# Photocatalytic Arene Functionalization via Arene Radical Cations

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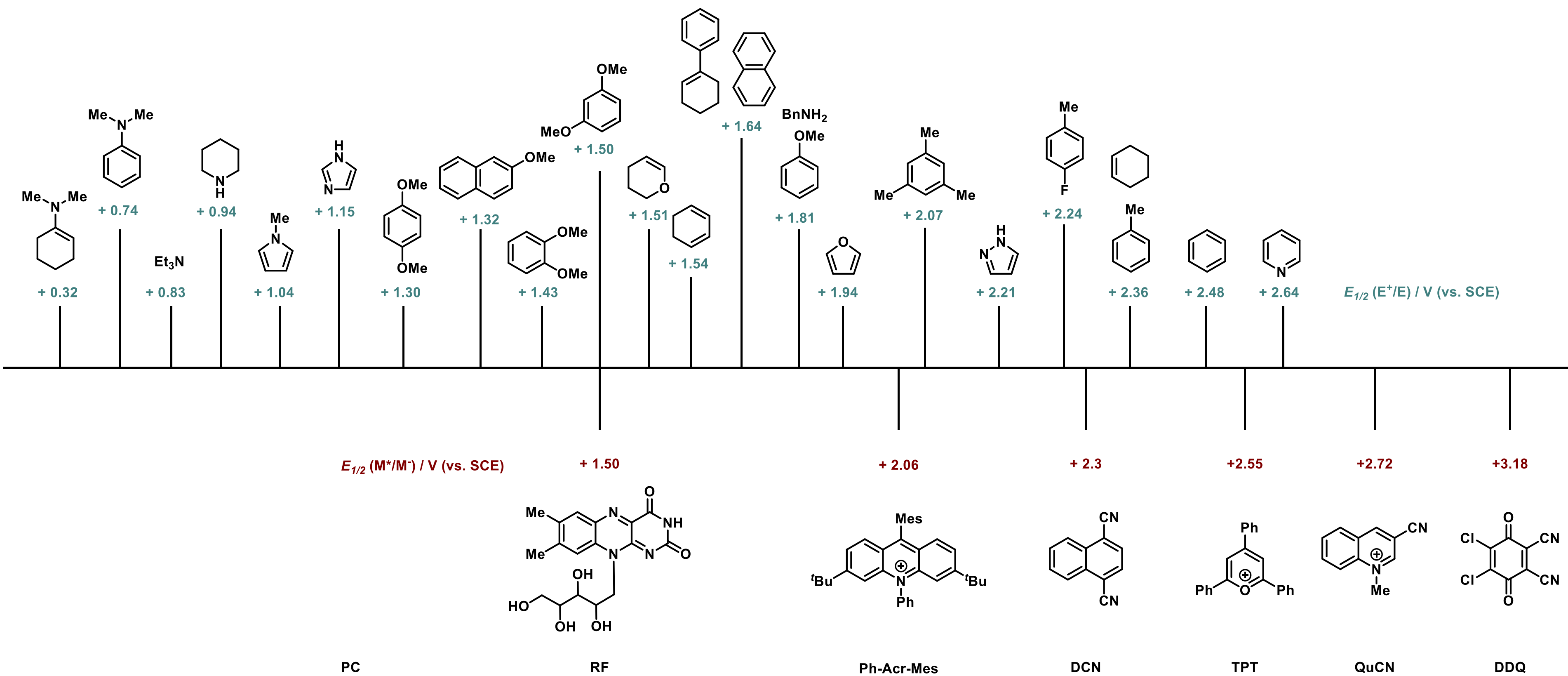
# Outline

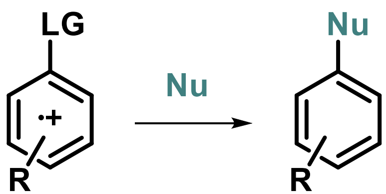
- Introduction
- Cation-type C-X Bond Formation
    - Oxidative Arene C-H Functionalization
    - Arene C-X Substitution: CRA-$S_N$Ar
- Radical-type C-C Bond Formation
- Summary & Outlook

# Oxidation Potentials for Selected Arenes and PCs

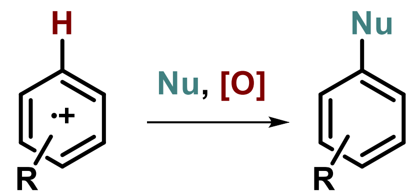



Hudson, G. R. *et al. Synlett.* **2016**, *27*, 714.

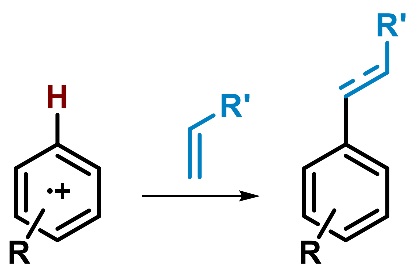
# Common Reaction Type for Arene Radical Cations



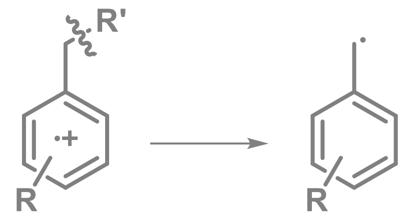

cation radical-accelerated-nucleophilic
aromatic substitution
(CRA-SNAr)




oxidative nucleophilic
C-H functionalization
via arene radical cations




oxidative radical
C-H functionalization
via arene radical cations




β-scission

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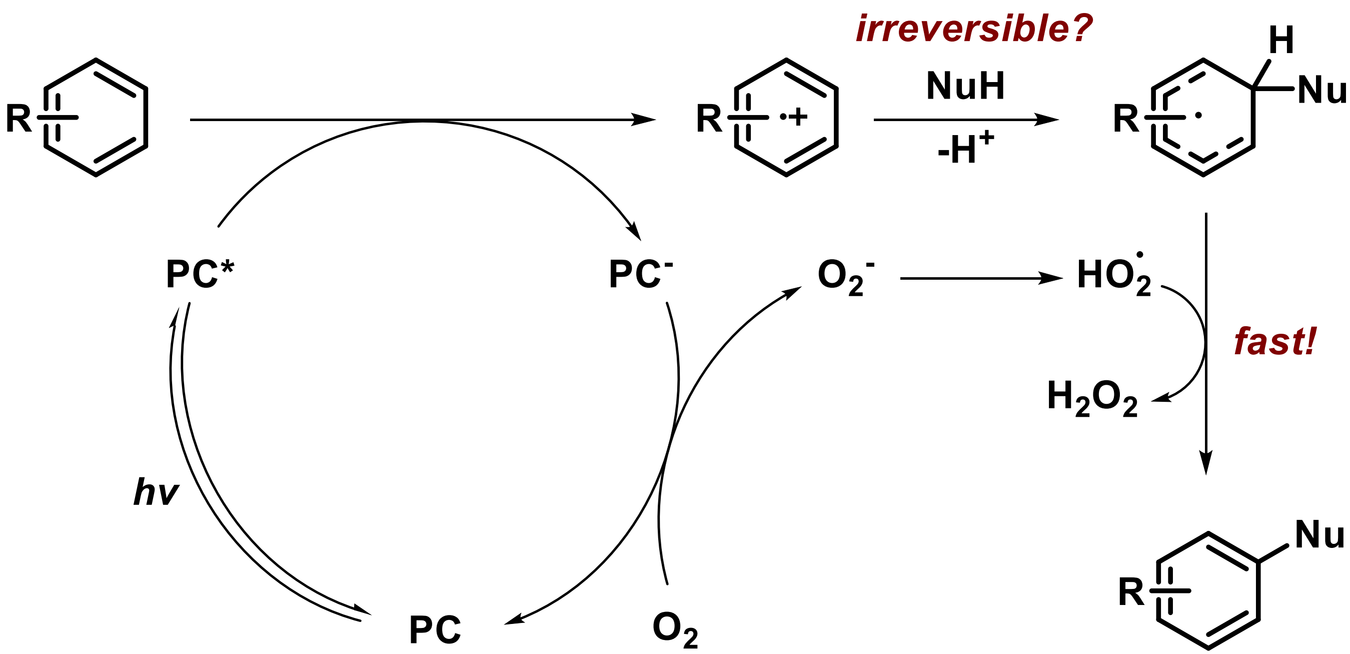
# General Scheme for Oxidative Arene C-H Functionalization

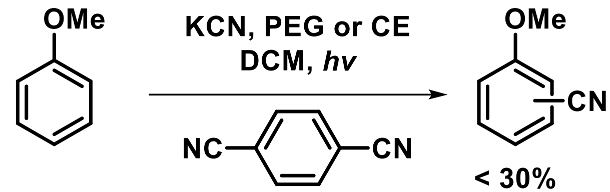



**(co)-oxidants:**

**TEMPO, $S_2O_8^{2-}$, ROOR, $^t$BuONO**

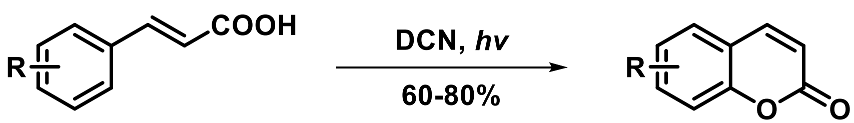
**[Co]**

# Early Study: Cyanoarene-based PCs

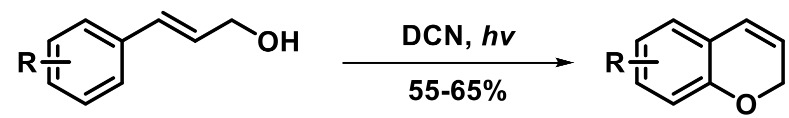



**Suzuki, 1980**

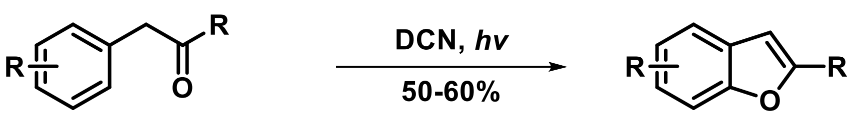
Suzuki, N. *et al. J. Chem. Soc., Chem. Commun.* **1980**, 1253.



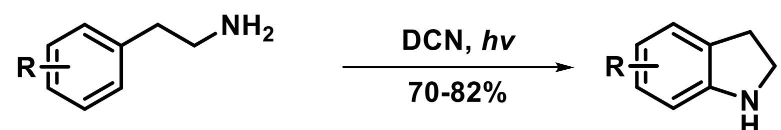

**Pandey, 1986**




**Pandey, 1988**




**Pandey, 1989**

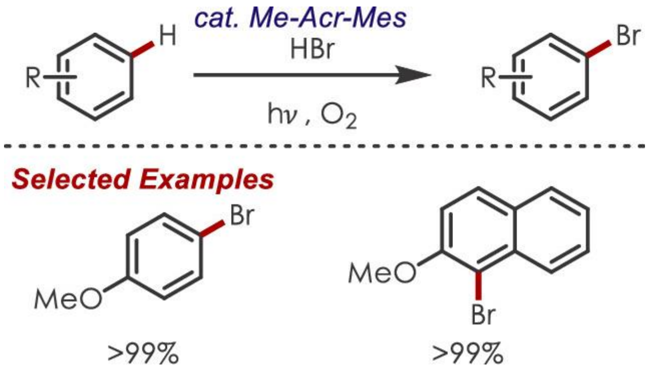



**Pandey, 1990**

Pandey, G. *et al. Tetrahedron Lett.* **1986**, *27,* 4075.
Pandey, G. *et al. Tetrahedron Lett.* **1989**, *30,* 1867.

Pandey, G. *et al. J. Org. Chem.* **1988**, *53,* 2364.
Pandey, G. *et al. Tetrahedron Lett.* **1990**, *31, 5373*.

# Acridinium-catalyzed Arene C-H Halogenation

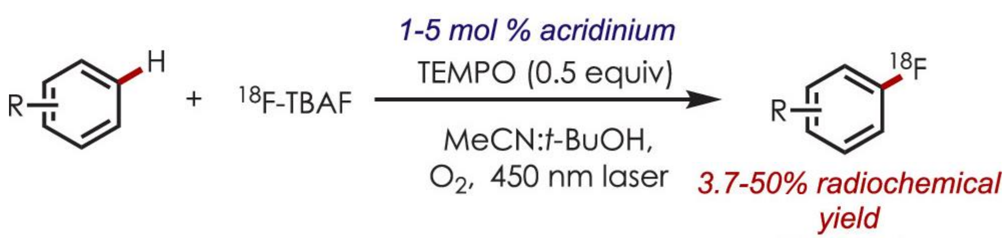



**Fukuzumi, 2001, 2011**

Fukuzumi, S. *et al. J. Am. Chem. Soc.* **2001**, *123*, 8459.
Ohkubo, K. *et al. Chem. Sci.* **2011**, *2*, 715.


**Fukuzumi, 2013**

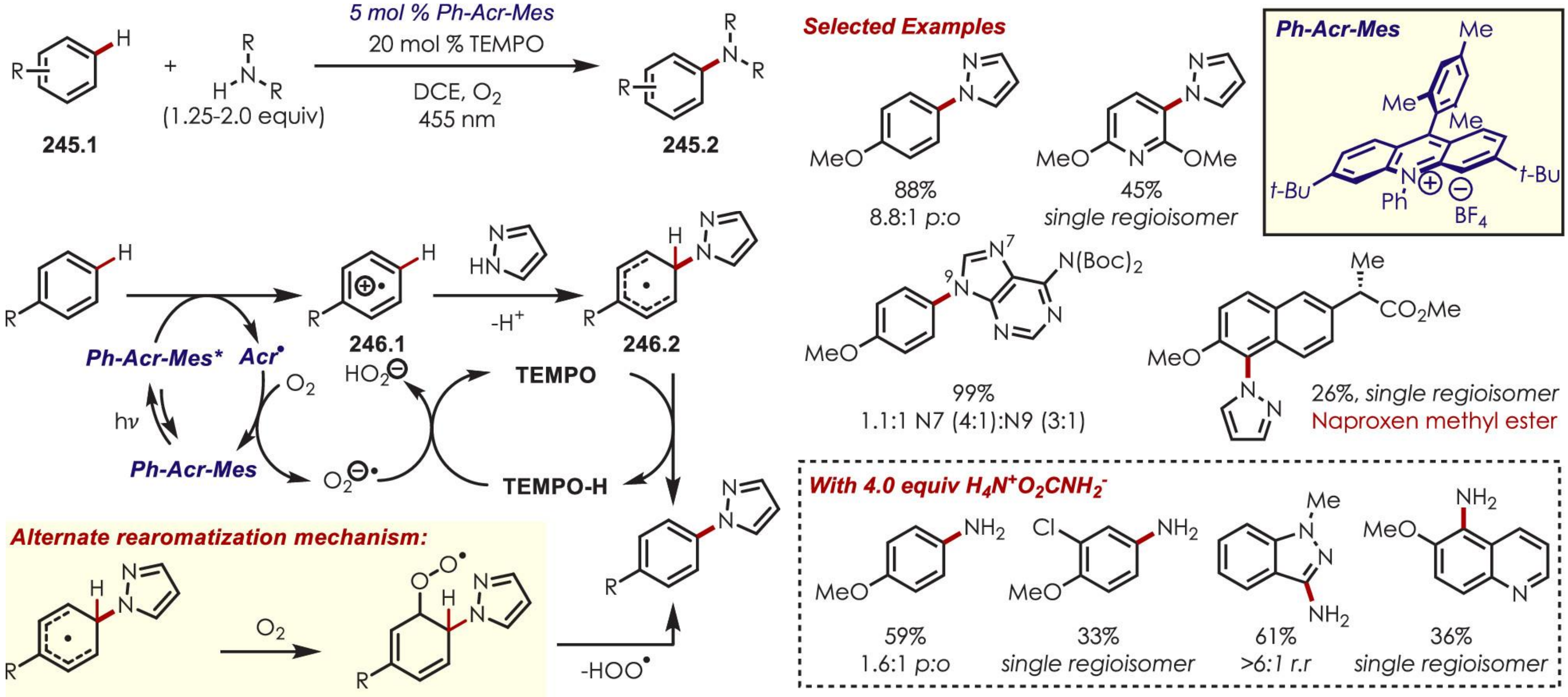
Ohkubo, K. *et al. Res. Chem. Intermed.* **2013***, 39,* 205.




**Nicewicz and Li, 2019**

Chen, W. *et al. Science* **2019***, 364,* 1170.

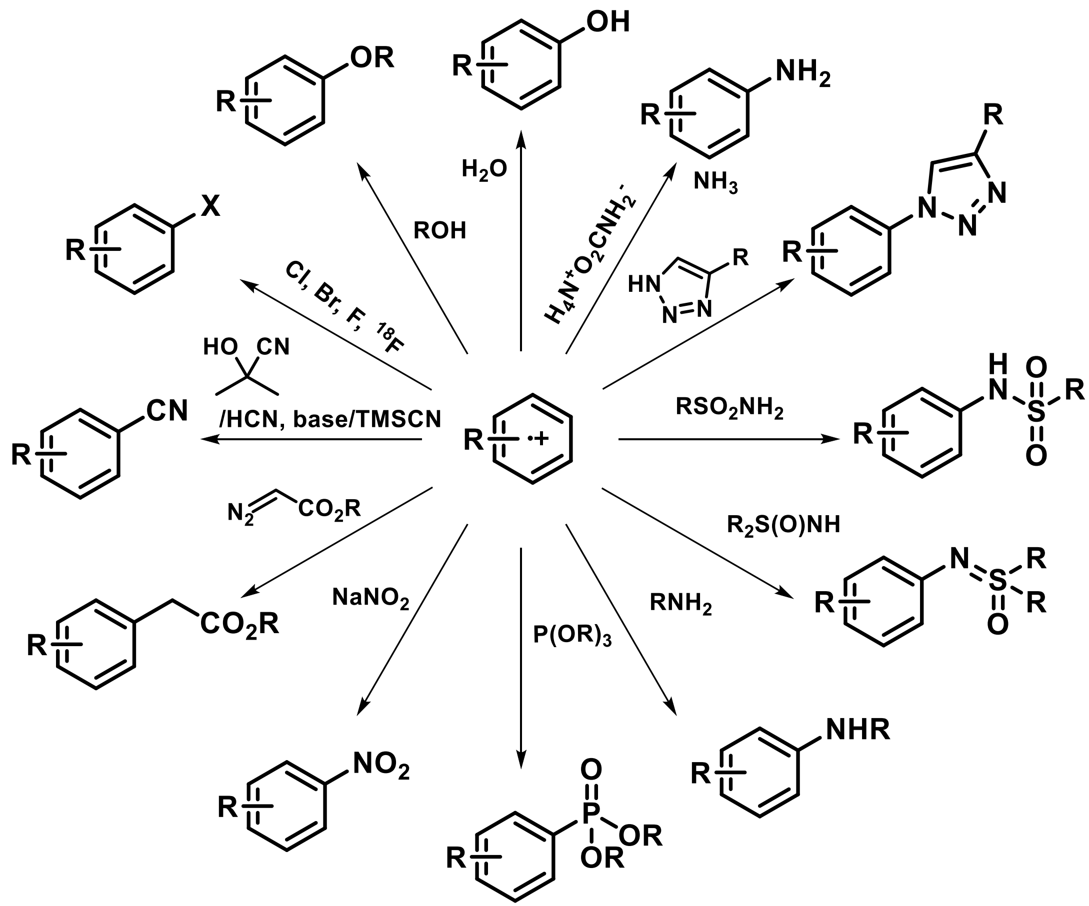
# Acridinium-catalyzed Arene C-H Amination




**TEMPO accelerates rearomatization, thus suppresses the product inhibition.**

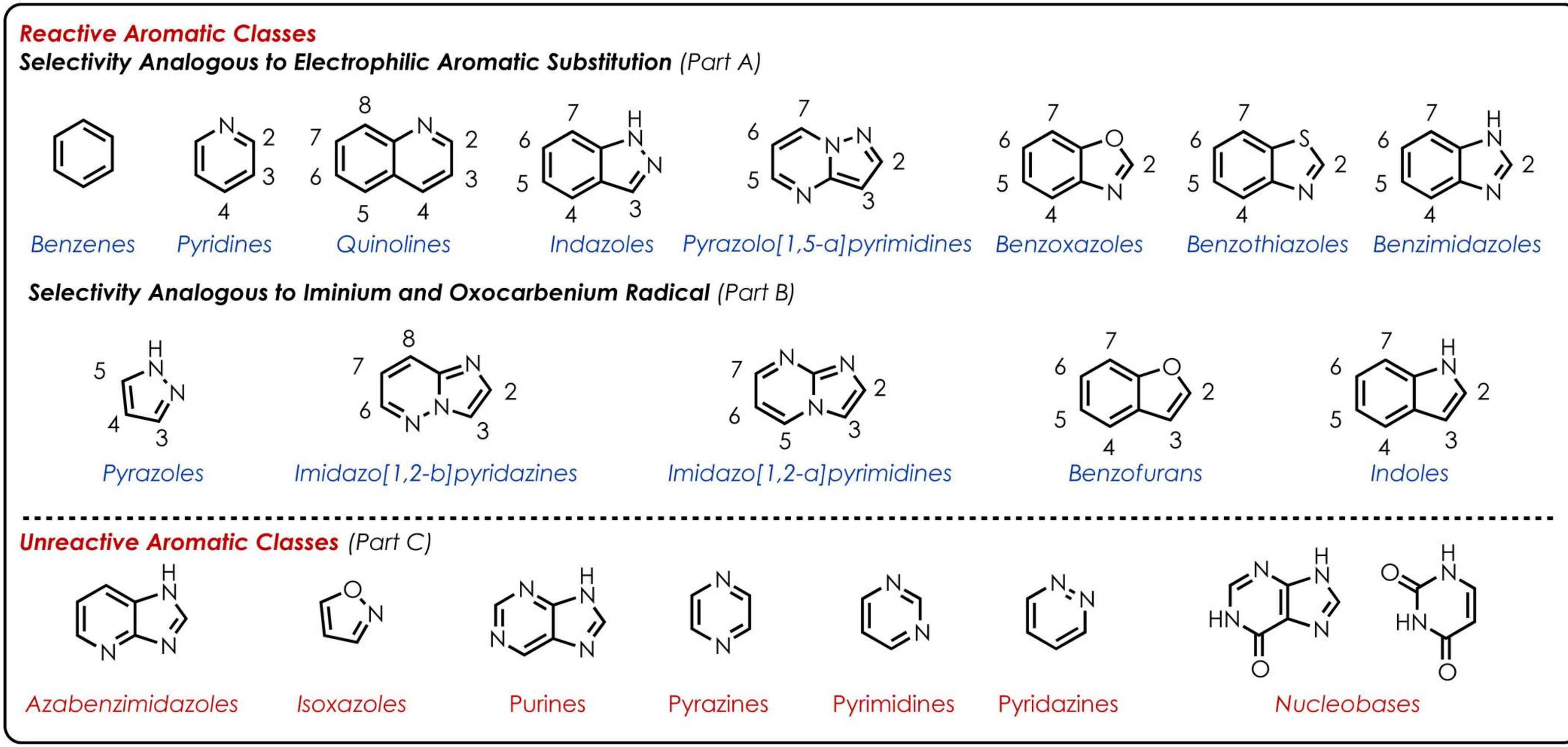
Romero, N. A. *et al. Science* **2015**, *349,* 6254.

# Nucleophile Scope




Zheng, Y.-W. *et al. J. Am. Chem. Soc.* **2016**, *138*, 10080.; Romero, N. A. *et al. Science* **2015**, *349,* 6254.; Song, C. *et al. Chem. Commun.* **2017**, *53,* 3689.; Meyer, A. U. *et al. Chem. Commun.* **2016**, *52,* 10918.; Lämmermann, H. *et al. Synlett* **2018**, *29,* 2679.; Margrey, A. *et al. Angew. Chem., Int. Ed.* **2017**, *56,* 15644.; Niu, L. *et al. ACS Catal.* **2017**, *7,* 7412.; Düsel, S. J. S. *et al. J. Org. Chem.* **2018**, *83,* 2802.; Holmberg-Douglas, N. *et al. Angew. Chem., Int. Ed.* **2020**, *59*, 7425.; McManus, J. B. *et al. J. Am. Chem. Soc.* **2017**, *139,* 2880.; Chen, W. *et al. Science* **2019**, *364*, 1170.; Song, C. *et al. Chem. Commun.* **2017**, *53,* 3689.

# Arene Scope




Margrey, K. A. *et al. J. Am. Chem. Soc.* **2017**, *139*, 11288.

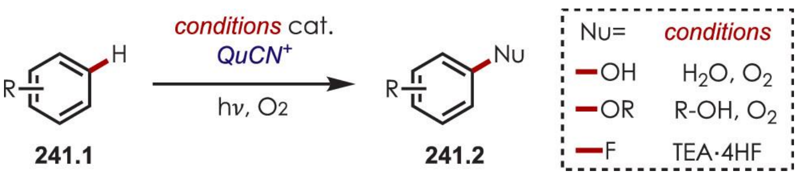
C8-akloxy purine: Zhe, L. *et al. J. Org. Chem.* **2022**, *87*, 11558.

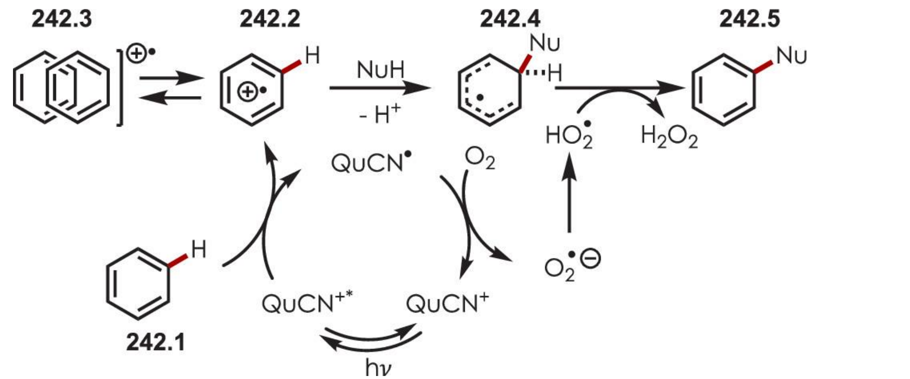
**Thiophenes and pyrroles are also candidates for C-H (sulf)amidation:**

Song, C. *et al. Chem. Commun.* **2017**, *53*, 3689.

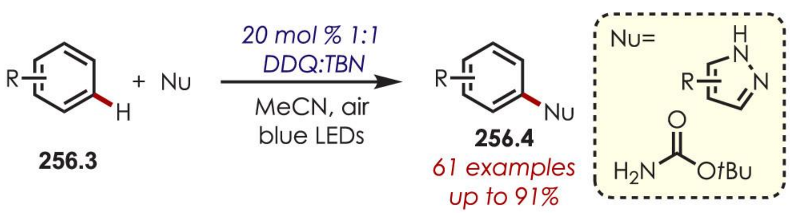
Wimmer A. *et al. Adv. Synth. Catal.* **2018**, *360*, 3277.

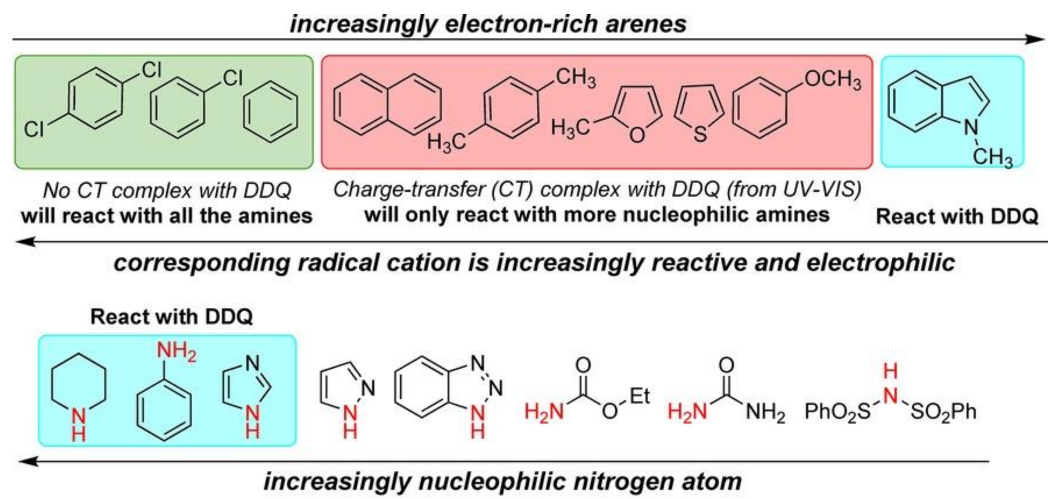
# Electron-deficient Arenes: QuCN+ or DDQ



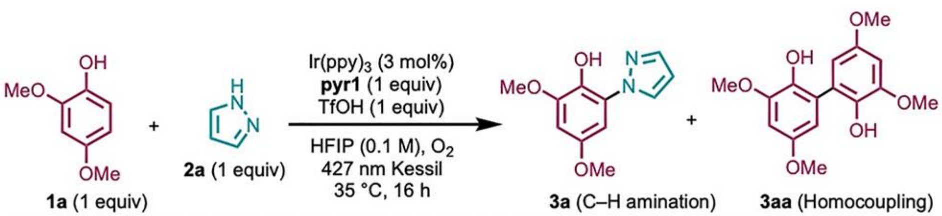

Ohkubo, K. *et al. Opt. Express* **2012**, *20,* A360.



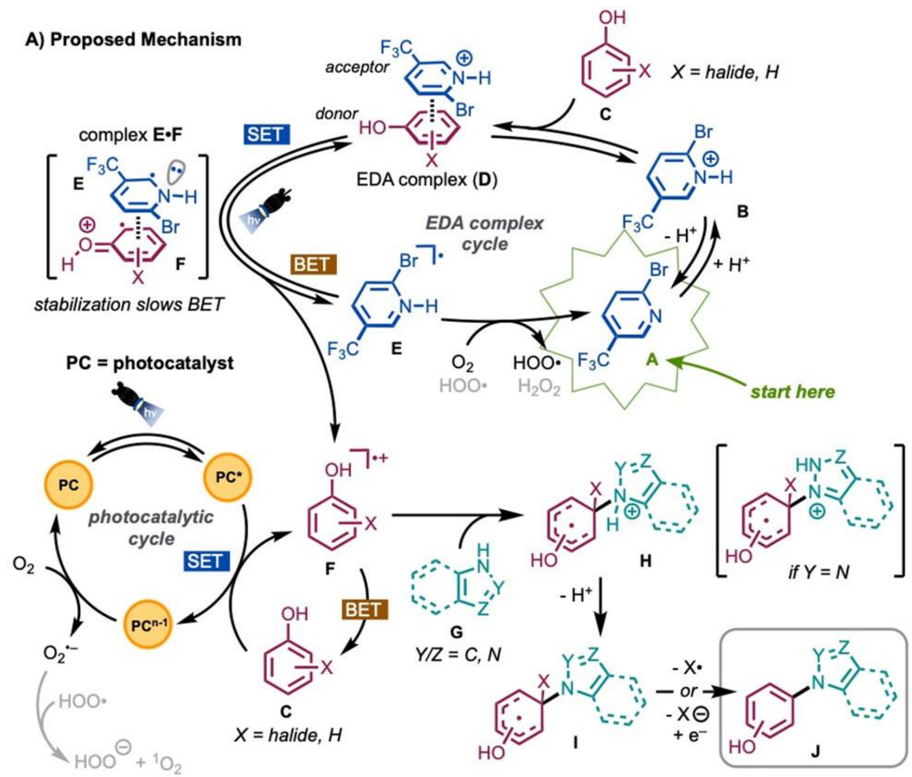



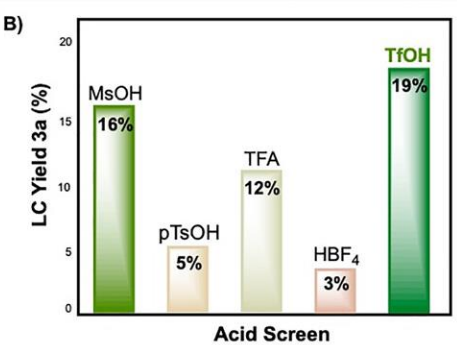

Das, S. *et al. Chem. - Eur. J.* **2017**, *23,* 18161.

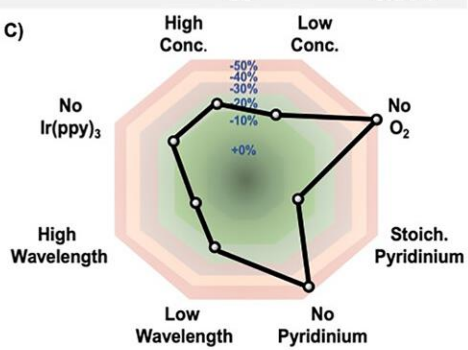
# Phenol Radical Cation Generated via EDA Complex




| Entry | Deviations from Above Conditions | LC Yield **3a** (%) | LC **3a**:**3aa** |
|---|---|---|---|
| 1 | 2 equiv **1a** | 11 | 0.3 : 1 |
| 2 | 3.5 equiv **2a** | 43 | 4.0 : 1 |
| 3 | 3.5 equiv **2a** + 10 mol% **pyr1** & TfOH | 35 | 3.6 : 1 |
| 4 | 3.5 equiv **2a** + 30 mol% **pyr1** & TfOH | 44 | 4.2 : 1 |
| 5 | 3.5 equiv **2a** + 30 mol% **pyr1** & TfOH + 0.08 M HFIP | 52 (51) | 15.9 : 1 |
| 6 | 3.5 equiv **2a** + 390 nm Kessil | 31 | 5.4 : 1 |
| 7 | 3.5 equiv **2a** + No $Ir(ppy)_3$ | 35 | 5.7 : 1 |
| 8 | 3.5 equiv **2a** + No light | 0 | – |
| 9 | 3.5 equiv **2a** + Under Ar | 0 | – |
| 10 | 3.5 equiv **2a** + No **pyr1** & TfOH | 0 | – |
| 11 | 3.5 equiv **2a** + No TfOH | trace | – |
| 12 | 3.5 equiv **2a** + No **pyr1** | 33 | 9.8 : 1 |

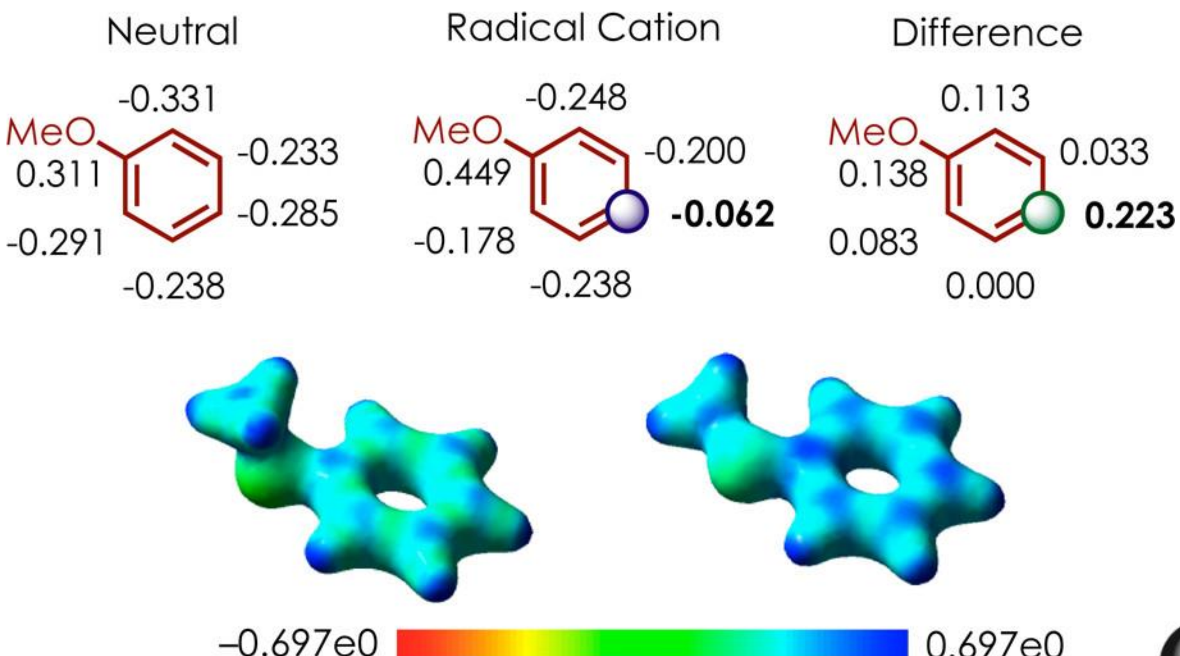


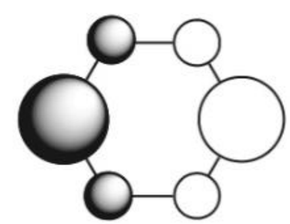



# Regioselectivity: ΔNPA, Orbital Control

**“aryl carbon possessing the greatest difference in natural population analysis (NPA) values between the cation radical and neutral species would be the most electrophilic”**



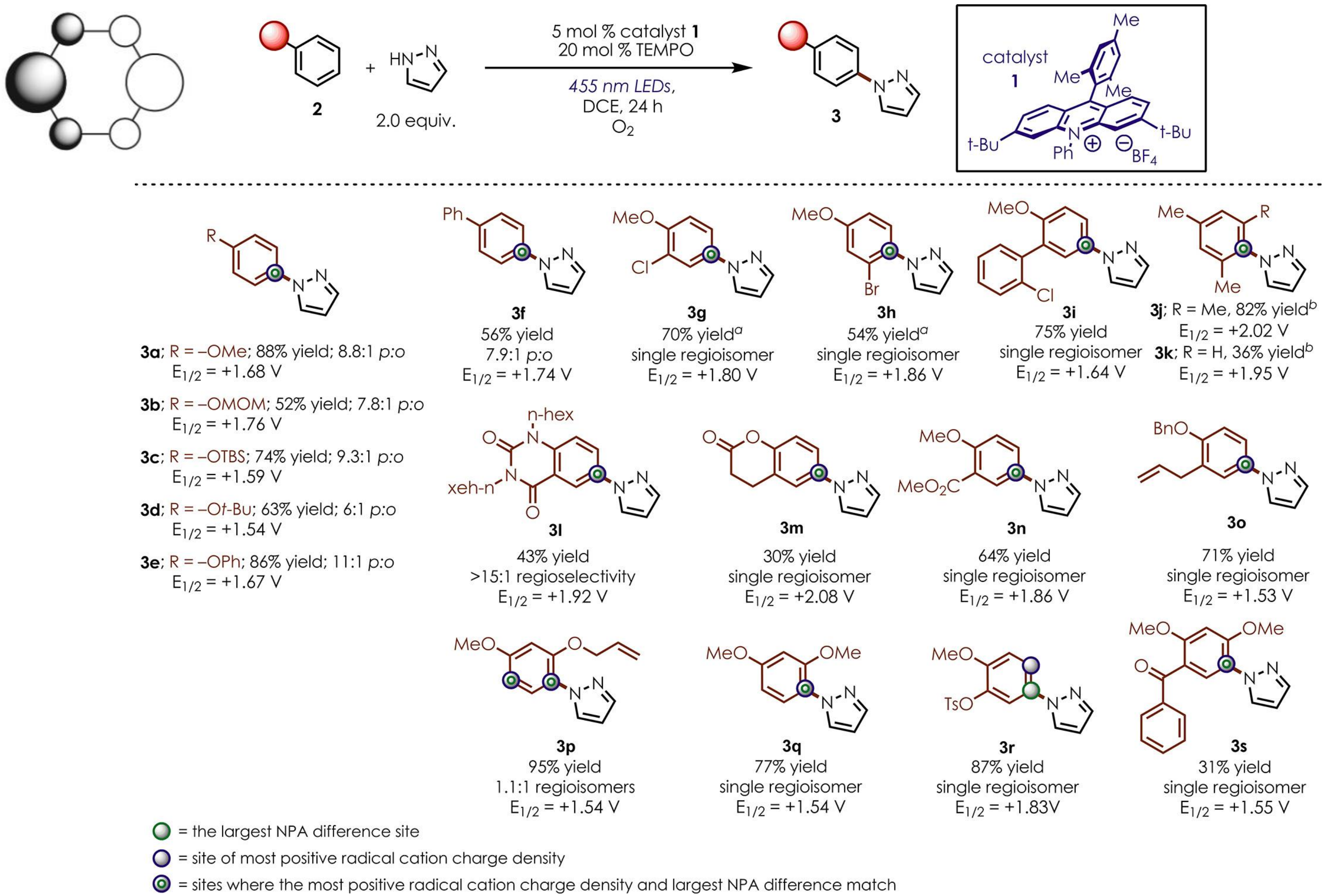

Margrey, K. A. *et al. J. Am. Chem. Soc.* **2017**, *139*, 11288.



**Δ(Atom charge) ~ Condensed Fukui function ~ Spin population ~ SOMO distribution!**

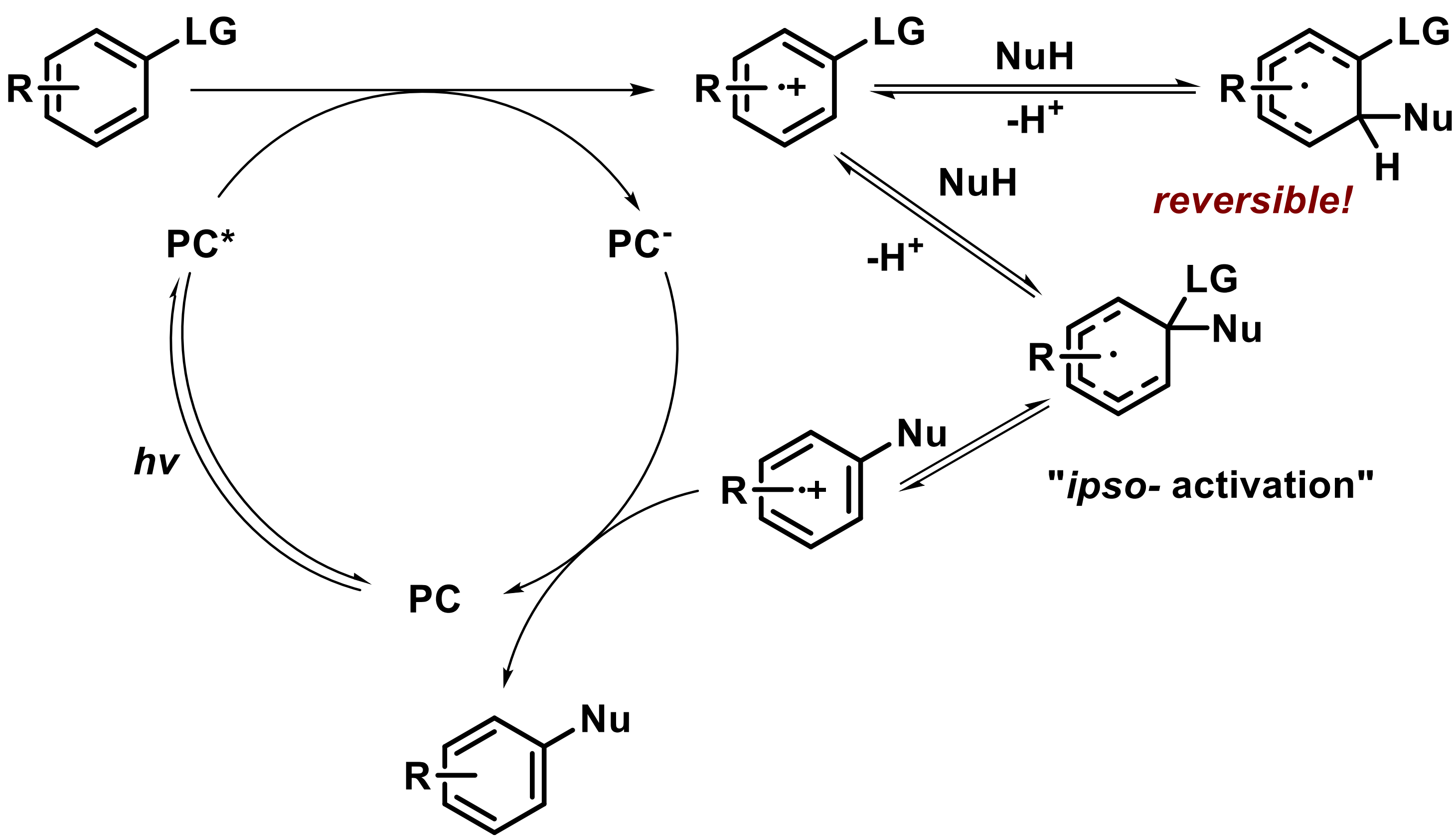
Parr, R. G.; Yang, W. *J. Am. Chem.* Soc. **1984**, *106*, 4049.

# Regioselectivity: Orbital Control

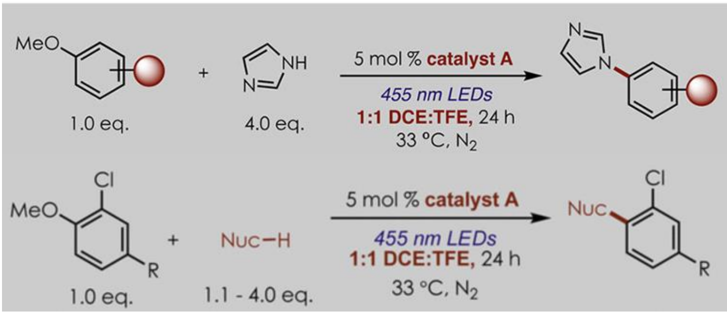


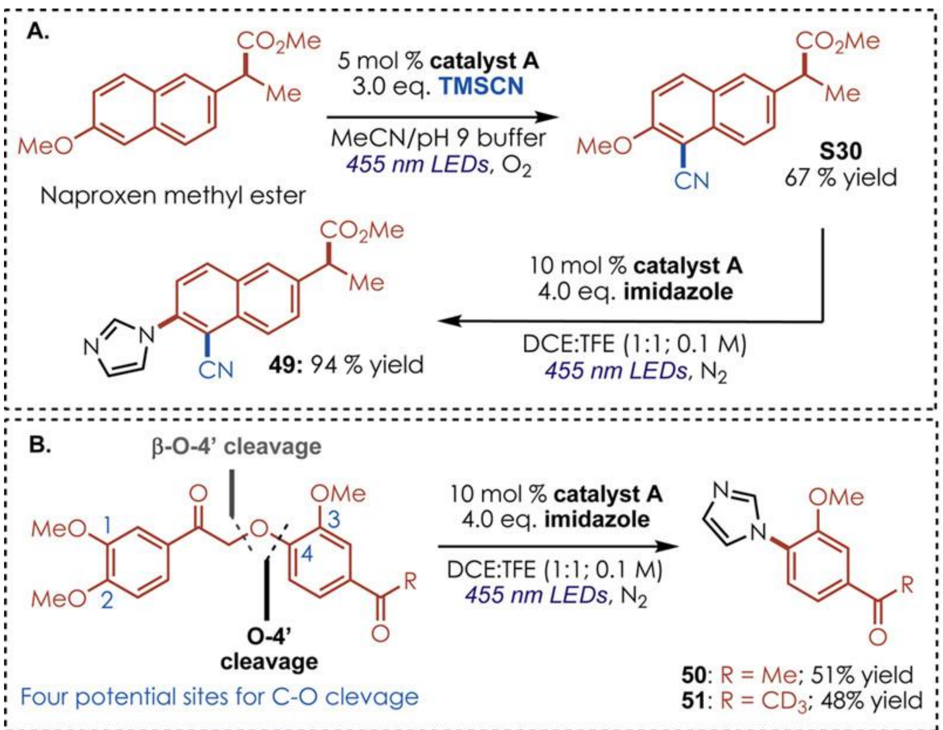

Margrey, K. A. *et al. J. Am. Chem. Soc.* **2017**, *139*, 11288.

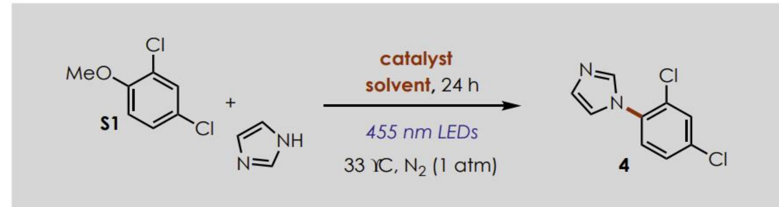
# General Scheme for CRA-$S_N$Ar: Reversible



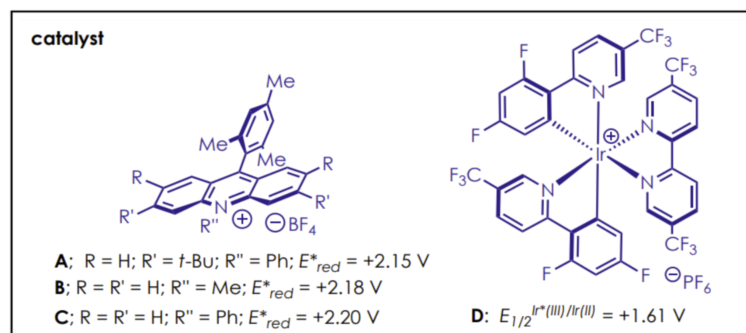
# C-O to C-N: *ipso*- Transformation



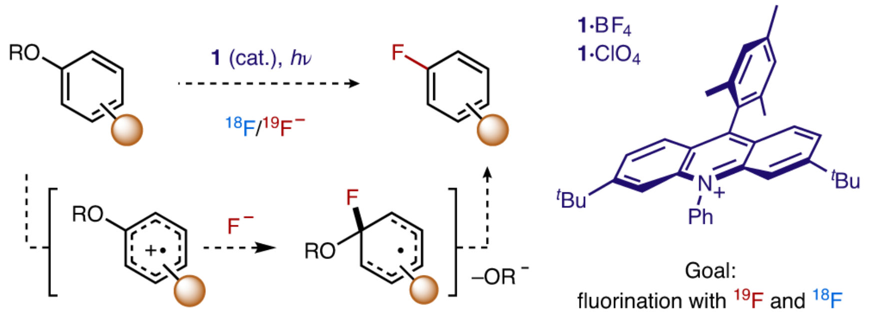




| entry | conditions | catalyst | solvent [M] | yield |
|---|---|---|---|---|
| 1 | As described | A | MeCN [0.10] | 4% |
| 2 | As described | A | TFT [0.10] | 6% |
| 3 | As described | A | MeOH [0.10] | 13% |
| 4 | As described | A | TFE [0.10] | 87% |
| 5 | As described | A | DCE:TFE (9:1) [0.10] | 23% |
| **6** | **As described** | **A** | **DCE:TFE (1:1) [0.10]** | **95%** |
| 12 | $O_2$ atmosphere | A | DCE:TFE (1:1) [0.10] | 66% |
| 13 | Air atmosphere | A | DCE:TFE (1:1) [0.10] | 88% |
| 14 | As described | B | DCE:TFE (1:1) [0.10] | 27% |
| 15 | As described | C | DCE:TFE (1:1) [0.10] | 65% |
| 16 | As described | D | DCE:TFE (1:1) [0.10] | 0% |
| 17 | 20 mol% TEMPO | A | DCE:TFE (1:1) [0.10] | 18% |

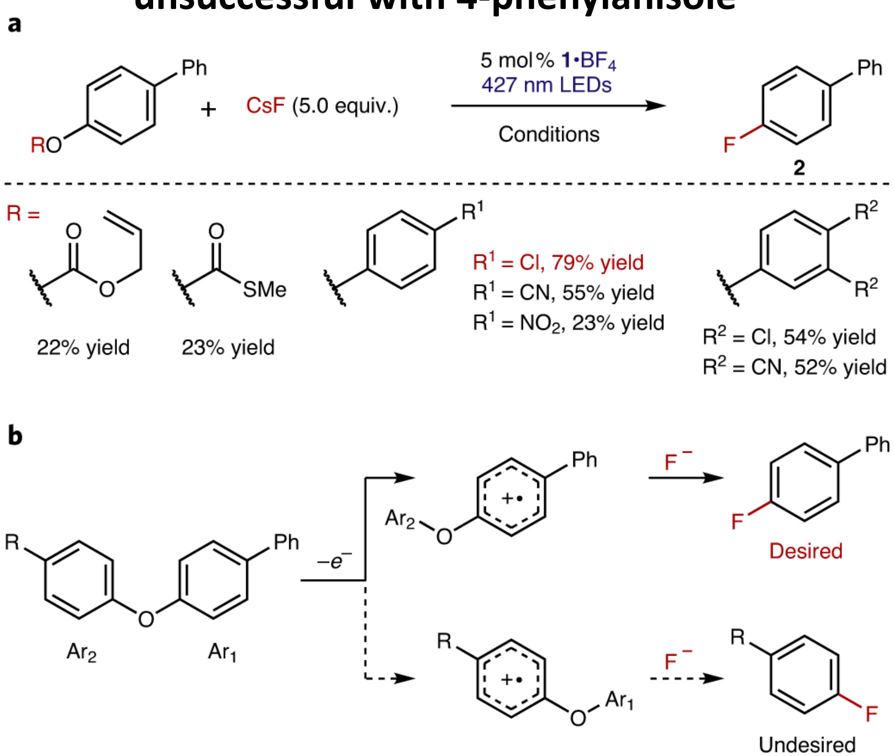


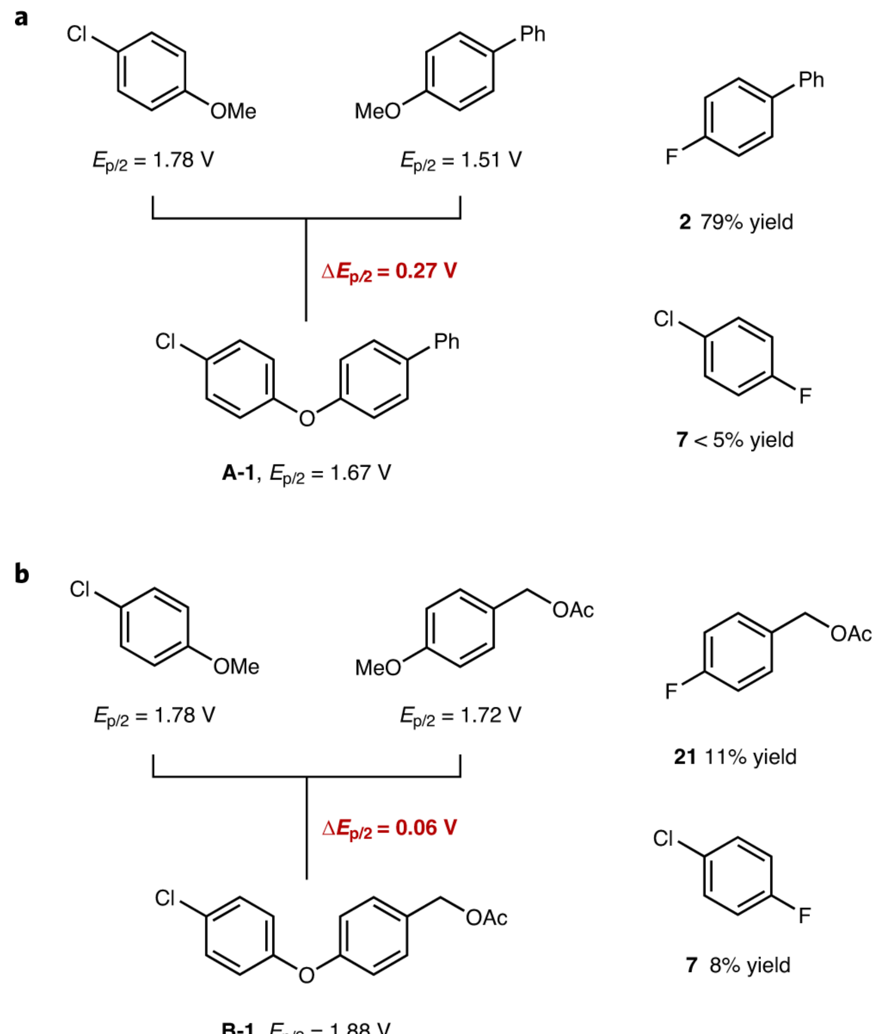

Tay, N. E. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2017**, *139*, 16100.

# C-O to C-F: Aryloxy Nucleofuge




**"unsuccessful with 4-phenylanisole"**

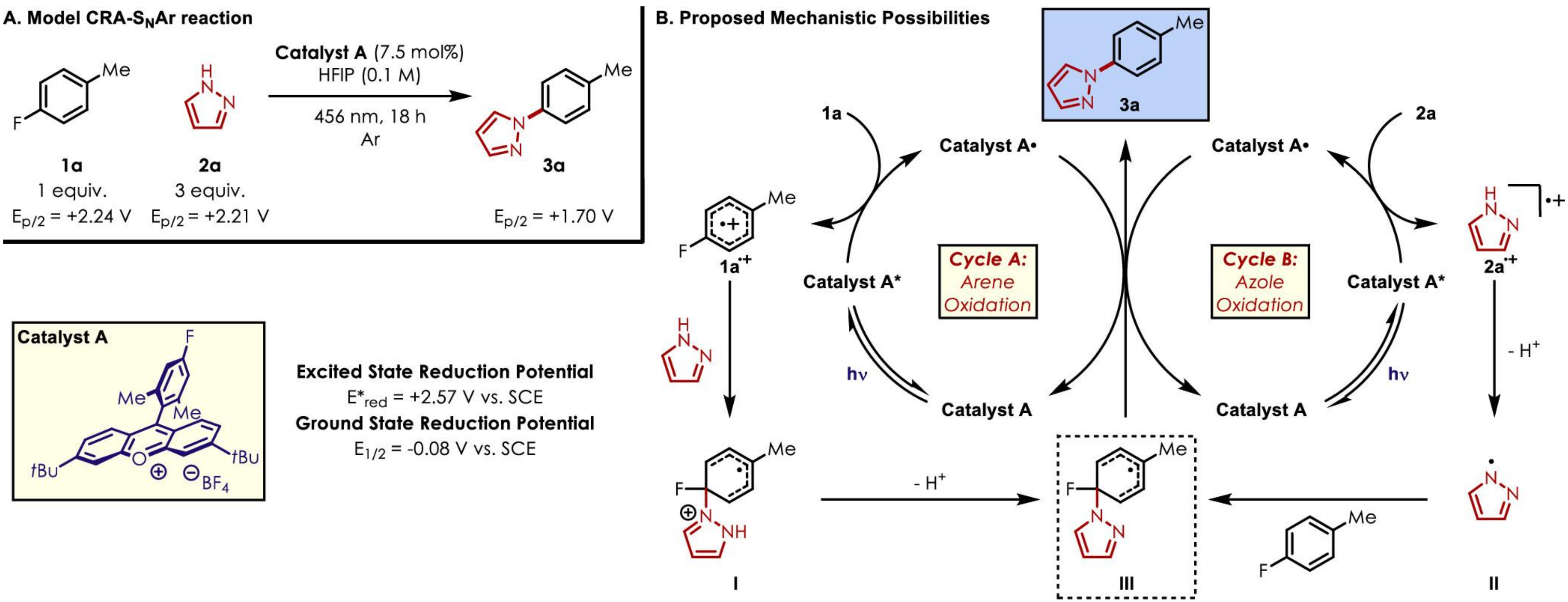



Tay, N. E. S. *et al. Nat. Catal.* **2020**, *3*, 734.

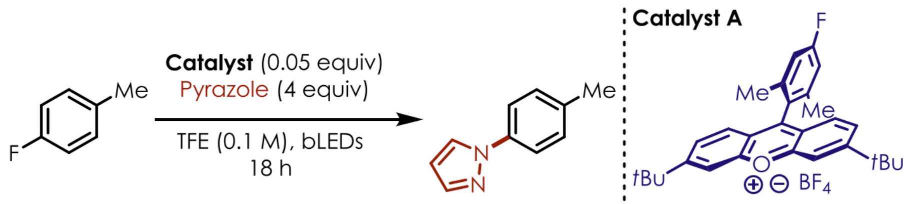
# C-F Transformation: Unactivated Fluoroarene

## Xanthylium salts as potent photooxidant

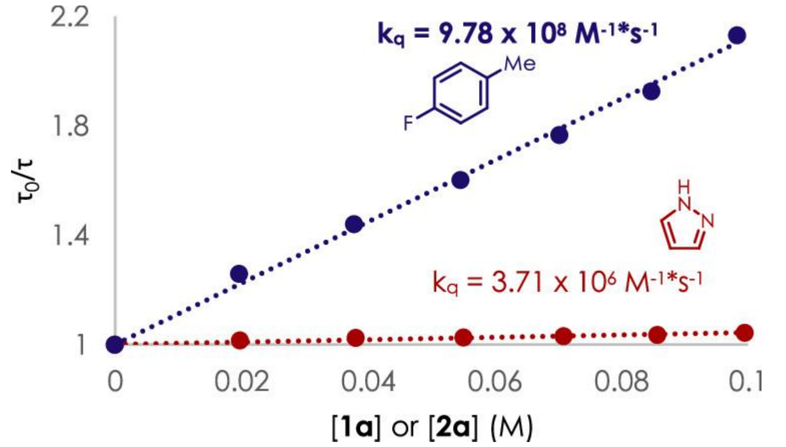


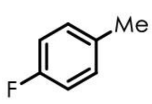

Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2022**, *144*, 15118.

# Oxidation: Solvent Matters

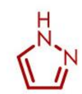



| entry | deviations from the above conditions | yield[a] |
|---|---|---|
| 1 | none | 55% |
| 2 | DCM | 4% |
| 3 | MeCN | 10% |
| 4 | HFIP as solvent | 72% |

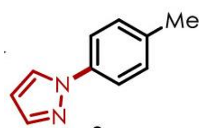


1a



2a

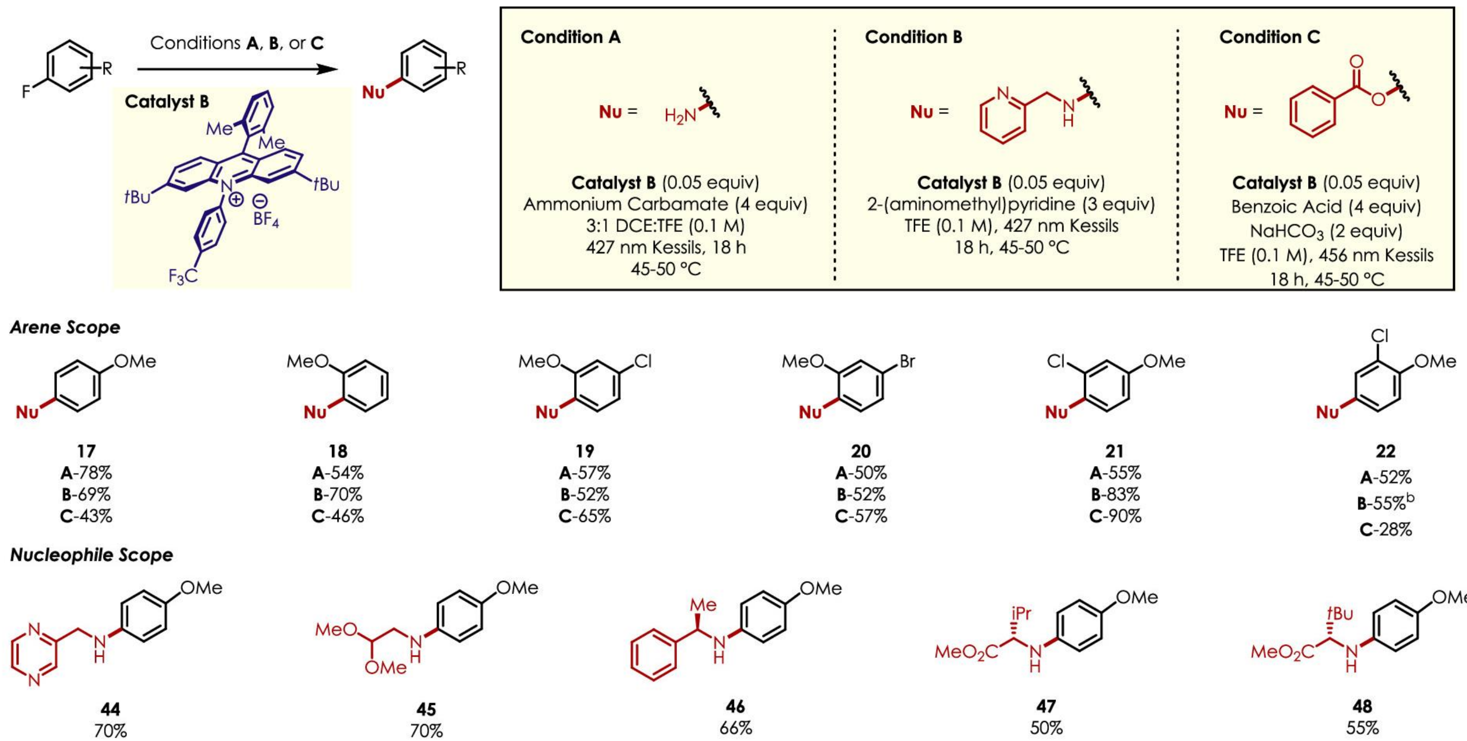


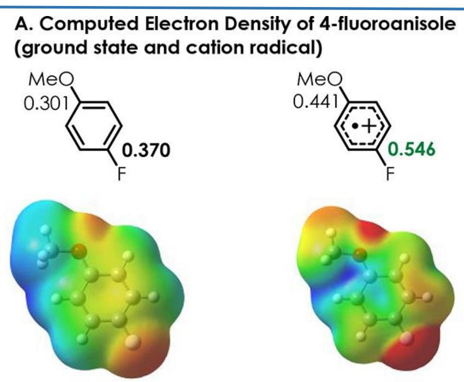
3a

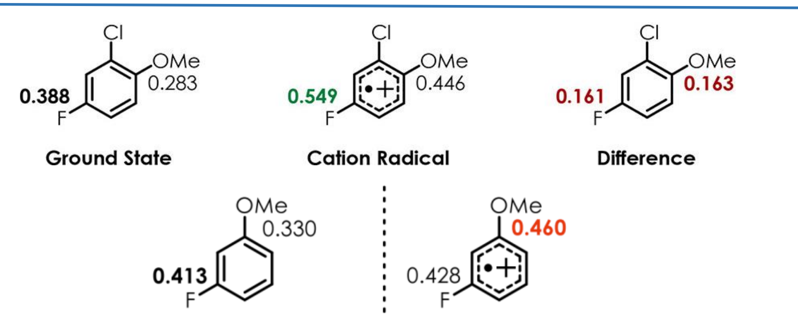
| Entry | Solvent | Catalyst A | | | 1a | | 2a | | 3a | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | $E_{0,0}$ (eV) | $E_{1/2}$ (V) | $E^{*red}_{1/2}$ (V) | $E_{p/2}$ (V) | $\Delta G_{ET}$ (kcal/mol) | $E_{p/2}$ (V) | $\Delta G_{ET}$ (kcal/mol) | $E_{p/2}$ (V) | $\Delta G_{ET}$ (kcal/mol) |
| 1 | MeCN | +2.65 | -0.08 | +2.57 | +2.24 | -8.07 | +2.21 | -8.76 | +1.70 | -20.06 |
| 2 | HFIP | +2.66 | -0.61 | +2.05 | +1.96 | -2.08 | +2.12 | +1.61 | +1.52 | -12.22 |


Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2020**, *142*, 17187.
Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2022**, *144*, 15118.

# Electron-rich Fluoroarene: C-O vs. C-F

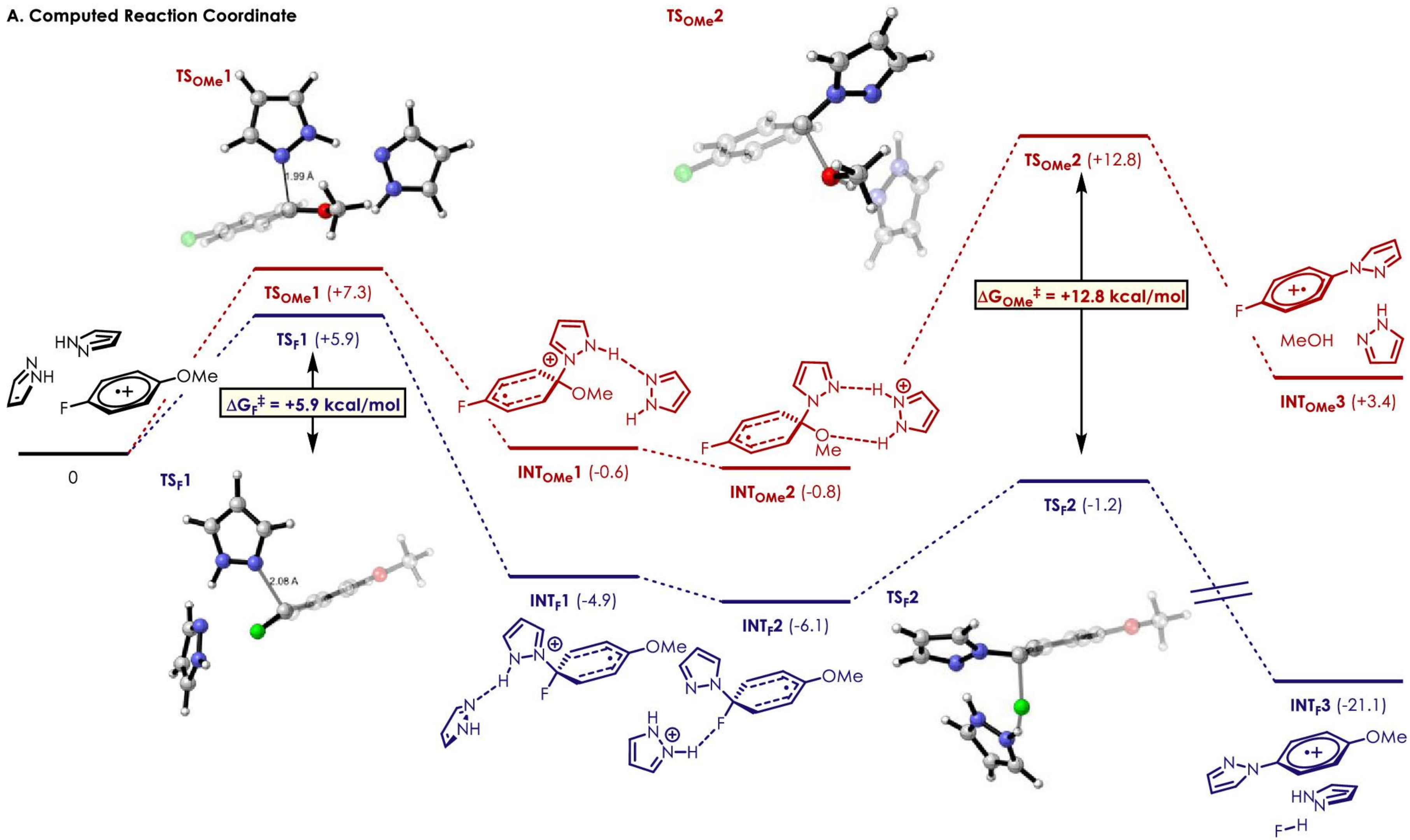


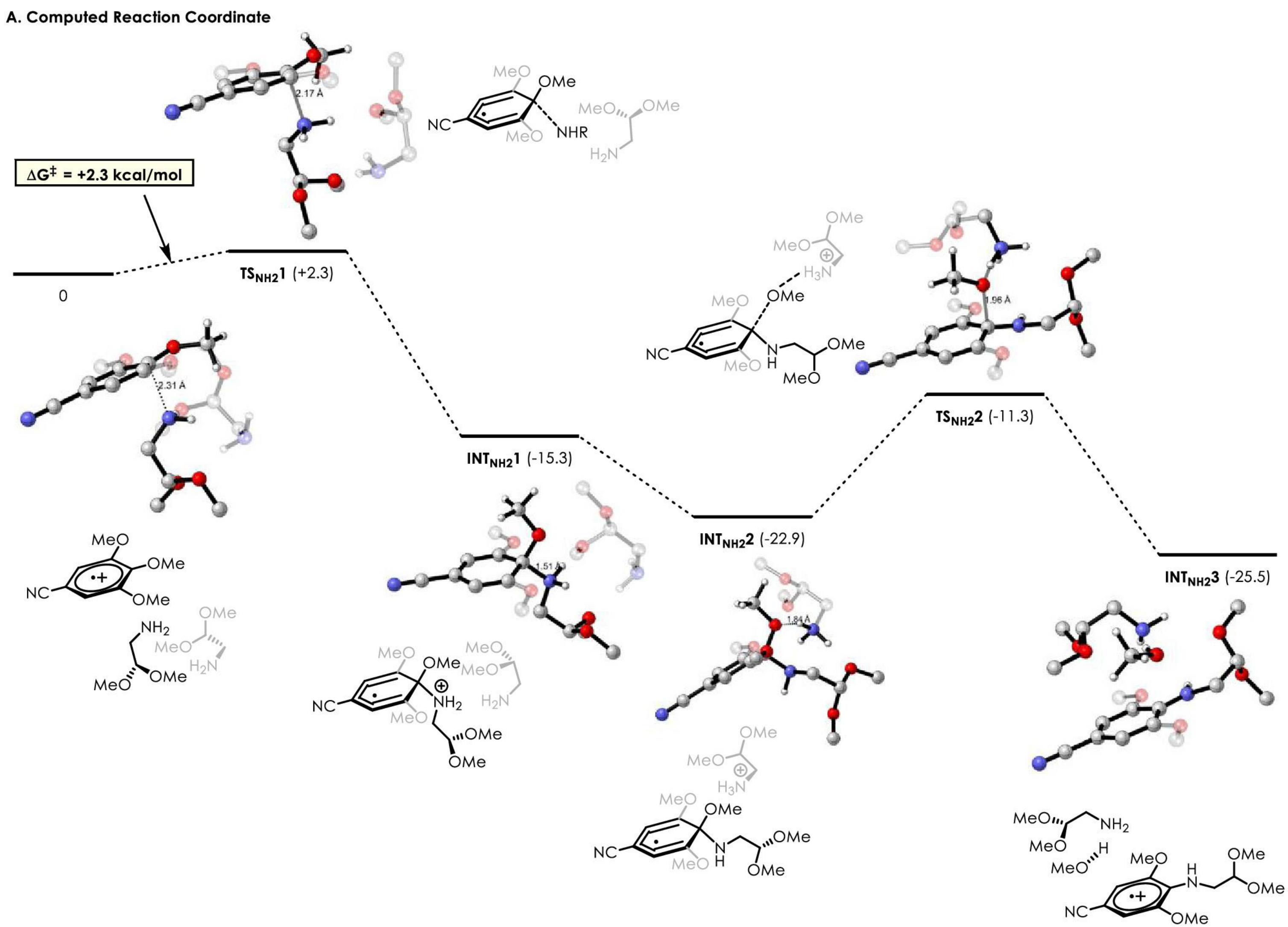

Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2020**, *142*, 17187.

# RDS Determination: Leaving Group Ability (& Δ*G*?)




Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2022**, *144*, 15118.

# -OMe as LG: Ambiguous RDS?

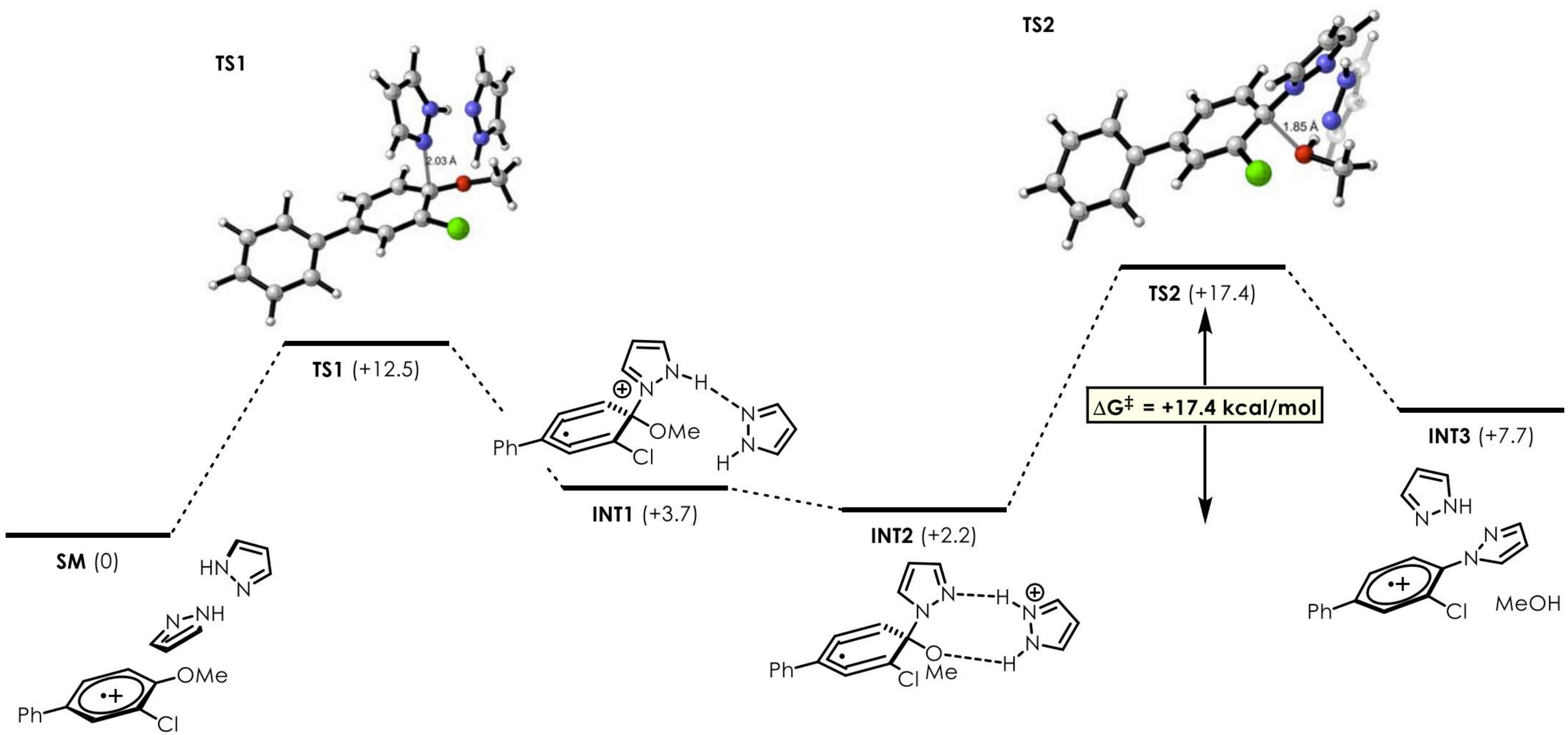



Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2022**, *144*, 15118.

# -OMe as LG: Ambiguous RDS?

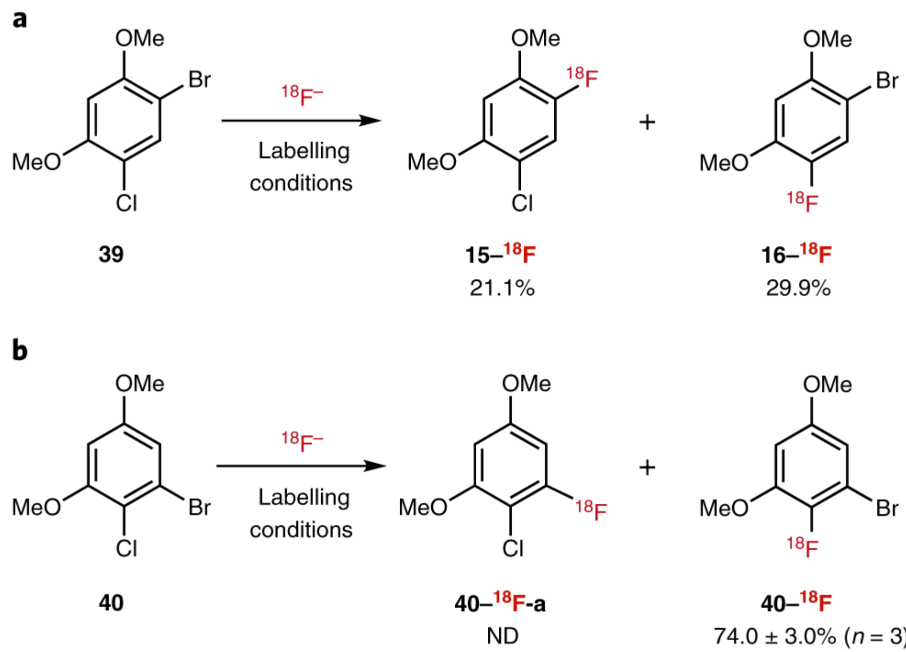
**Δ*G*(SM to INT3) > 0, Nu is the better leaving group, step2 is rate-limiting**

**Δ*G*(SM to INT3) < 0, LG is the better leaving group, step1 is rate-limiting**



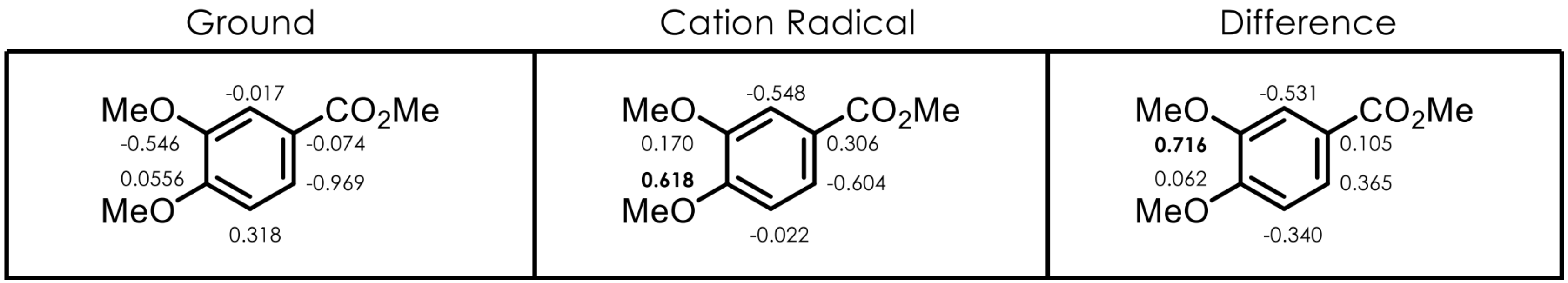

Pistritto, V. A. *et al. J. Am. Chem. Soc.* **2022**, *144*, 15118.

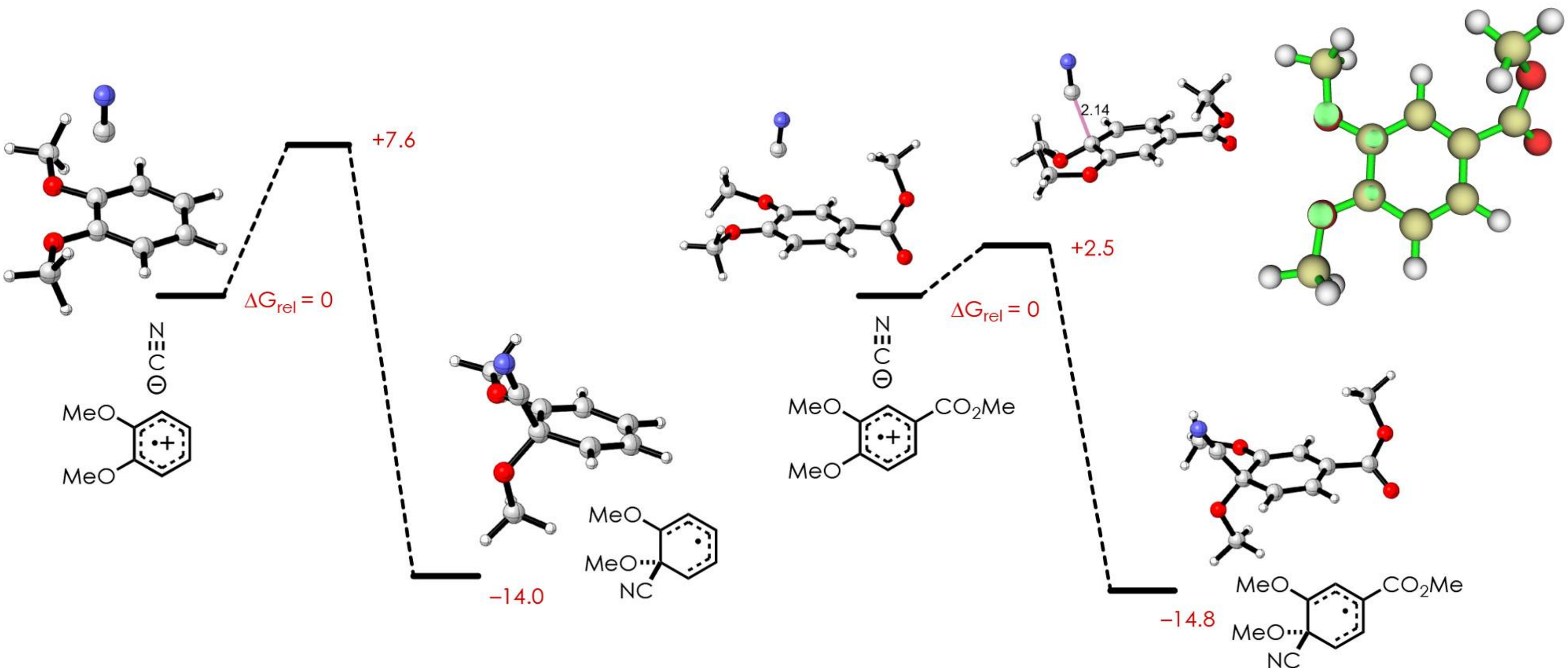
# Step1 is Rate-limiting: Regioselective Nu Addition



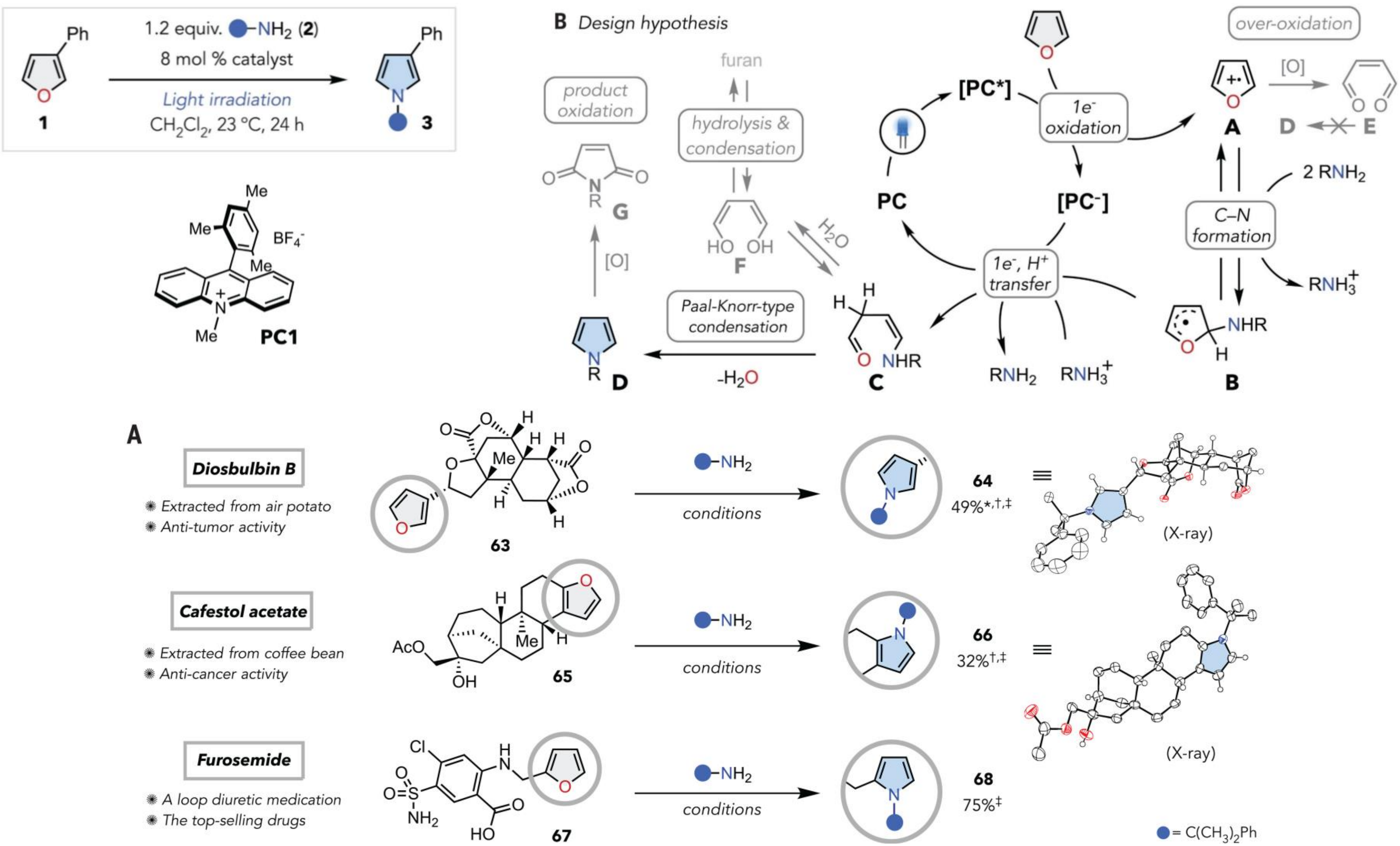

Chen, W. *et al. Nat. Chem.* **2022**, *14*, 216.

# Step2 is Rate-limiting: Regioselective LG Leaving



# Furan to Pyrrole Atom Editing




Donghyeon, K. *et al. Science* **2024**, *386, 99*.

# Outline

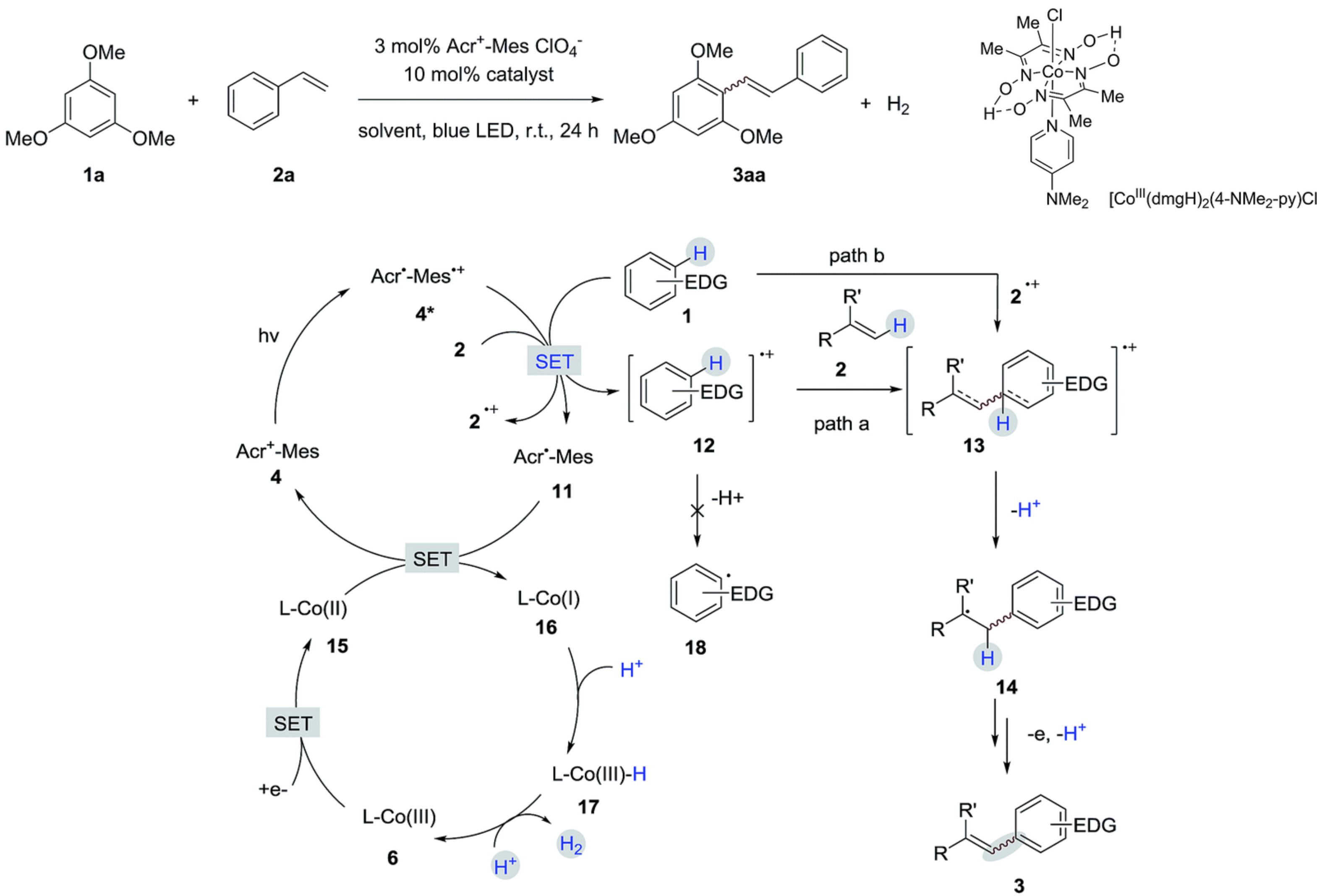
- Introduction
- Cation-type C-X Bond Formation

    Oxidative Arene C-H Functionalization

    Arene C-X Substitution: CRA-$S_N$Ar

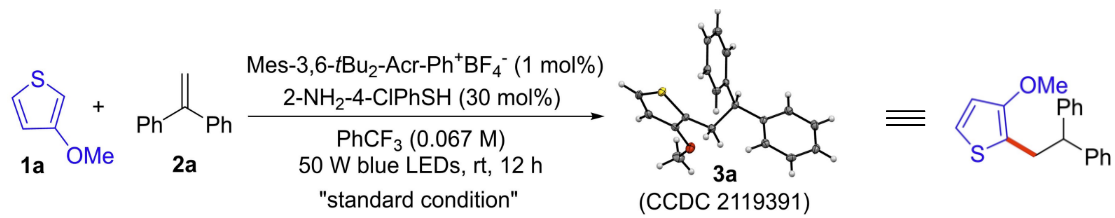
- Radical-type C-C Bond Formation
- Summary & Outlook

# Dehydrogenative Coupling

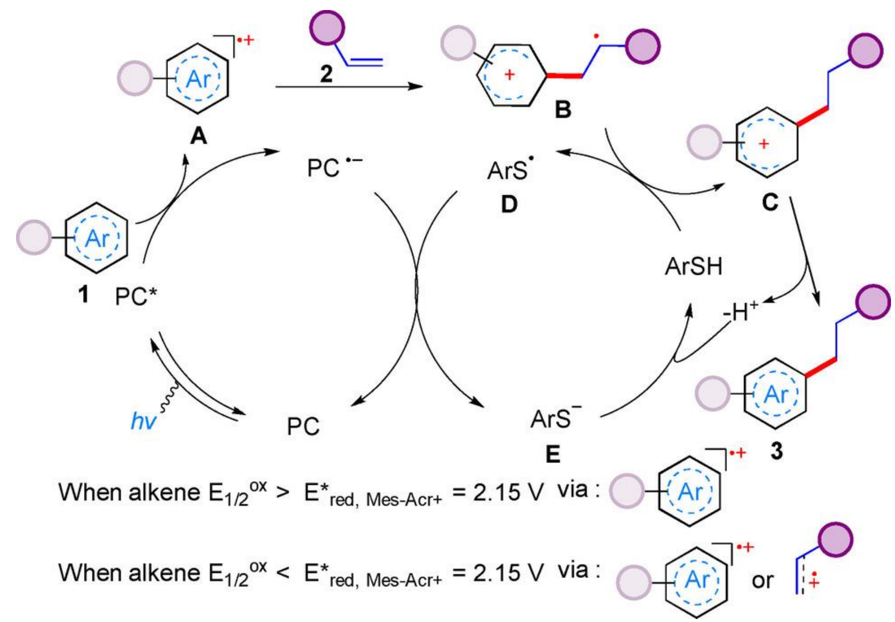



Hu, X. *et al. Chem. Sci.* **2018**, *9, 1521*.

# Thiol Catalyzed Radical-type Coupling




| entry | variation from "standard condition" | yield of **3 a**[a] |
|---|---|---|
| 1 | none | 91 % (89 %)[b] |
| 2 | Mes-2,7-$Me_2$-Acr-$Ph^+BF_4^-$ | 75 % |
| 3 | Mes-Acr-$Ph^+BF_4^-$ | 70 % |
| 4 | Mes-Acr-$Me^+ClO_4^-$ | 63 % |
| 5 | $Ir(dF(CF_3)ppy)_2(4,4'\text{-}dCF_3bpy)PF_6$ | 32 % |
| 6 | 2-$NH_2$PhSH | 78 % |
| 7 | 3-$NH_2$PhSH | 79 % |
| 8 | 4-$NH_2$PhSH | 82 % |
| 9 | 4-ClPhSH | 62 % |
| 10 | DCE | 86 % |
| 11 | DCM | 78 % |
| 12 | $CH_3CN$ | 31 % |
| 13 | toluene | 63 % |
| 14 | dioxane | 30 % |
| 15 | No light | N.R. |
| 16 | No PC/thiol | trace |




Chen, B. *et al. Angew. Chem. Int. Ed.* **2022**, *61,* e202200773.

# Outline

- Introduction
- Cation-type C-X Bond Formation
  - Oxidative Arene C-H Functionalization
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# Summary & Outlook

- **Regioselectivity:**

  **Oxidative C-H functionalization: Irreversible, orbital control**

  **CRA-$S_N$Ar: Reversible, RDS matters**

- **Dearomatization:**

  **Milder & higher functional group tolerance?**

  **Product inhibition?**

  **Quaternary carbon center?**