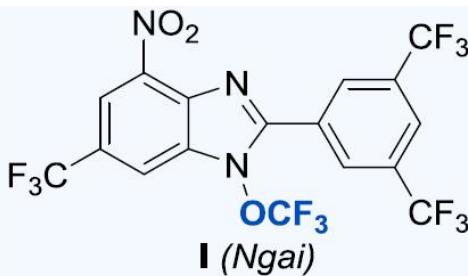


2010

Limitations :

- Use of difficult-to-handle, highly reactive and toxic gaseous reagents
- requirement of specialized apparatus

2012



2018



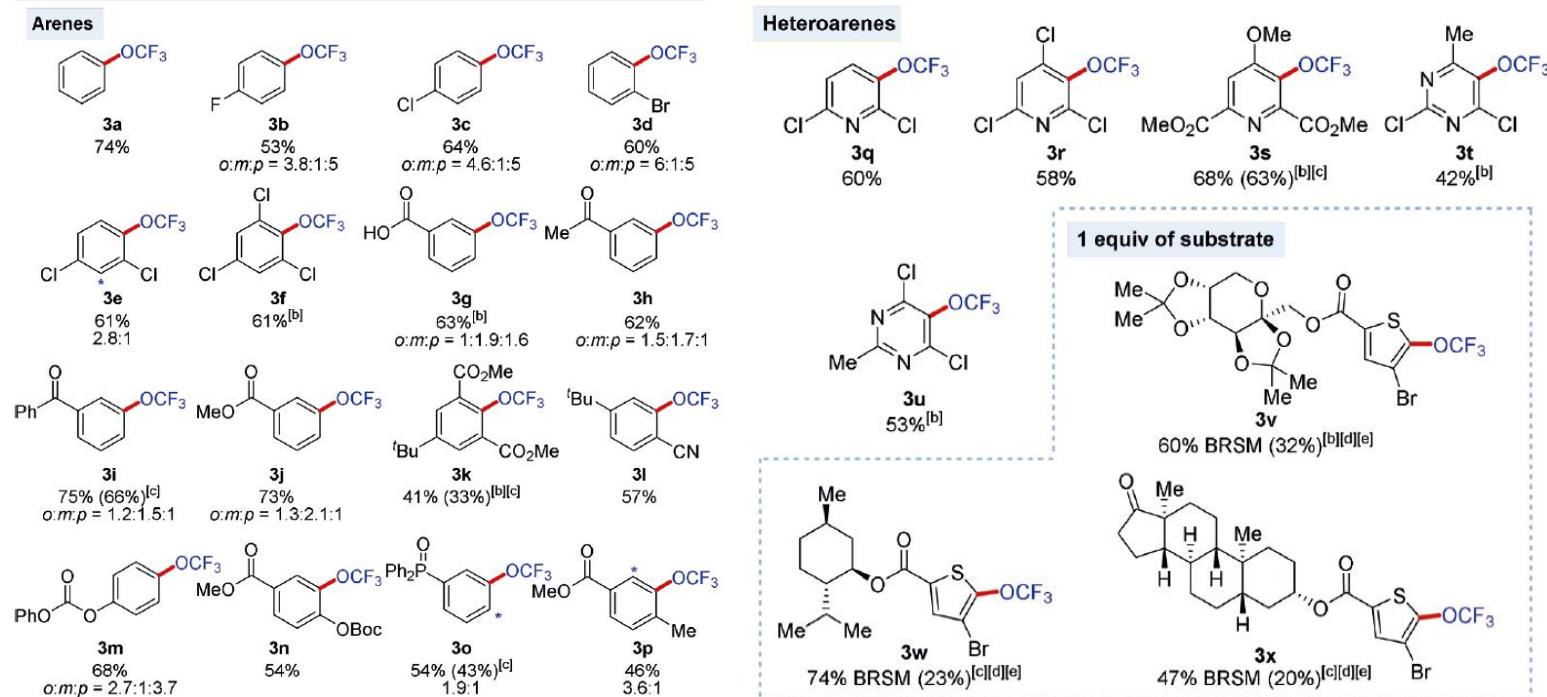
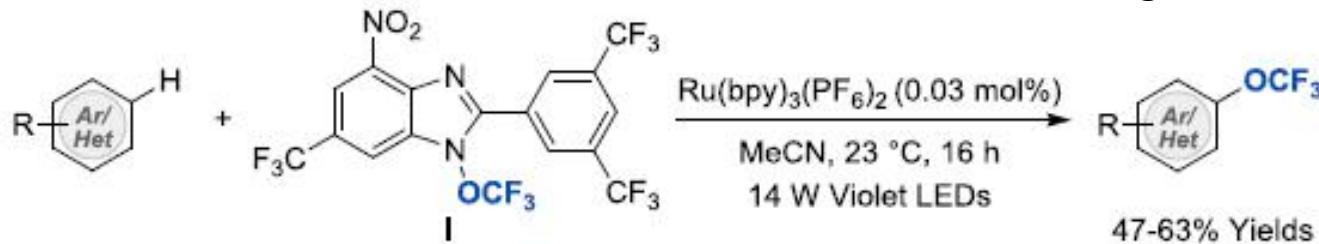
- Easy to handle
- Bench stable
- Room temperature

Bench Stable Solids



2.2 Radical Trifluoromethylation

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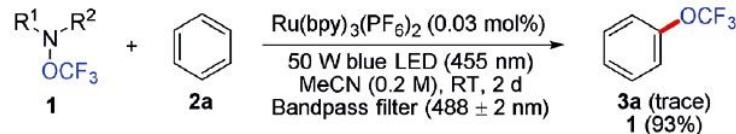


2.2 Radical Trifluoromethylation

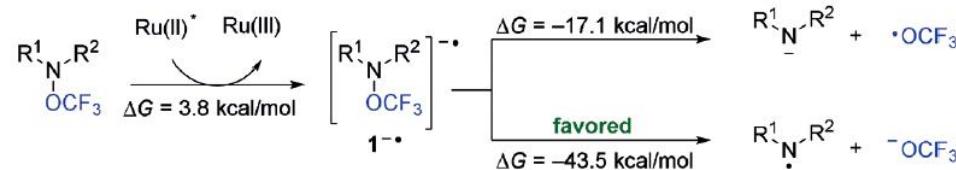
Mechanistic Study

(a) Probing the pathway for the formation of the $\bullet\text{OCF}_3$ radical

(i) Trifluoromethylation reaction using a band pass filter



(ii) Energy of mesolytic cleavage of the N-OCF_3 bond from $1^{-\bullet}$

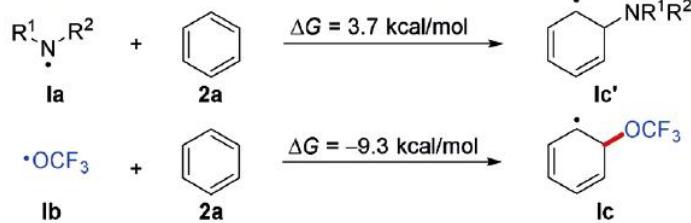


Implications: ■ Photoexcitation of 1 is needed

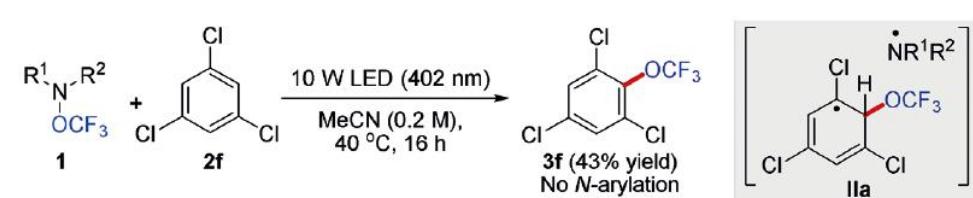
■ Formation of the $\bullet\text{OCF}_3$ via SET between $^*\text{Ru(II)}$ and 1 is unlikely

(b) Examination of the relative reactivity of the $\bullet\text{NR}^1\text{R}^2$ and $\bullet\text{OCF}_3$ radicals

(i) Energy of the addition of the $\bullet\text{NR}^1\text{R}^2$ and $\bullet\text{OCF}_3$ to benzene



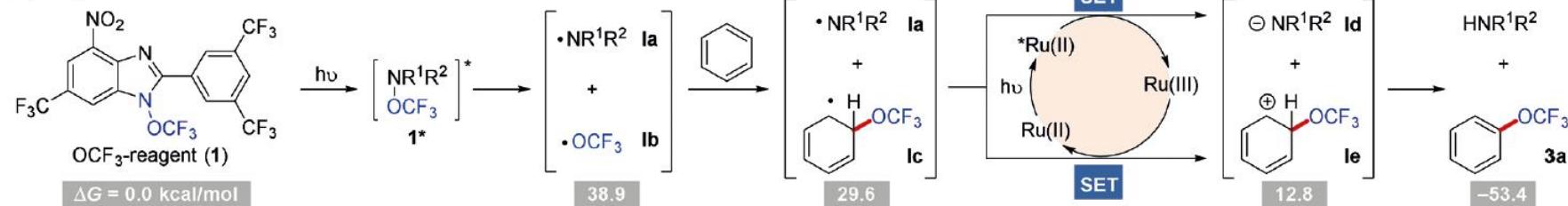
(ii) Trifluoromethylation reaction using 1,3,5-trichlorobenzene without $\text{Ru(bpy)}_3(\text{PF}_6)_2$



Implications: ■ $\bullet\text{OCF}_3$ is more reactive than $\bullet\text{NR}^1\text{R}^2$ and adds to the arene first

■ Formation of 3f should proceed via intermediate IIa

(c) Proposed reaction mechanism



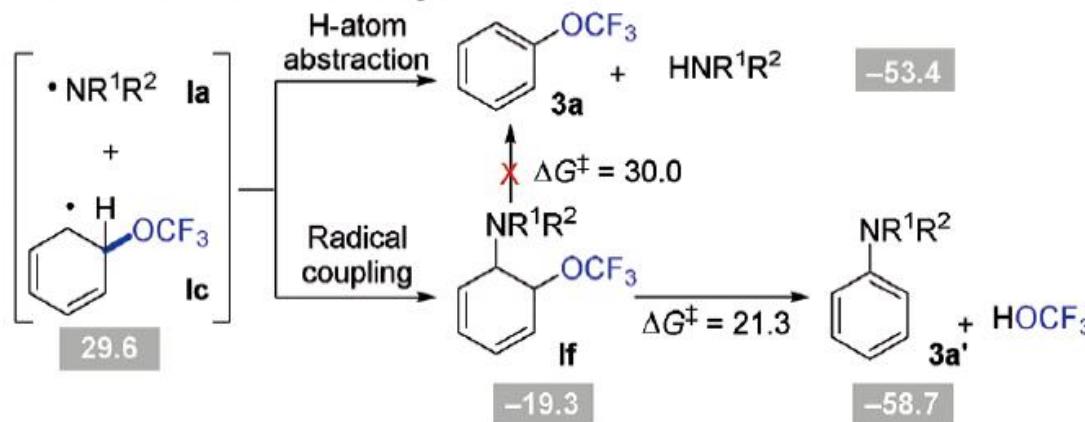
2.2 Radical Trifluoromethoxylation

Mechanistic Study

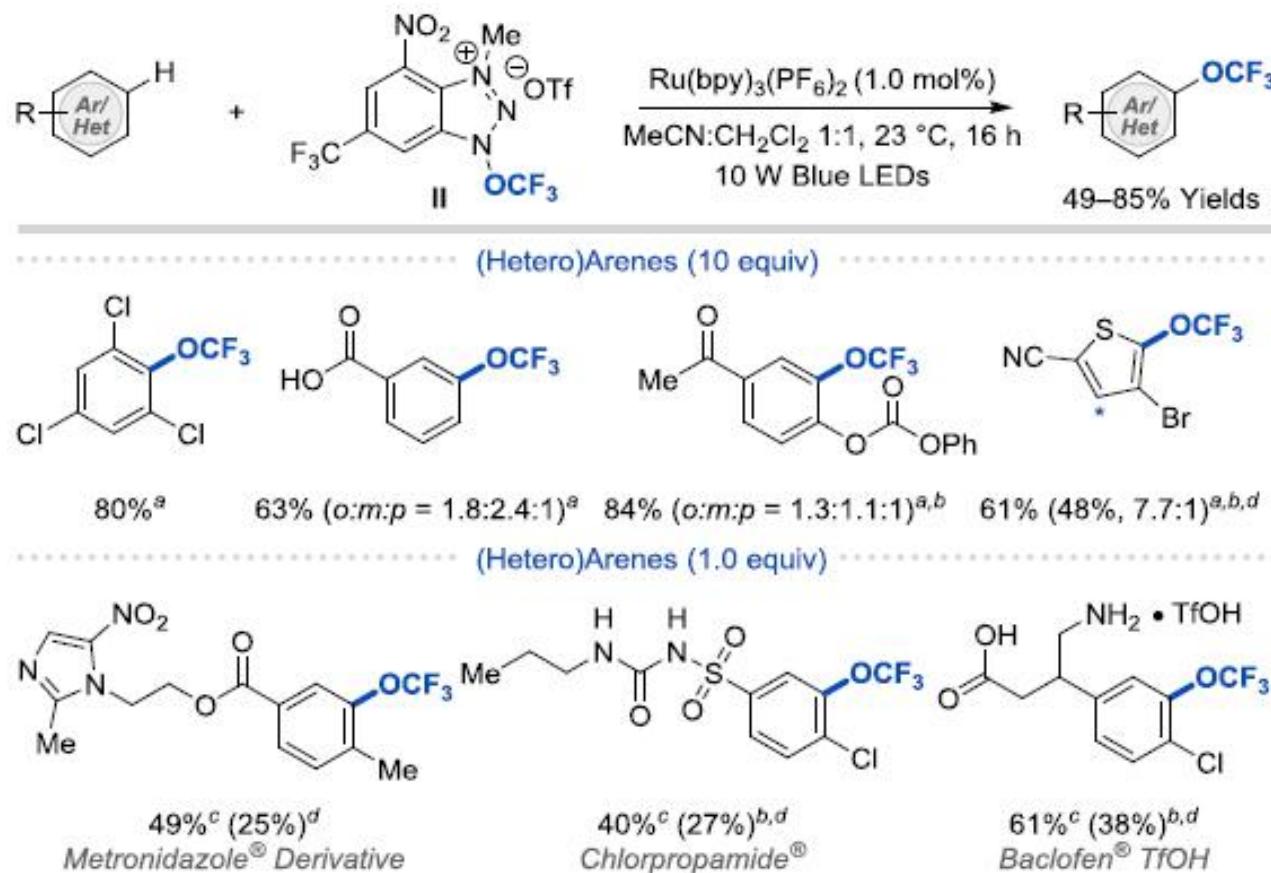
Table 1: Selected optimization experiments.^[a]

		catalyst MeCN (0.2 M)	10 W LED (402 nm) RT, 16 h	2a	3a	R ₁ -N(R ₂)OCF ₃	R ₁ -N(R ₂)Ph	3a'
Entry	Catalyst					Yield ^[b]		Selectivity
						3a	3a'	3a:3a'
1	-					20%	38%	1:2
2	Cu(OTf) ₂ (20 mol%)					61%	20%	3:1
3	Cu(MeCN) ₄ PF ₆ (20 mol%)					64%	10%	6:1
4	Ru(bpy) ₃ (PF ₆) ₂ (0.03 mol%)					70%	3%	23:1

without a redox-active catalyst

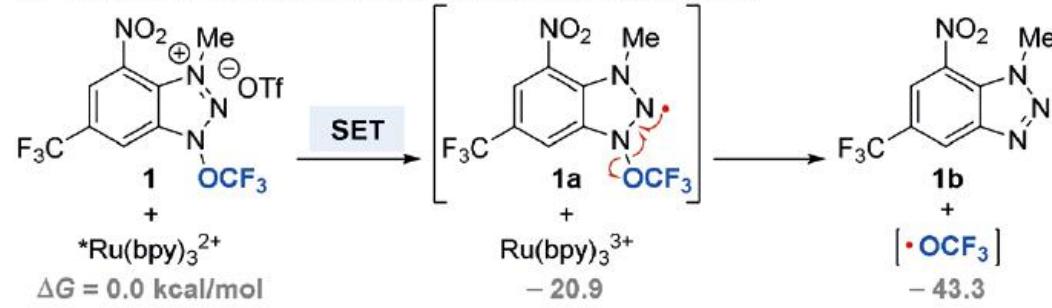


2.2 Radical Trifluoromethylation

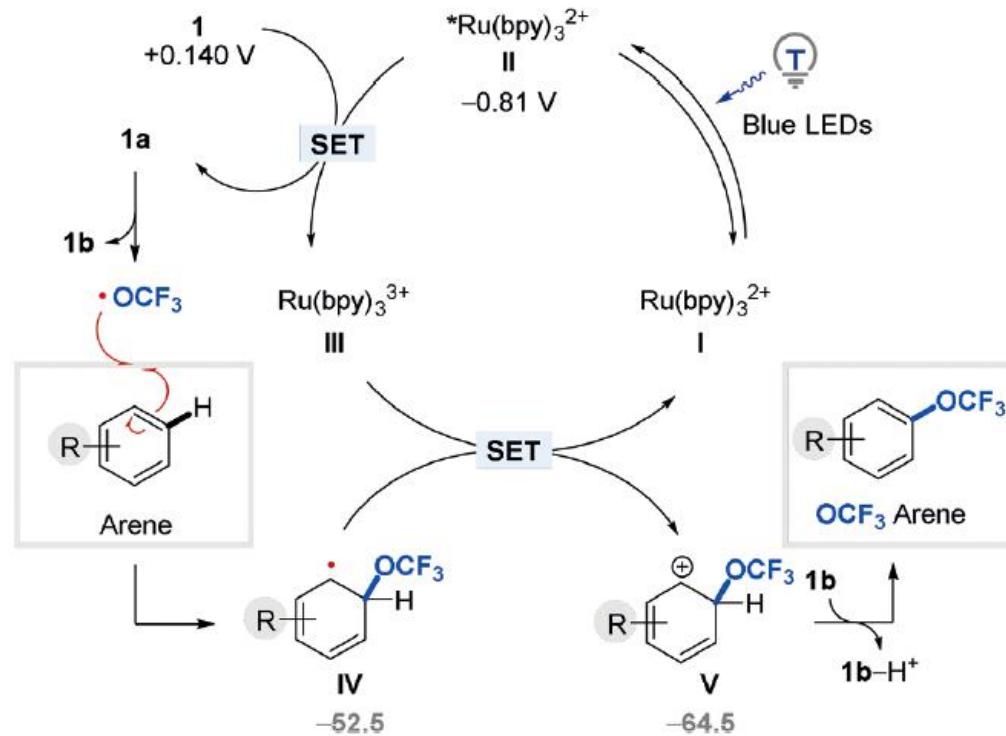


2.2 Radical Trifluoromethoxylation

a. Energies of SET and the formation of the OCF₃ radical

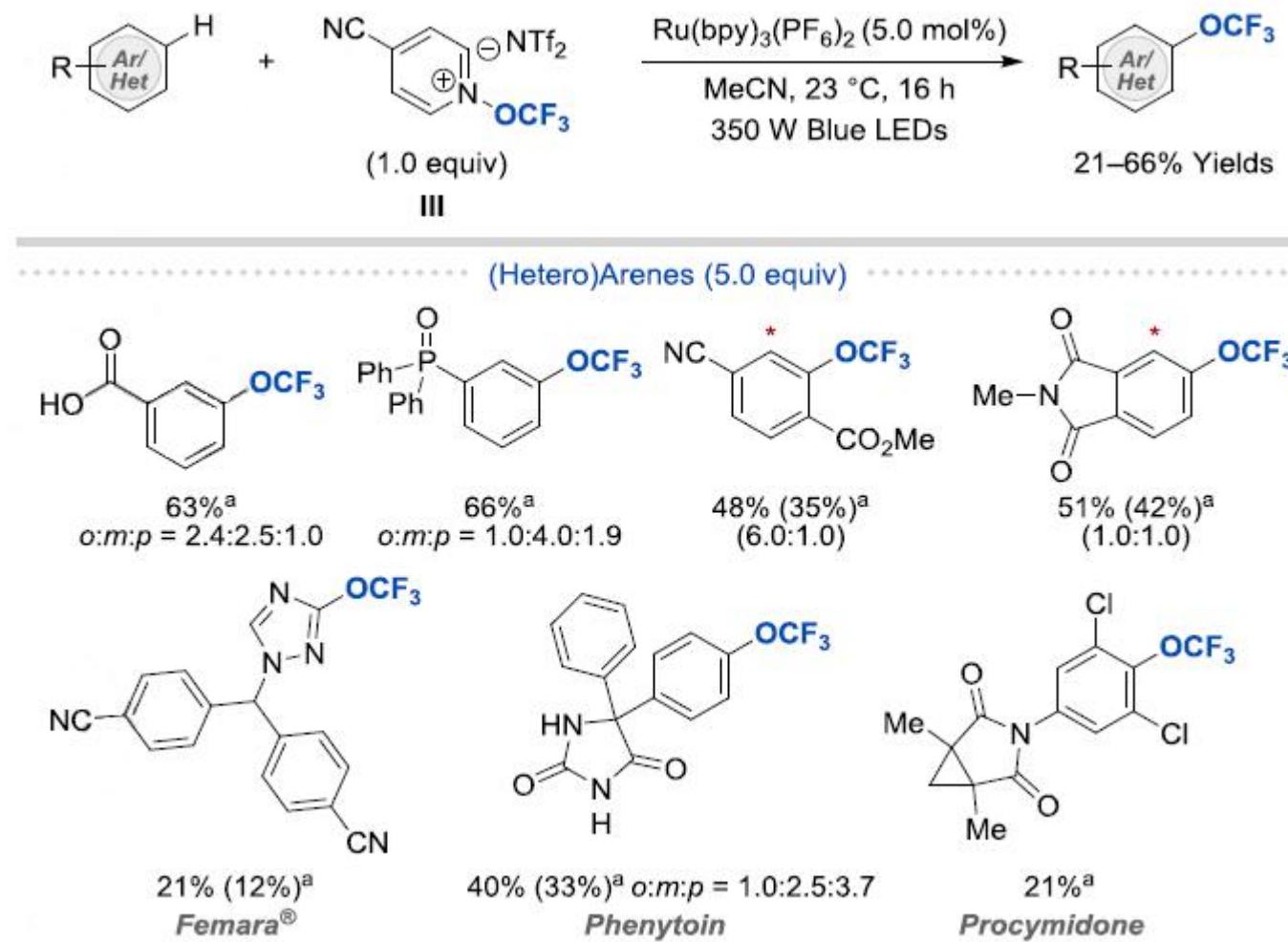


b. Mechanism hypothesis for the trifluoromethoxylation of arenes



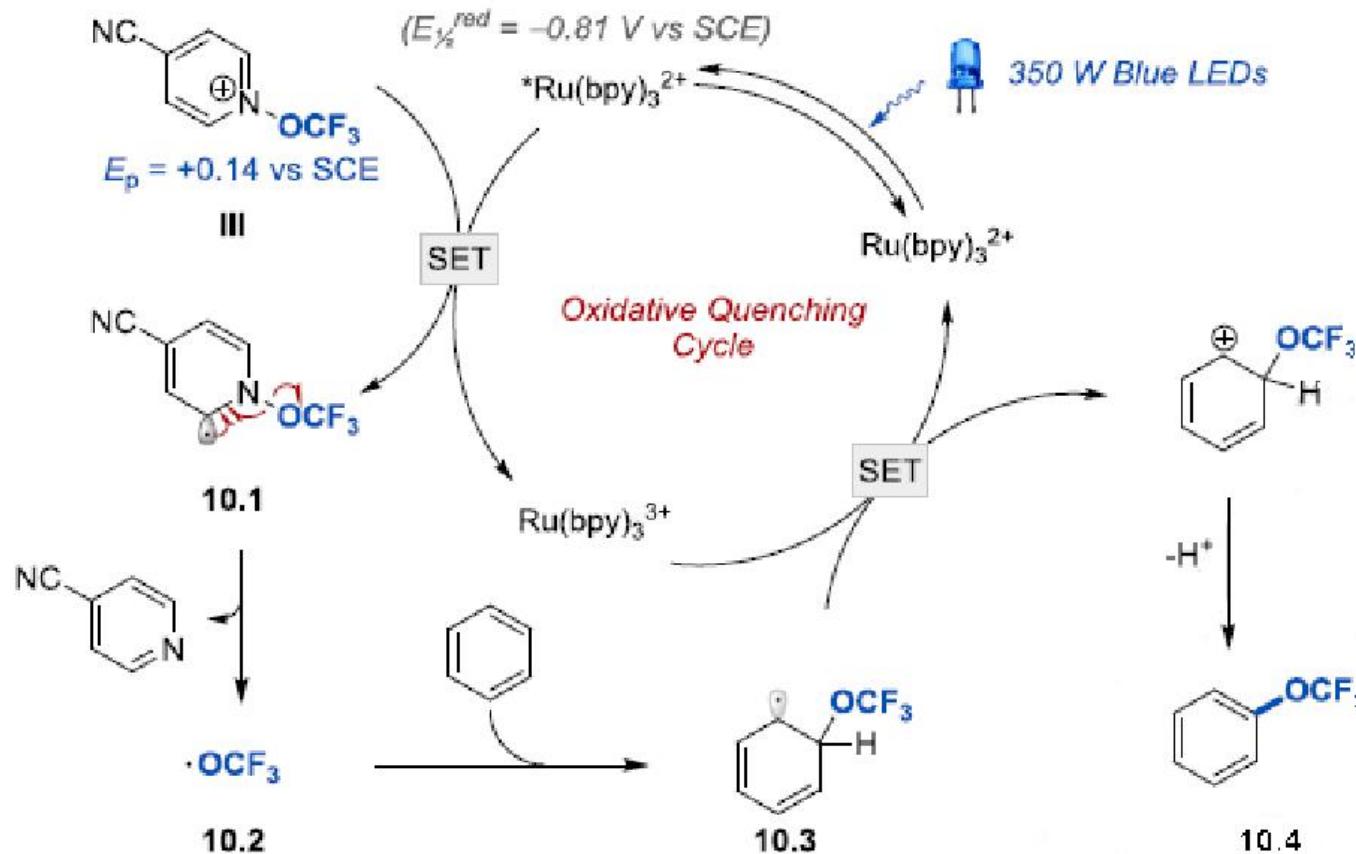
2.2 Radical Trifluoromethoxylation

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2.2 Radical Trifluoromethylation

Proposed Reaction Mechanism



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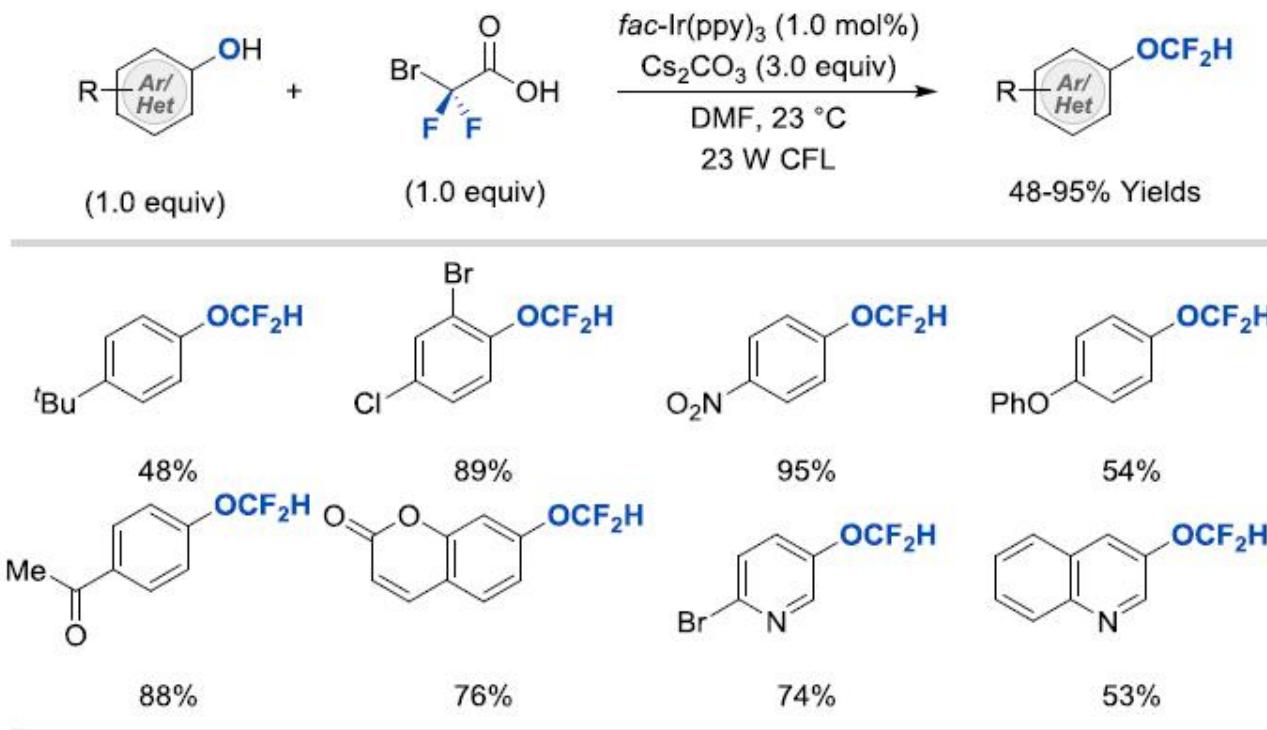
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4. Conclusion

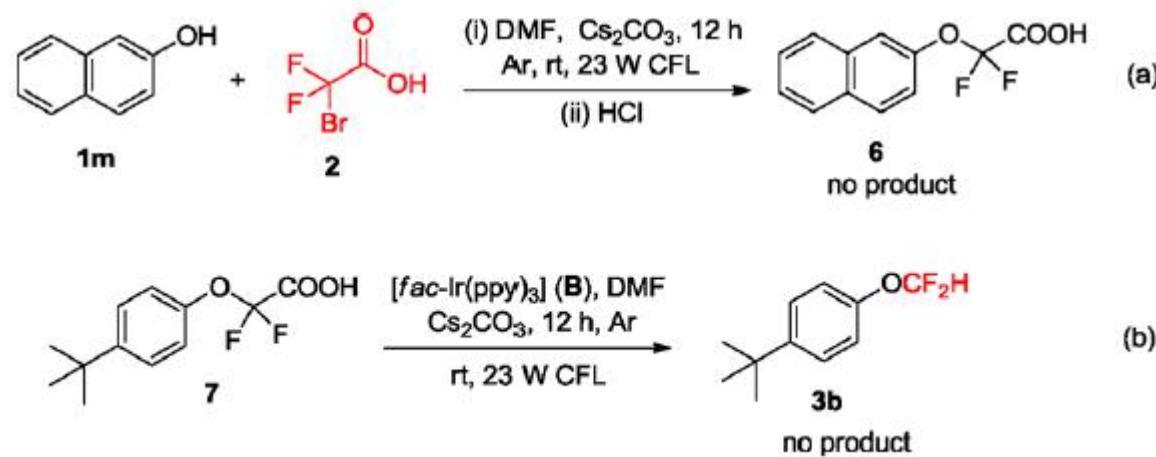
3.1 Photocatalytic Difluorocarbene Protocol

Fu and co-workers



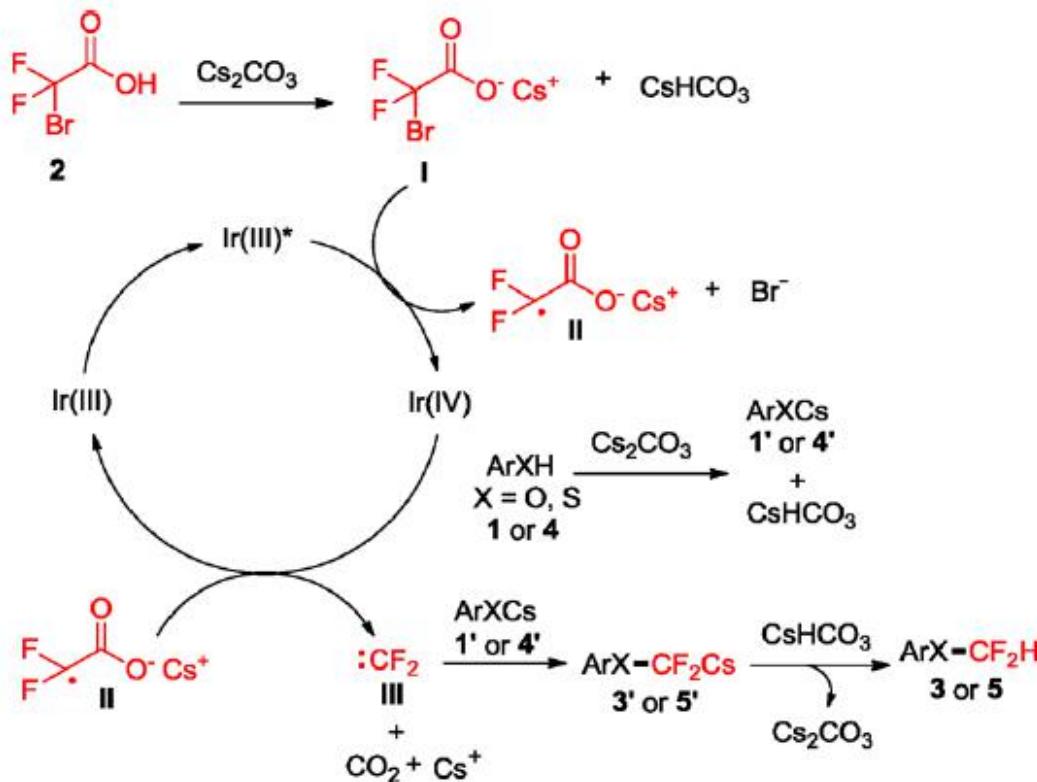
3.1 Photocatalytic Difluorocarbene Protocol

Scheme 2. (a) Treatment of 2-Naphthol (**1m**) with Difluorobromoacetic Acid (**2**) in the Absence of Photocatalyst. (b) Treatment of Compound **7** under the Standard Conditions



3.1 Photocatalytic Difluorocarbene Protocol

Scheme 3. Plausible Mechanism on the Visible-Light Photoredox Difluoromethylation



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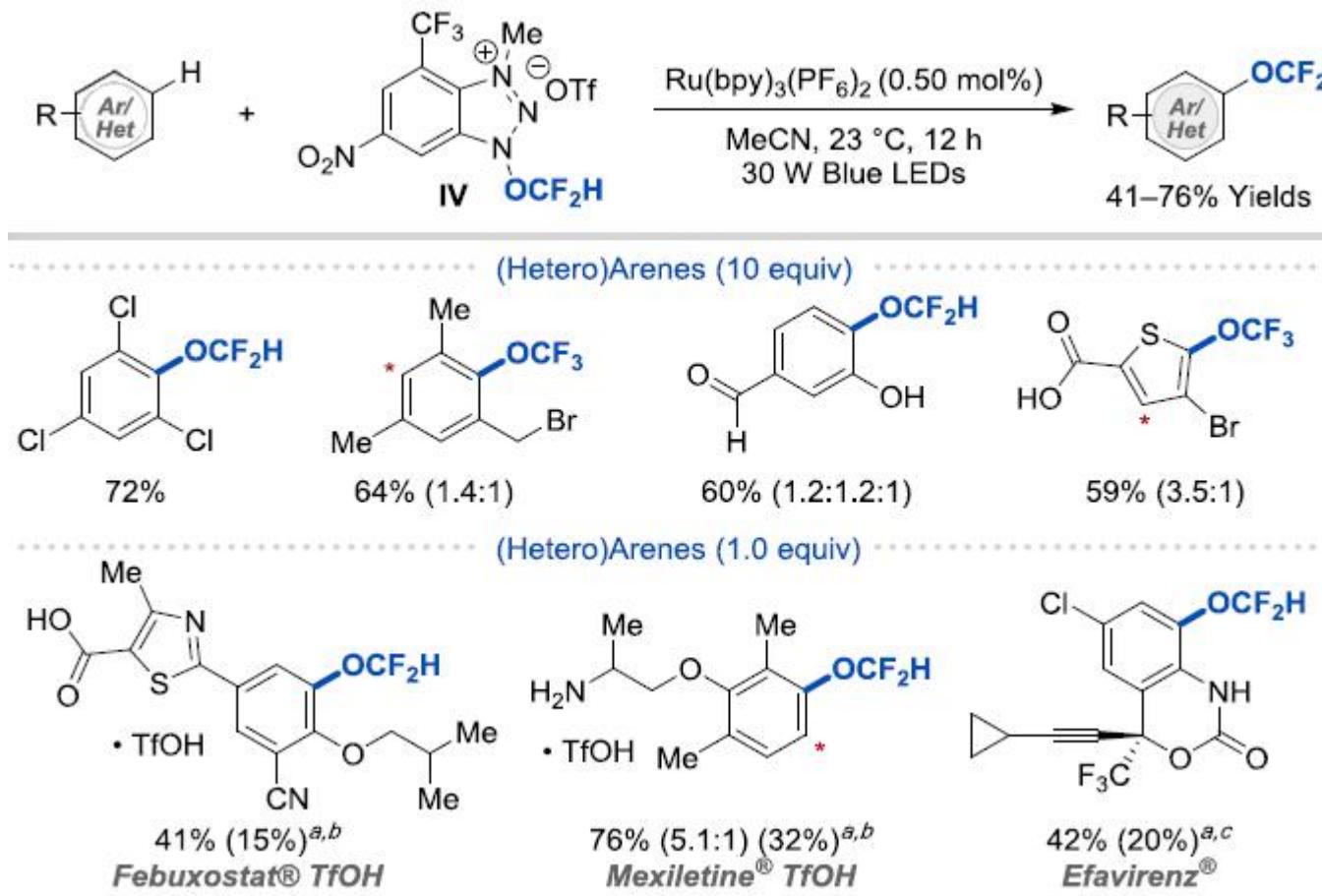
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3.2 Radical Difluoromethoxylation

Ngai and coworkers

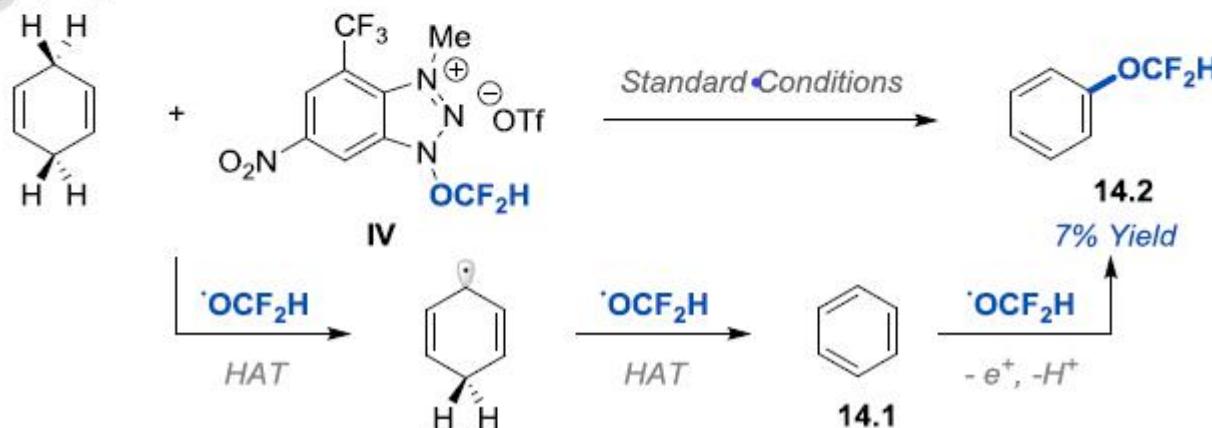


3.2 Radical Difluoromethoxylation

a. Quantum Yield Determination

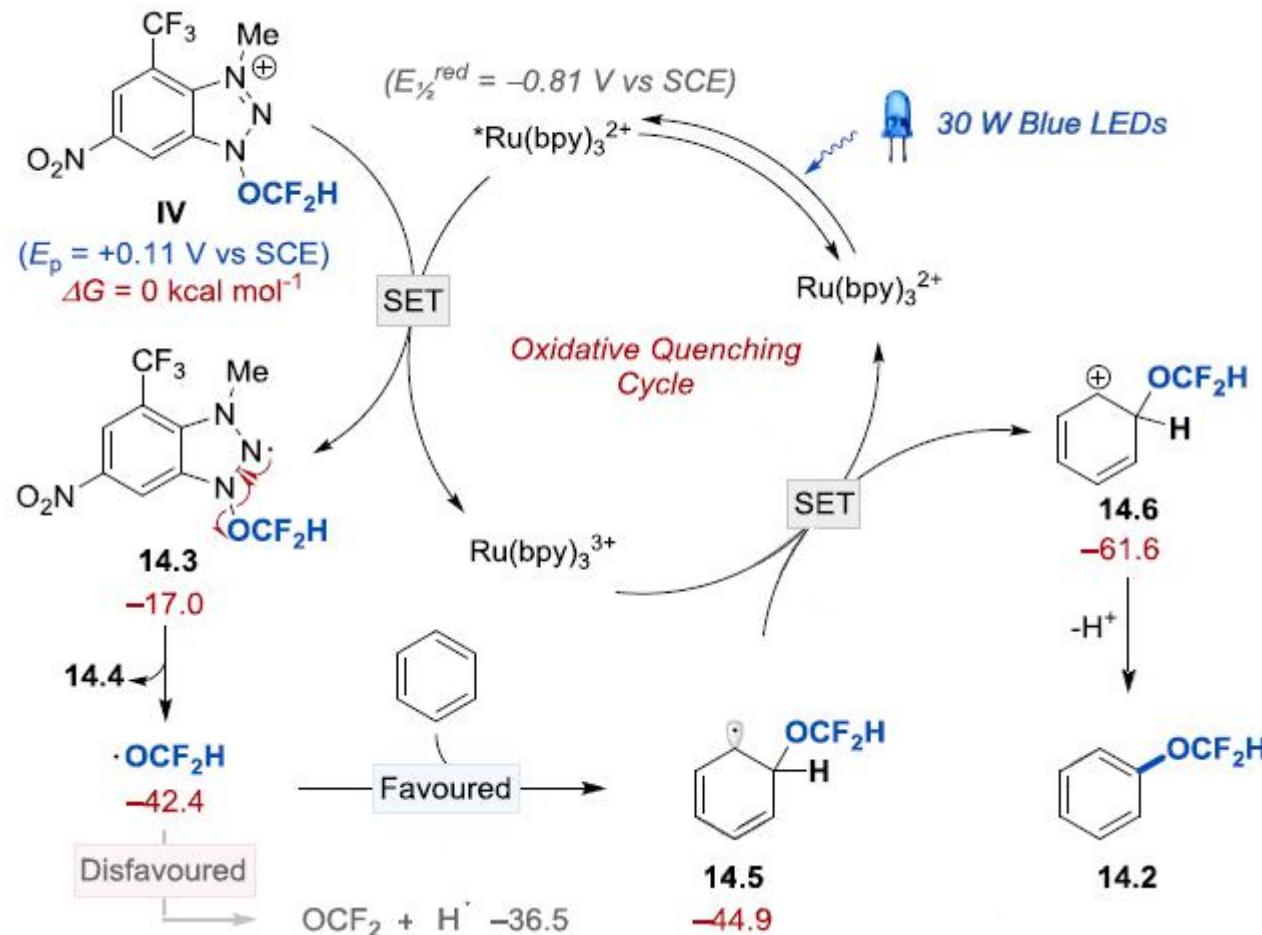


b. 1,4-Cyclohexadiene as a Radical Probe



3.2 Radical Difluoromethoxylation

c Proposed Reaction Mechanism



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4. Conclusion

1. Novel synthetic strategies
2. Moderate to good yields under mild conditions
3. Late-stage functionalization of biologically-relevant molecules
4. Generating multiple OCF₃- and OCF₂ analogues in a single operation

Thanks for Your Attention !