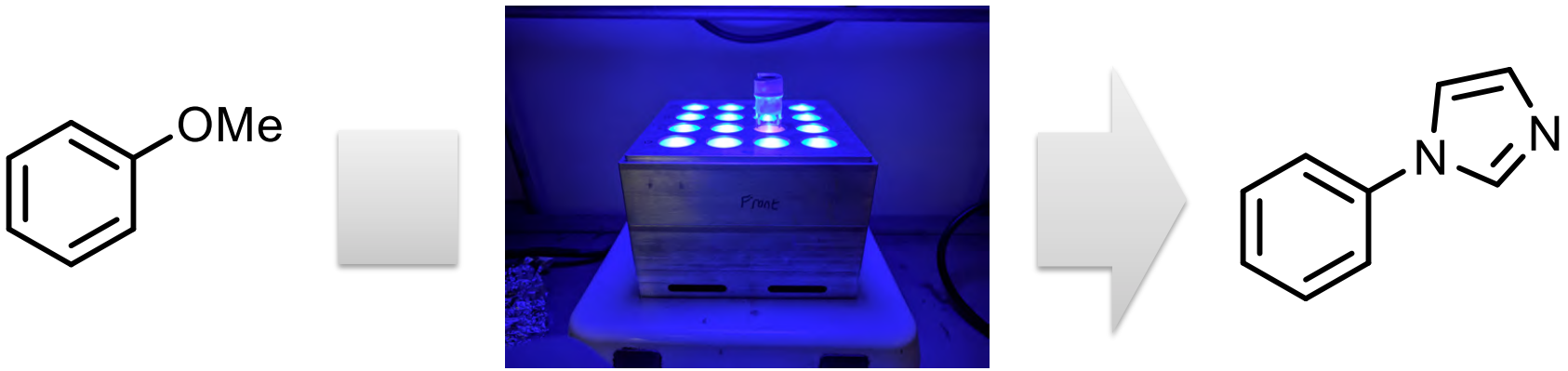
Current Literature Dec. 16 2017
Keita Takubo -Wipf group-

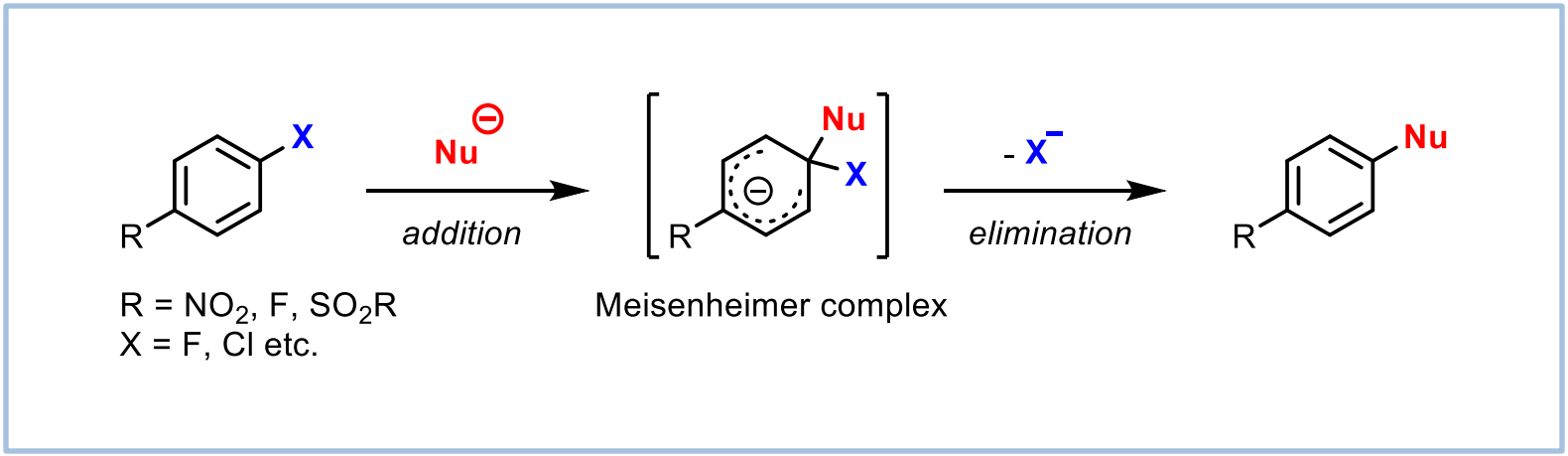
Cation Radical Accelerated Nucleophilic Aromatic Substitution via Organic Photoredox Catalysis

Nicholas E. S. Tay and David A. Nicewicz*

J. Am. Chem. Soc. **2017**, *139,* 16100–16104



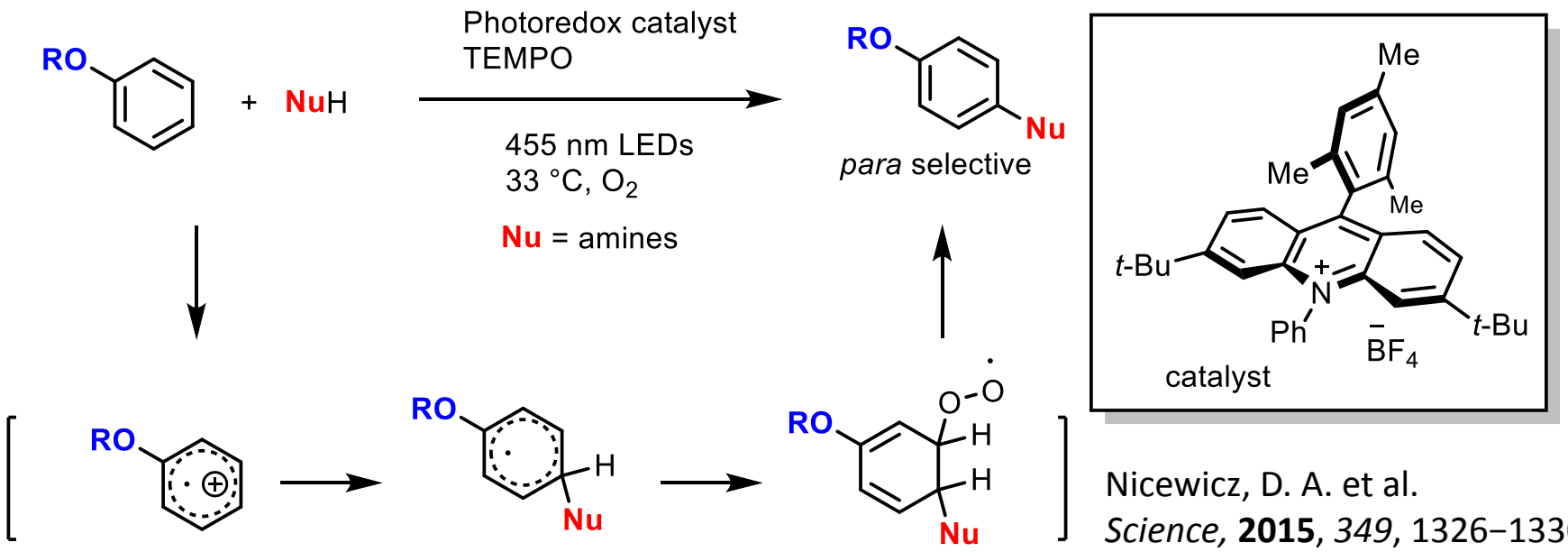
Nucleophillic Aromatic Substitution (S_NAr)



S_NAr requires **electron-withdrawing groups**

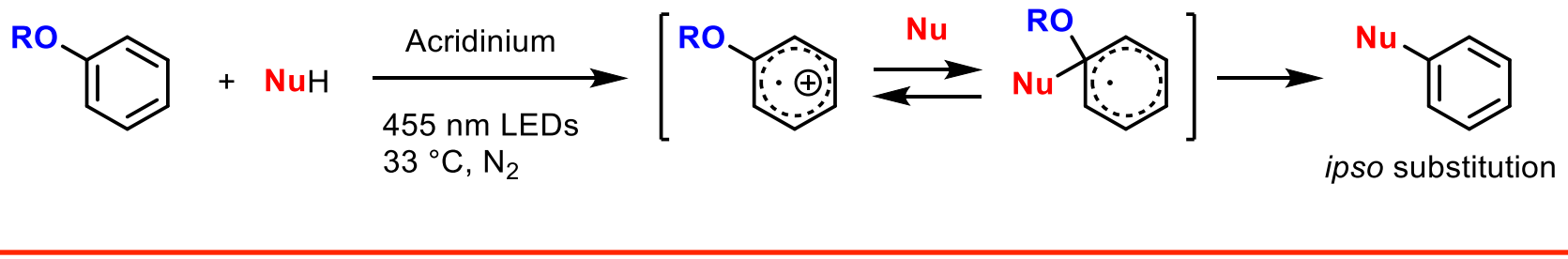
at either the ***ortho*** or ***para*** positions

Nicewicz group work

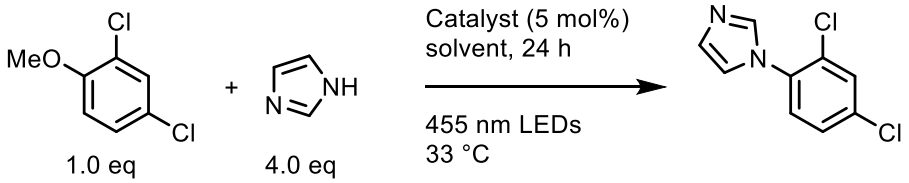


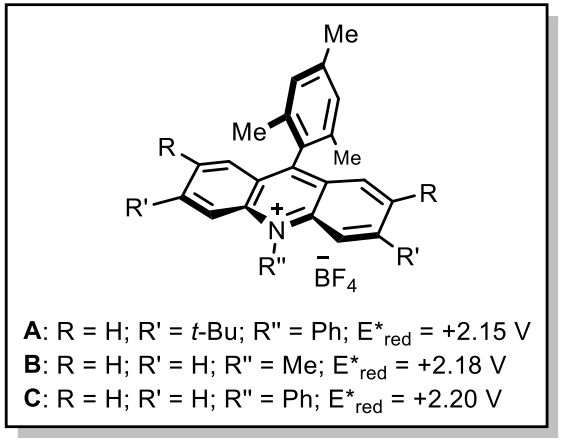
Nicewicz, D. A. et al.
Science, **2015**, *349*, 1326–1330.

In the absence of O_2



Reaction optimization

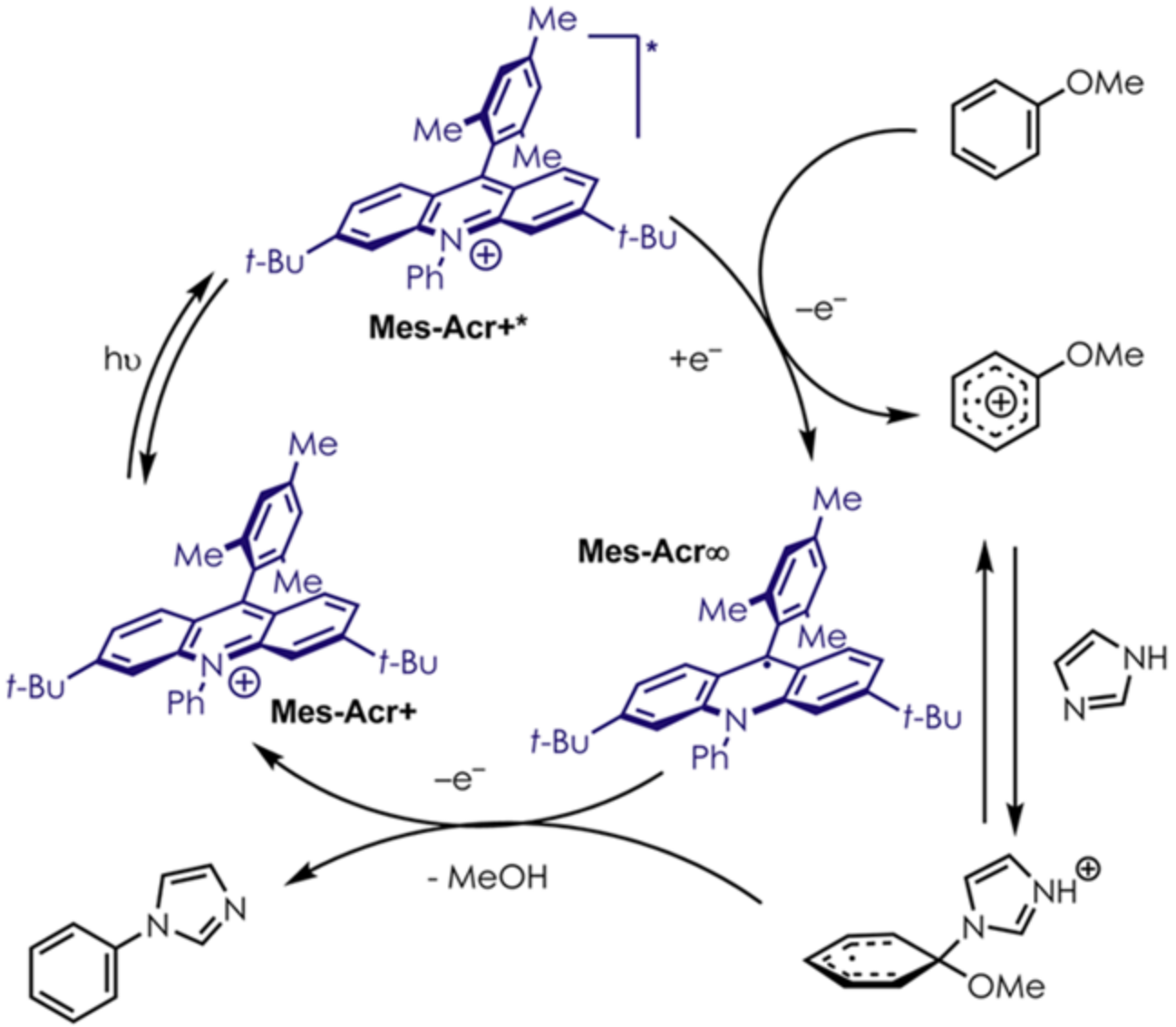




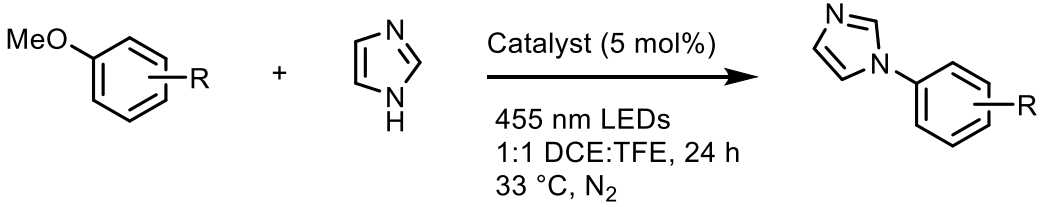
Entry	conditions	catalyst	solvent	Yield
1	As described	A	MeCN	4%
2	As described	A	TFT	6%
3	As described	A	MeOH	13%
4	As described	A	TFE	87%
5	As described	A	DCE:TFE (9:1)	23%
6	As described	A	DCE:TFE (1:1)	95%
7	No catalyst	—	DCE:TFE (1:1)	0%
8	No light	A	DCE:TFE (1:1)	0%

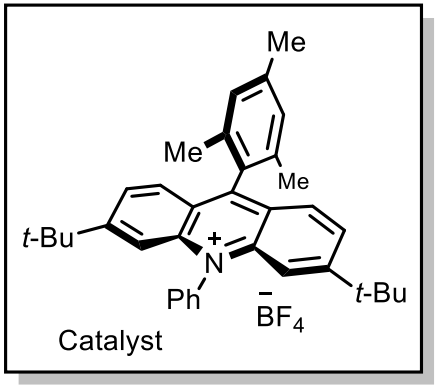
Entry	conditions	catalyst	solvent	Yield
9	O_2 atmosphere	A	DCE:TFE (1:1)	66%
10	Air atmosphere	A	DCE:TFE (1:1)	88%
11	As described	B	DCE:TFE (1:1)	27%
12	As described	C	DCE:TFE (1:1)	65%
13	20 mol% TEMPO	A	DCE:TFE (1:1)	18%
14	2.0 eq. nucleophile	A	DCE:TFE (1:1)	84%

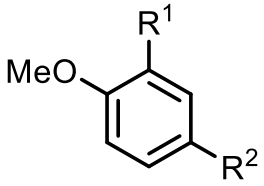
Proposed Mechanism



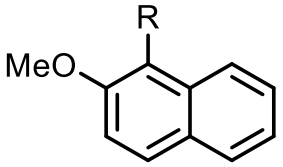
Benzenoids and naphthalenes



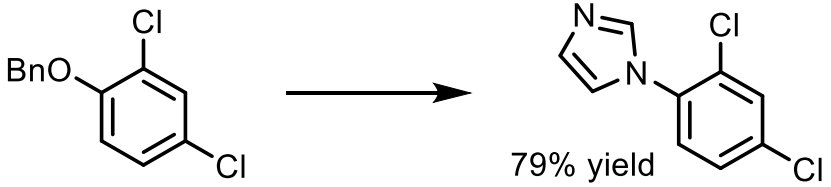




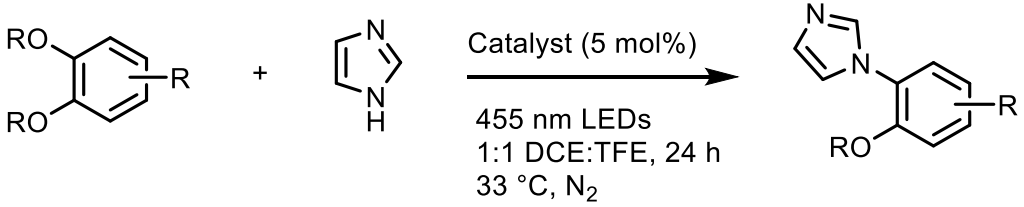
R^1	R^2	Yield
Cl	Cl	79%
Cl	Br	57%
Br	Cl	78%
Cl	F	30%
F	Cl	56%
Cl	*t*-Bu	87%
Cl	Ph	99%
H	Cl	93%
Cl	H	64%
H	H	39%

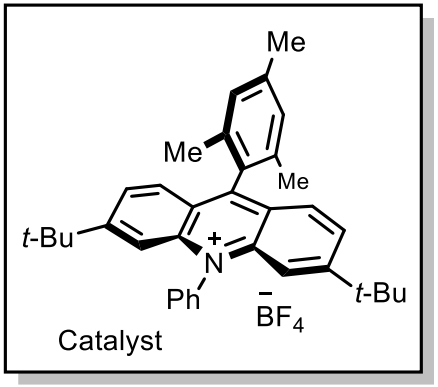


R = Cl: 52% yield
R = CN: 99% yield

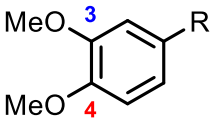


Guaiacol and veratrole derivatives

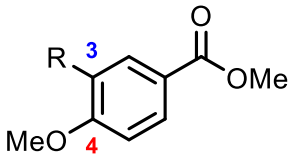




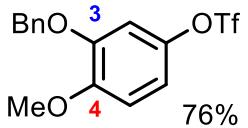
C4 selective



R	Yield (%)	C4 : C3
CO_2Me	92	7 : 1
CN	99	15 : 1
OTf	76	2 : 1
CHO	44	1 : 8

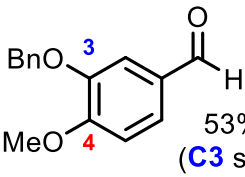


R = OBn: 80% yield (**C4** selective)
R = OTIPS: 80% yield (**C4** selective)

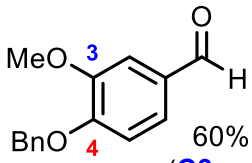


76% yield
(**C4** selective)

C3 selective

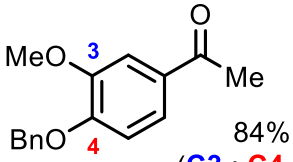


53% yield
(**C3** selective)

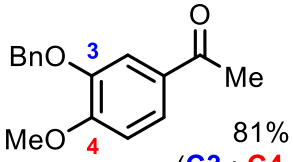


60% yield
(**C3** selective)

non selective

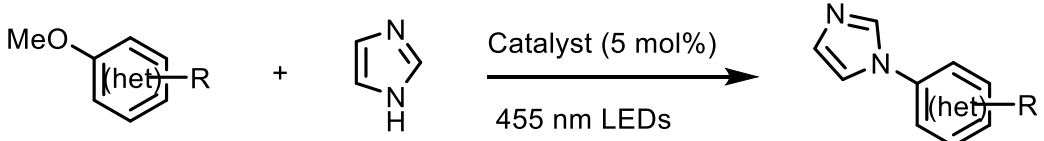


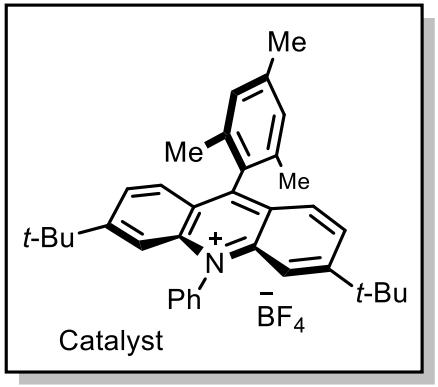
84% yield
(**C3** : **C4** = 1.1 : 1)

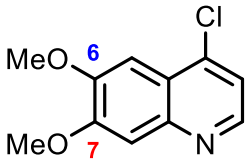


81% yield
(**C3** : **C4** = 1 : 1.1)

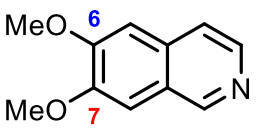
Heterocycles and complex arenes



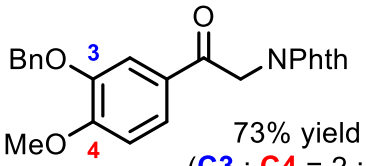




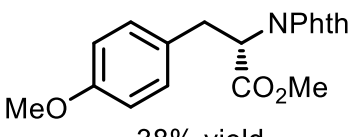
99% yield
(**C7** selective)



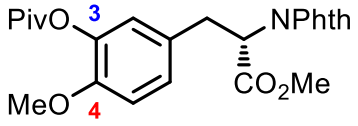
97% yield
(**C7** selective)



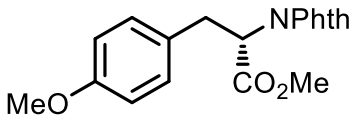
73% yield
(**C3** : **C4** = 2 : 1)



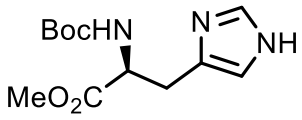
38% yield

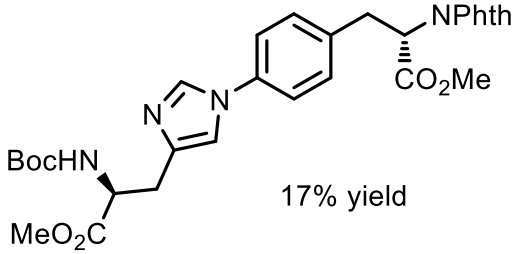


56% yield
(**C4** selective)



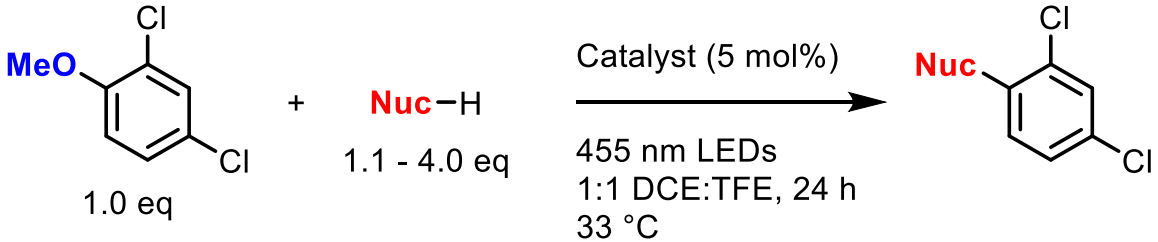
+

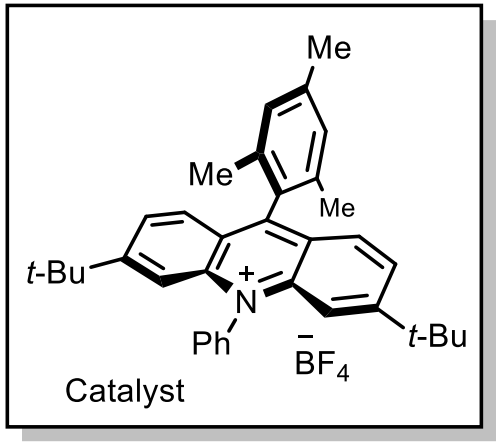




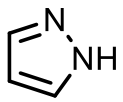
17% yield

Nucleophile Scope

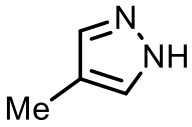




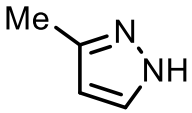
Nuc–H



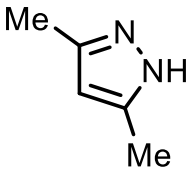
94% yield



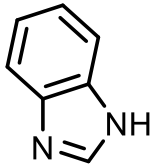
74% yield



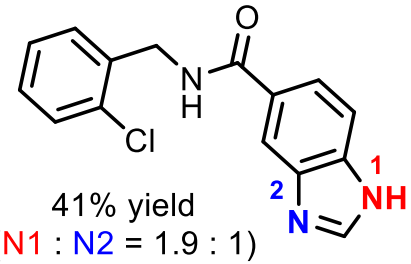
96% yield
one isomer



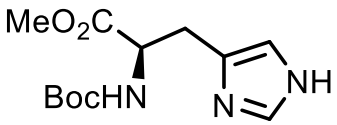
33% yield



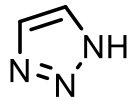
54% yield



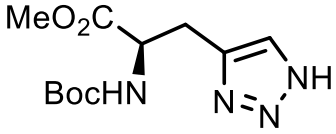
41% yield
(N1 : N2 = 1.9 : 1)



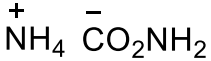
41% yield
one isomer



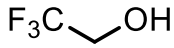
58% yield



27% yield
one isomer

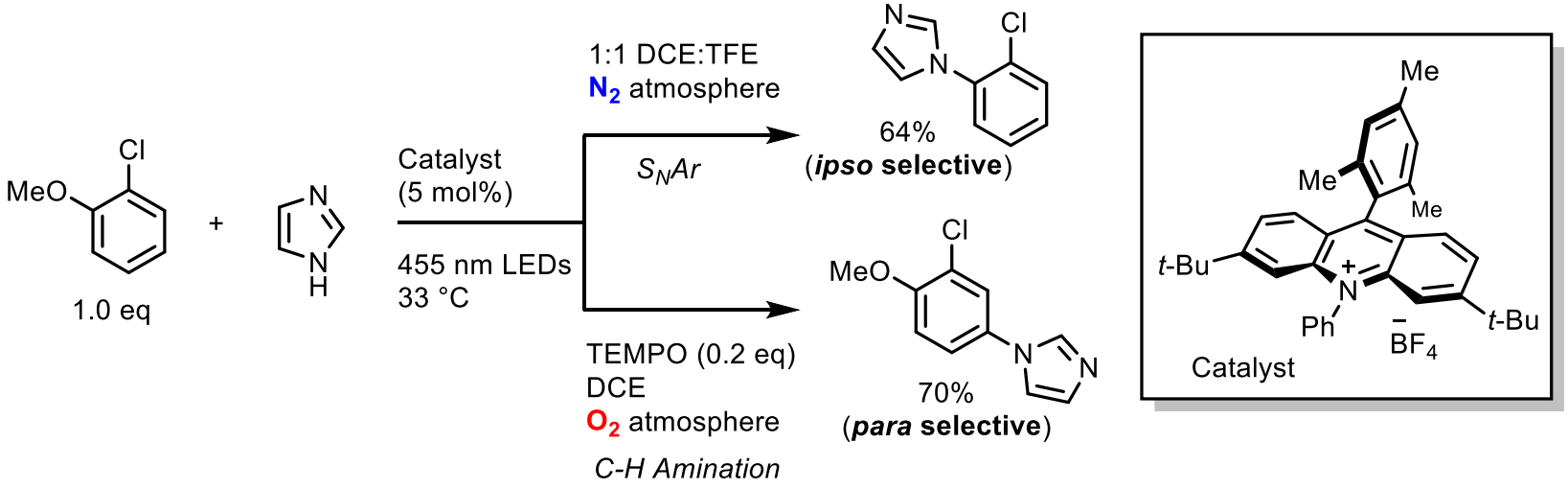


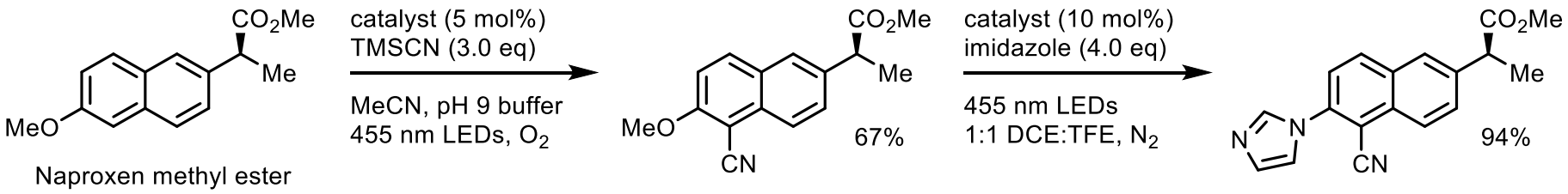
45% yield



44% yield

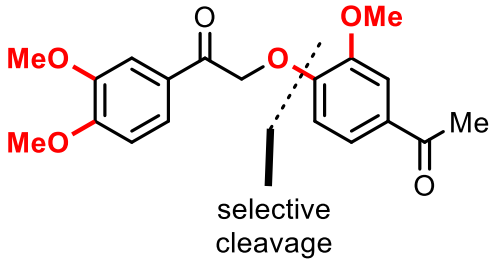
Complementary functionalizations





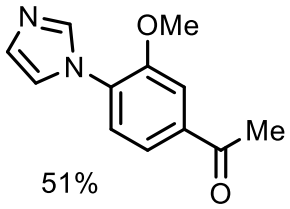
Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science,* **2015**, *349*, 1326−1330.
McManus, J. B.; Nicewicz, D. A. *J. Am. Chem. Soc*. **2017**, *139*, 2880−2883.

Selective C-O bond cleavage

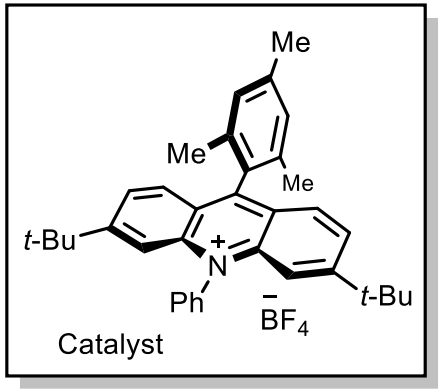


catalyst (10 mol%)
imidazole (4.0 eq)

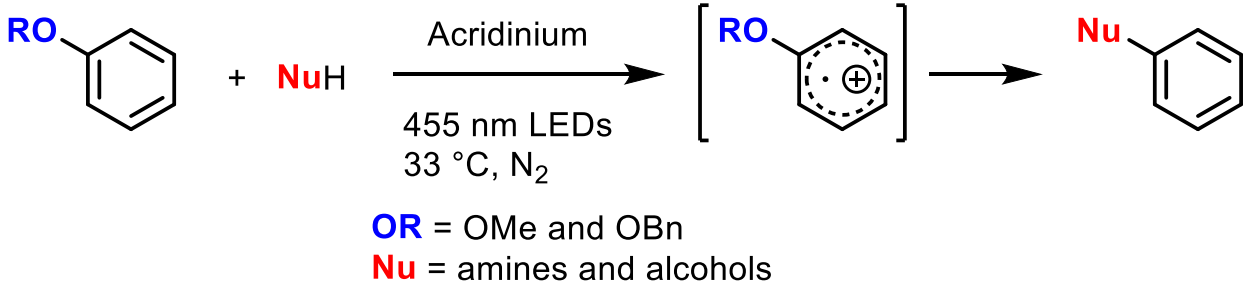
455 nm LEDs
1:1 DCE:TFE, N_2

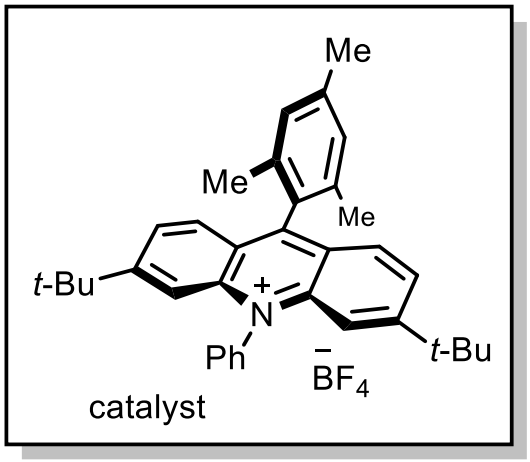


51%



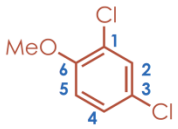
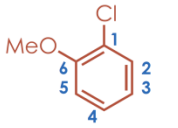
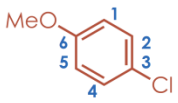
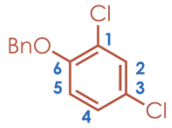
Conclusion

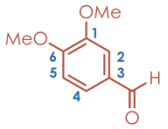
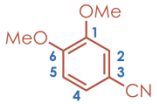
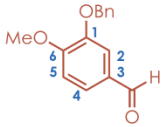
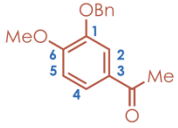


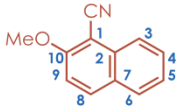
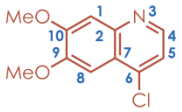
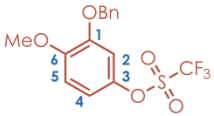
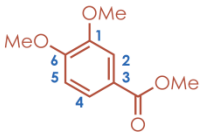


- Selective for OMe and OBn groups
- Amination and Oxygenation
- Mild and transition metal-free condition

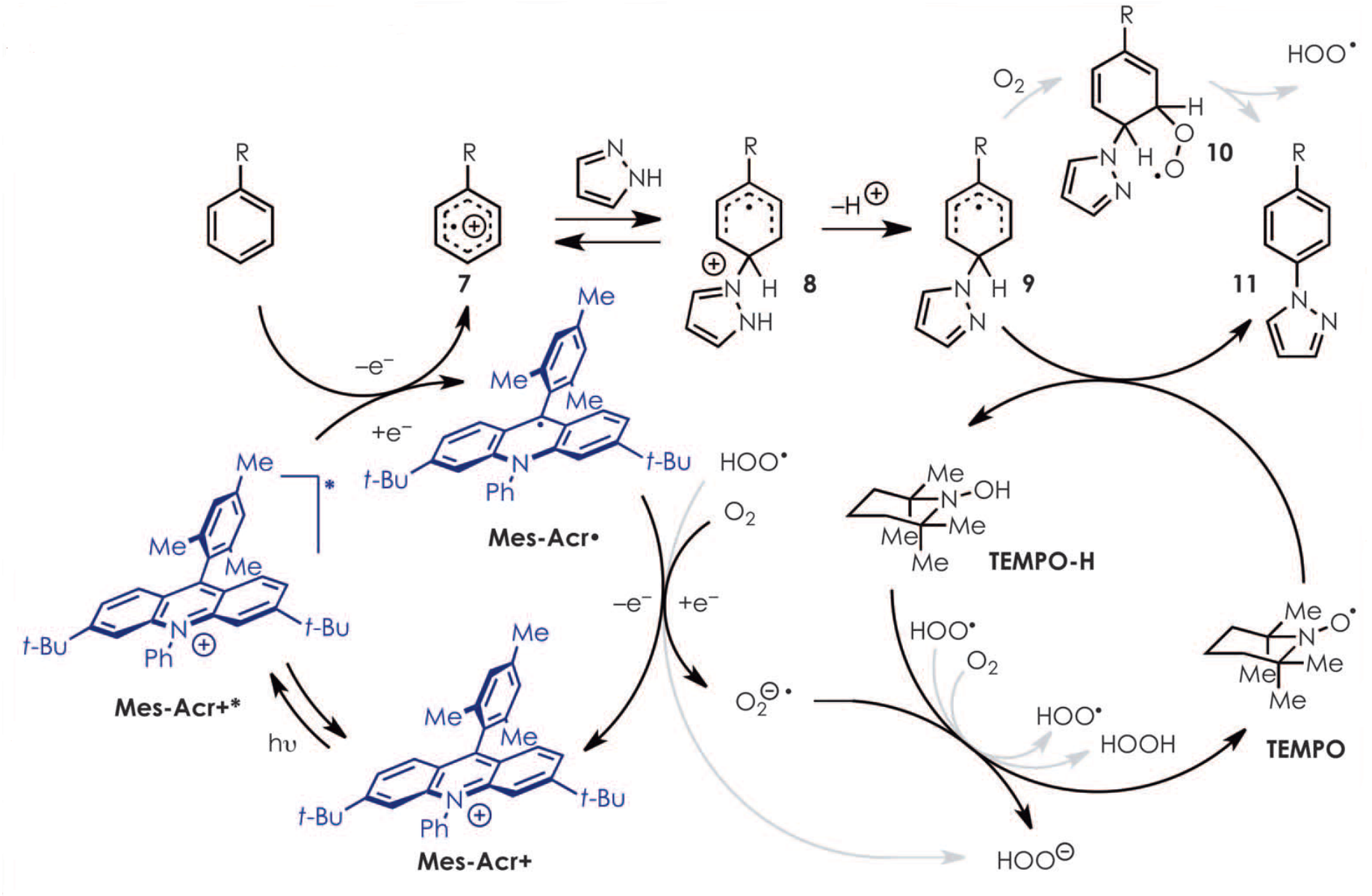
Natural population analyses

	Ground state	Radical cation
	1. - 0.067 2. - 0.239 3. - 0.056 4. - 0.211 5. - 0.257 6. 0.301	1. - 0.049 2. - 0.220 3. - 0.049 4. - 0.180 5. - 0.156 6. 0.440
	1. - 0.102 2. - 0.245 3. - 0.268 4. - 0.231 5. - 0.313 6. 0.304	1. - 0.023 2. - 0.257 3. - 0.088 4. - 0.164 5. - 0.276 6. 0.447
	1. - 0.232 2. - 0.216 3. - 0.070 4. - 0.212 5. - 0.277 6. 0.320	1. - 0.207 2. - 0.164 3. 0.049 4. - 0.195 5. - 0.148 6. 0.448
	1. - 0.055 2. - 0.239 3. - 0.054 4. - 0.210 5. - 0.253 6. 0.300	1. - 0.014 2. - 0.235 3. 0.045 4. - 0.146 5. - 0.215 6. 0.440

	Ground state	Radical cation
	1. 0.282 2. - 0.268 3. - 0.184 4. - 0.208 5. - 0.273 6. 0.304	1. 0.376 2. - 0.261 3. - 0.077 4. - 0.149 5. - 0.256 6. 0.434
	1. 0.288 2. - 0.266 3. - 0.190 4. - 0.208 5. - 0.273 6. 0.295	1. 0.376 2. - 0.261 3. - 0.077 4. - 0.149 5. - 0.256 6. 0.434
	1. 0.282 2. - 0.268 3. - 0.184 4. - 0.207 5. - 0.273 6. 0.305	1. 0.378 2. - 0.259 3. - 0.081 4. - 0.149 5. - 0.258 6. 0.434
	1. 0.280 2. - 0.274 3. - 0.148 4. - 0.225 5. - 0.271 6. 0.295	1. 0.377 2. - 0.271 3. - 0.040 4. - 0.159 5. - 0.258 6. 0.428
	1. 0.262 2. - 0.253 3. - 0.124 4. - 0.223 5. - 0.315 6. 0.288	1. 0.419 2. - 0.251 3. - 0.025 4. - 0.113 5. - 0.313 6. 0.380

	Ground state	Radical cation
	1. - 0.126 2. - 0.042 3. - 0.204 4. - 0.181 5. - 0.216 6. - 0.168 7. - 0.091 8. - 0.119 9. - 0.278 10. 0.360	1. 0.038 2. - 0.068 3. - 0.069 4. - 0.179 5. - 0.103 6. - 0.082 7. - 0.087 8. - 0.018 9. - 0.284 10. 0.441
	1. - 0.255 2. 0.159 3. - 0.468 4. 0.022 5. - 0.298 6. - 0.004 7. - 0.100 8. - 0.306 9. 0.306 10. 0.290	1. - 0.198 2. 0.170 3. - 0.436 4. 0.069 5. - 0.211 6. - 0.030 7. - 0.009 8. - 0.298 9. 0.348 10. 0.431
	1. 0.299 2. - 0.332 3. 0.261 4. - 0.283 5. - 0.252 6. 0.271	1. 0.379 2. - 0.334 3. 0.370 4. - 0.215 5. - 0.236 6. 0.419
	1. 0.280 2. - 0.275 3. - 0.169 4. - 0.215 5. - 0.270 6. 0.290	1. 0.380 2. - 0.271 3. - 0.057 4. - 0.145 5. - 0.260 6. 0.428

Proposed mechanism of photocatalysed C-H amination



Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science,* **2015**, *349*, 1326−1330.

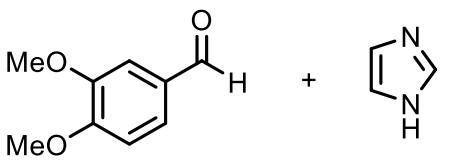
Solvent properties

Alcohol	Ionizing power, Y	Nucleophilicity, N
Ethanol–water (80:20 v/v)	0.00	0.00
2,2,2-Trifluoroethanol	1.74; 1.80	2.67; −3.0
HFP	3.82	
HFP–water (3% *m/m*)	3.53; 3.61	−4.91; −4.27
Formic acid	3.04	−2.35
Acetic acid	−0.61	−2.35
Trifluoroacetic acid	4.57	−4.74, −5.56

Solvent	δ ^{59}Co	AN	E^{N}_{T}	β	α	π^*
Methanol	91.0	41.3	0.762	0.62	0.93	0.60
Ethanol	129.3	37.1	0.654	0.77	0.83	0.54
Water	28.1	54.8	1.00	0.18	1.17	1.09
2,2,2-Trifluoro-ethanol	18.6	53.3	0.898	0.00	1.51	0.73
HFP	−22.5	83.6	1.068	0.00	1.96	0.65
Formic acid	−7.28	83.6	0.728			
Acetic acid	13.4	52.9	0.648		1.17	1.09
Trifluoroacetic acid		105.3				0.50

Eberson, L.; Hartshorn, M. P.; Persson, O.; Radner, F. *Chem. Commun*. **1996**, 2105–2112.

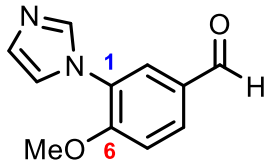
Comparison between experimental and caluculation data



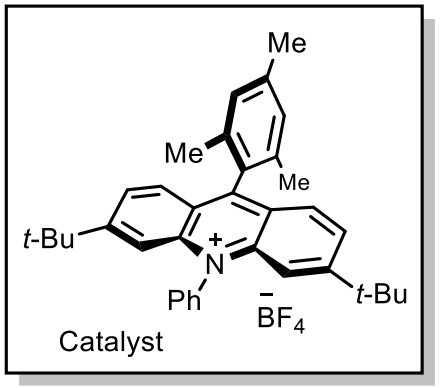
+

Catalyst (5 mol%)

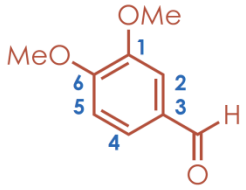
455 nm LEDs
1:1 DCE:TFE, 24 h
33 °C, N_2

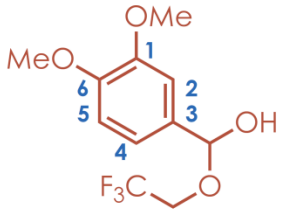


44%
(C1 : C6 = 8 : 1)



Catalyst

	Ground state	Radical cation
	1. 0.282 2. - 0.268 3. - 0.184 4. - 0.208 5. - 0.273 6. 0.304	1. 0.376 2. - 0.261 3. - 0.077 4. - 0.149 5. - 0.256 6. 0.434

	Ground state	Radical cation
	1. 0.262 2. - 0.253 3. - 0.124 4. - 0.223 5. - 0.315 6. 0.288	1. 0.419 2. - 0.251 3. - 0.025 4. - 0.113 5. - 0.313 6. 0.380