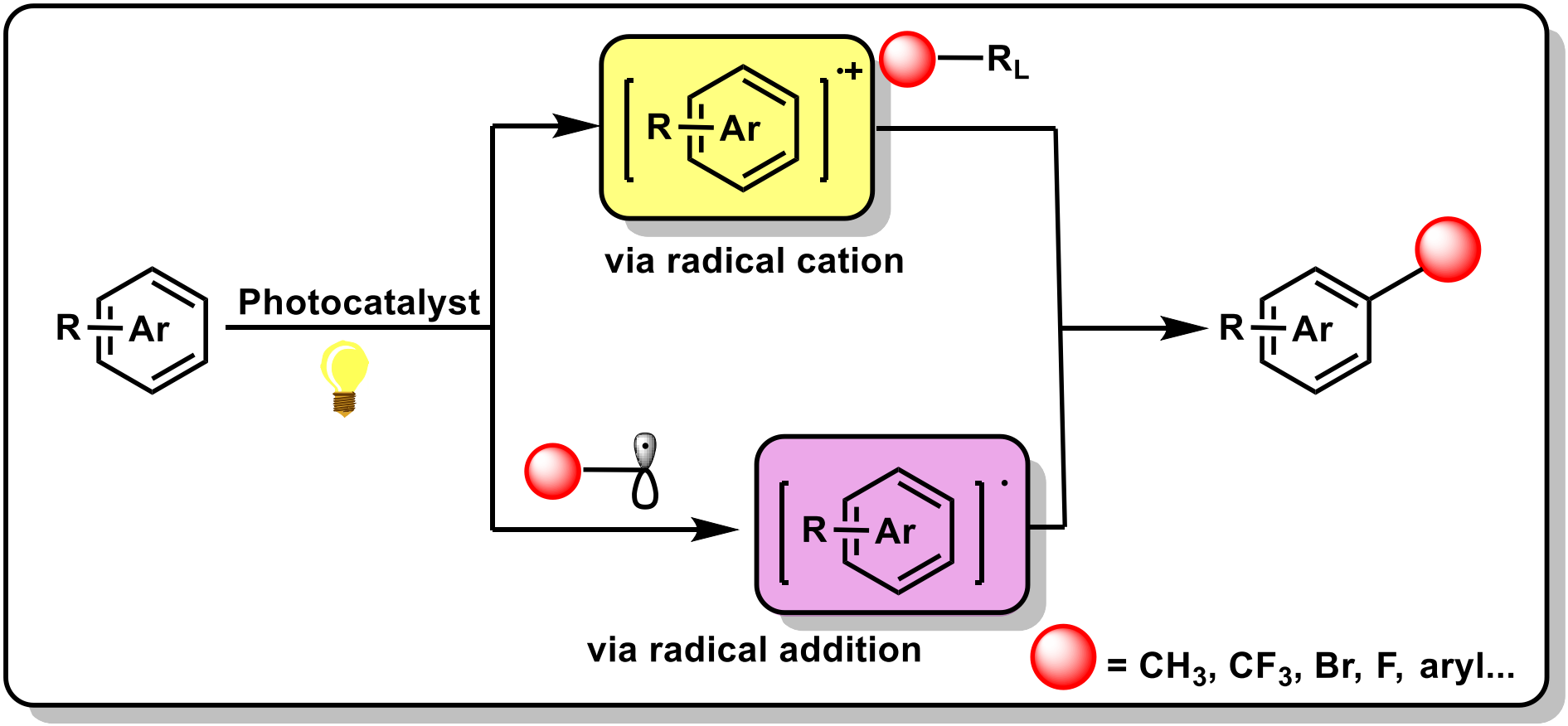
Functionalization of arene and heteroarene via organic photoredox catalysis

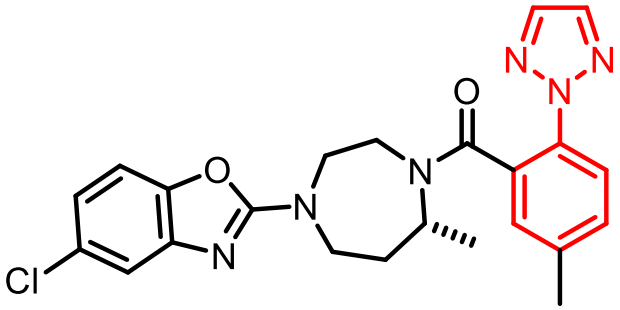


Reporter: Fengjin Wu
Supervisor: *Prof*. Huang
Date: 10. 23. 2017

Outline:

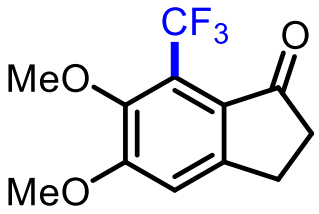
1. Background
2. Direct C-H bond functionalization of aromatic rings
    2.1. C-C bond formation on aromatic rings
    2.2. C-X bond formation on aromatic rings
3. Predictive model for site-selective functionalization
4. Conclusion
5. Acknowledgement

1. Background---Importance in late-stage functionalization (LSF)

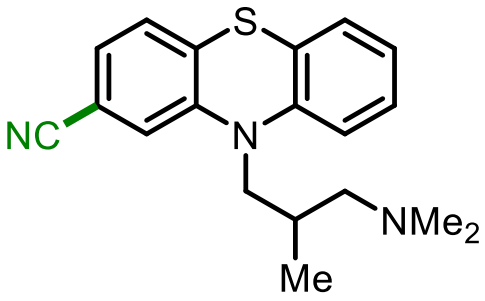


MK-4305

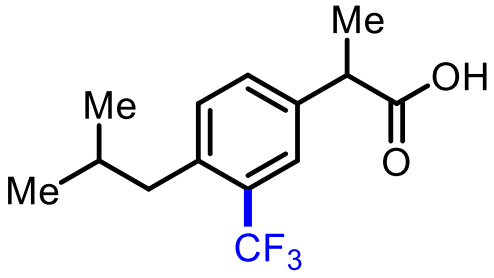
For the treatment of Insomnia in clinical trials



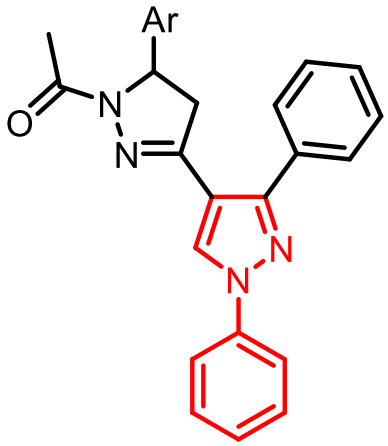
Anti-Alzheimer's CF_3-Aricept

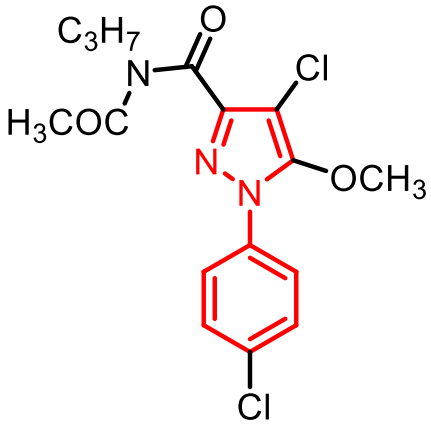


cyamemazine



Anti-inflammatory CF3-ibuprofen

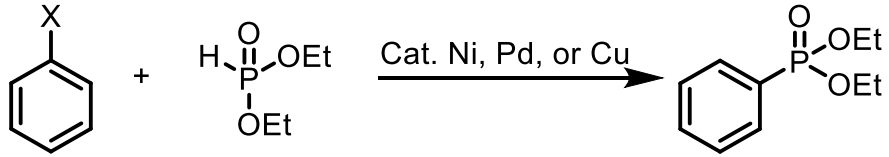




Growth inhibitors of some phytopathogenic fungi

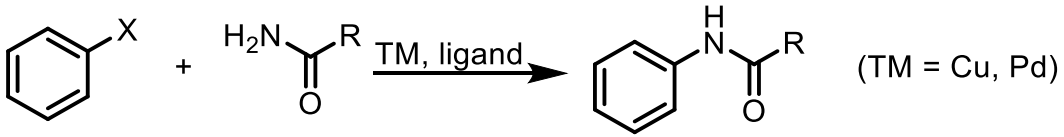
1. Background---Common methods to functionalize arene/heteroarene

Transitional-metal-catalyzed C-X bond activation phosphonylation:

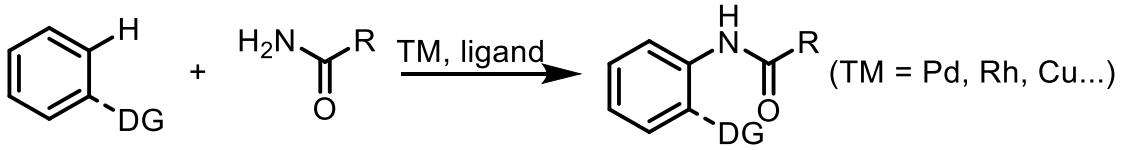


X = I, Br, OTf

Buchwald-Hartwig amidation:



Oxidative amidation:



DG = direct group

Expensive catalytic systems

often high reaction temperatures

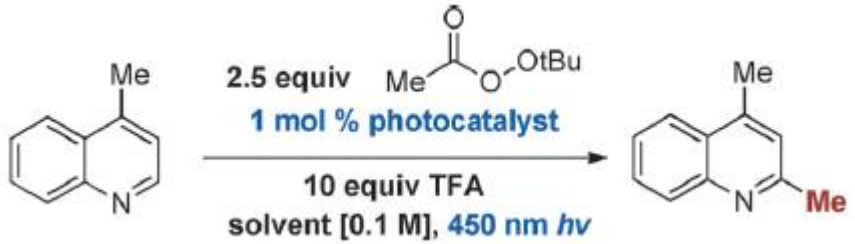
pre-functionalized substrates

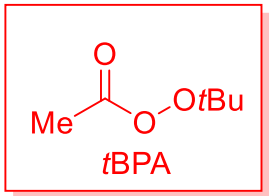
harsh reaction conditions

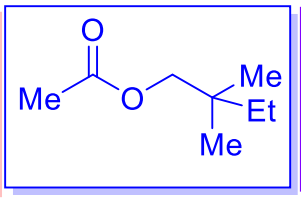
M. Min, D. Kang, S. Jung, S. Hong, *Adv. Synth. Catal*. **2016**, 358, 1296 ;
D. S. Surry and S. L. Buchwald, *Chem. Sci*. **2010**, 1, 13;
D. S. Surry and S. L. Buchwald, *Chem. Sci*. **2011**, 2, 27;
J. L. Jeffrey and R. Sarpong, *Chem. Sci*. **2013**, 4, 4092;

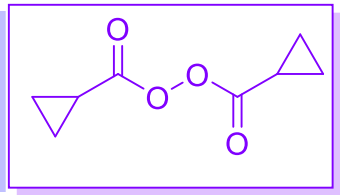
2. C-C bond formation on aromatic rings

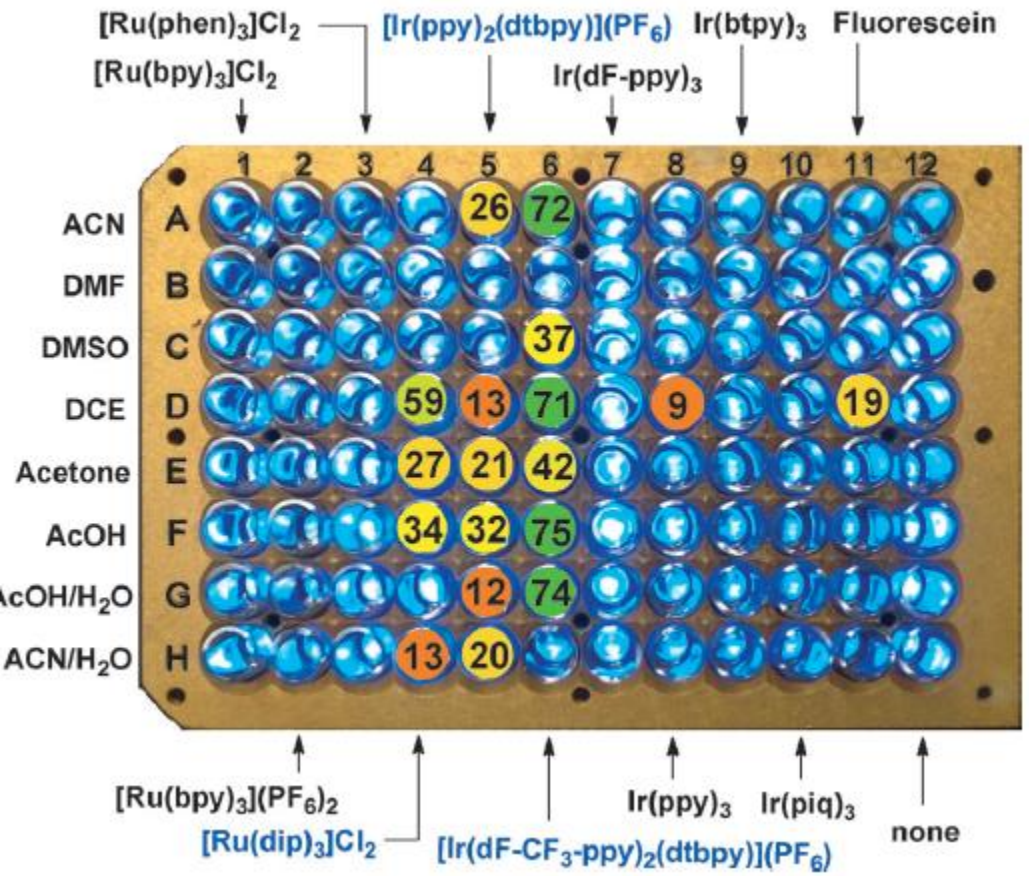
1）Alkylation of heteroarene: ***t*BPA** as alkylating agent

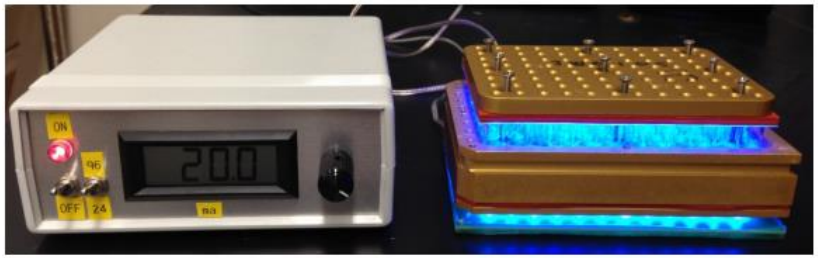








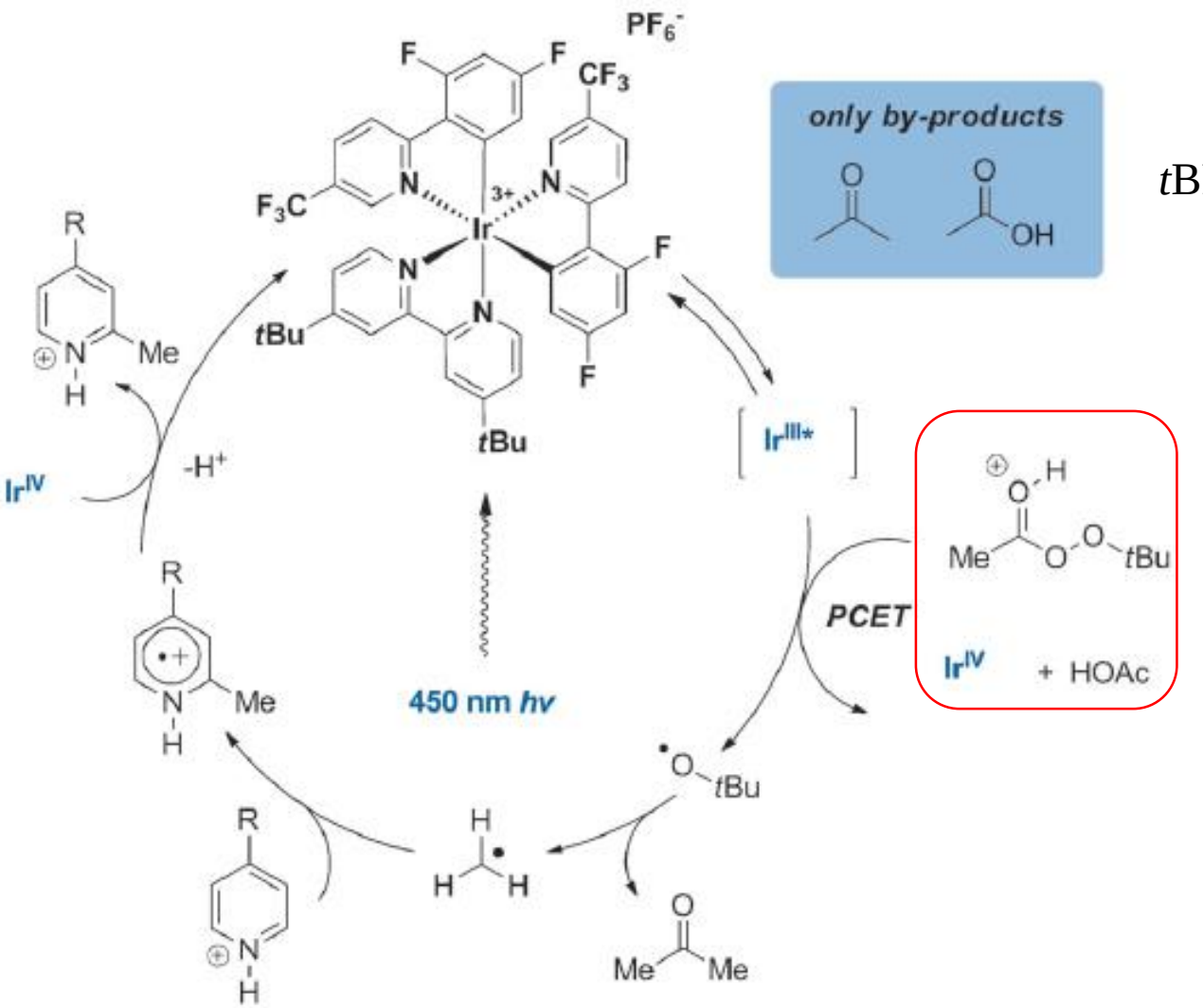




Daniel A. DiRocco, Kevin Dykstra, Shane Krska, Petr Vachal, Donald V. Conway, Matthew Tudge, *Angew. Chem. Int. Ed*. **2014**, 53, 4802.

2.1. C-C bond formation on aromatic rings

1）Alkylation of heteroarene: ***t*BPA** as alkylating agent



Proposed catalytic cycle for the photocatalyzed methylation of heterocycles with tBPA

*t*BPA (*t*BPB, E^0 = 1.95 V vs SCE)

Ir_{III}^* (E^0 = 0.89 V vs SCE)

proton-coupled electron transfer (PCET) under acidic conditions significantly lowers the barrier to reduction and may be kinetically feasible

2.1. C-C bond formation on aromatic rings

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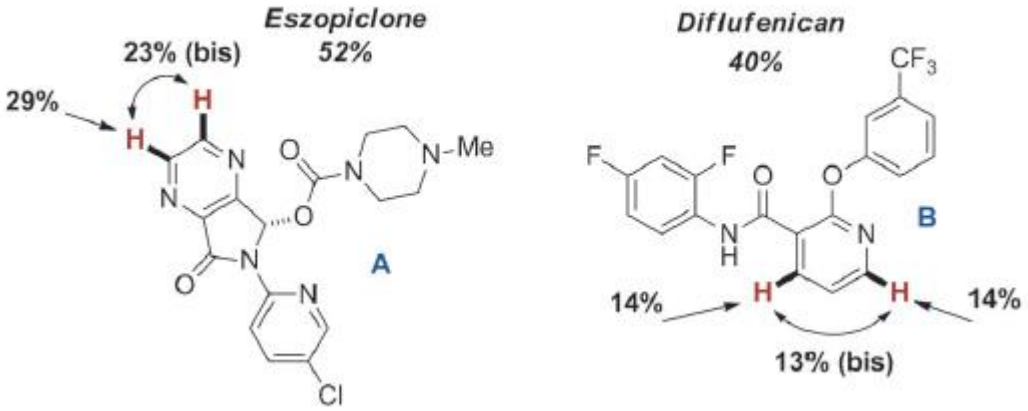
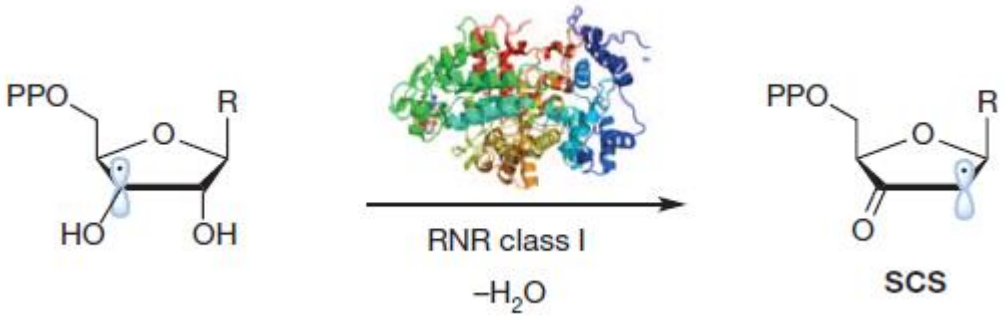


Poor regioselectivity

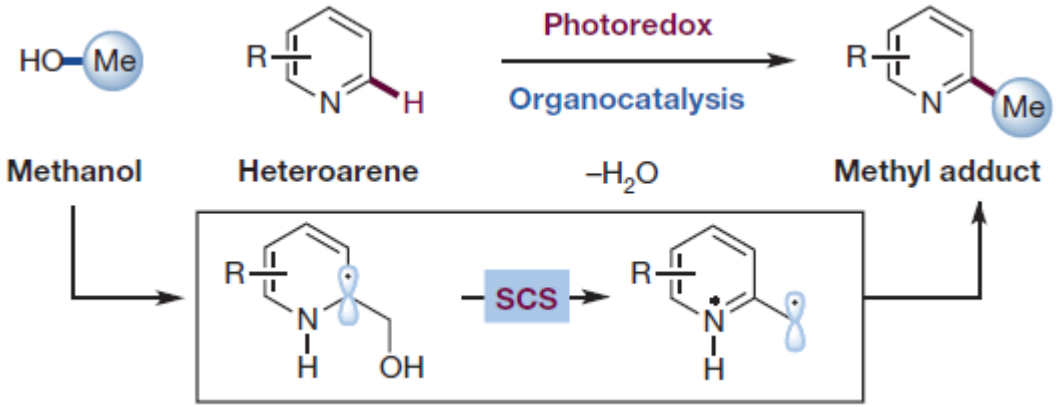
2.1. C-C bond formation on aromatic rings

1）Alkylation of heteroarene: **alcohol** as alkylating agent



DNA biosynthesis occurs via a spin-centre shift (SCS) process

Spin-centre shift (SCS): an alcohol C–O bond is cleaved, resulting in a carbon-centred radical intermediate

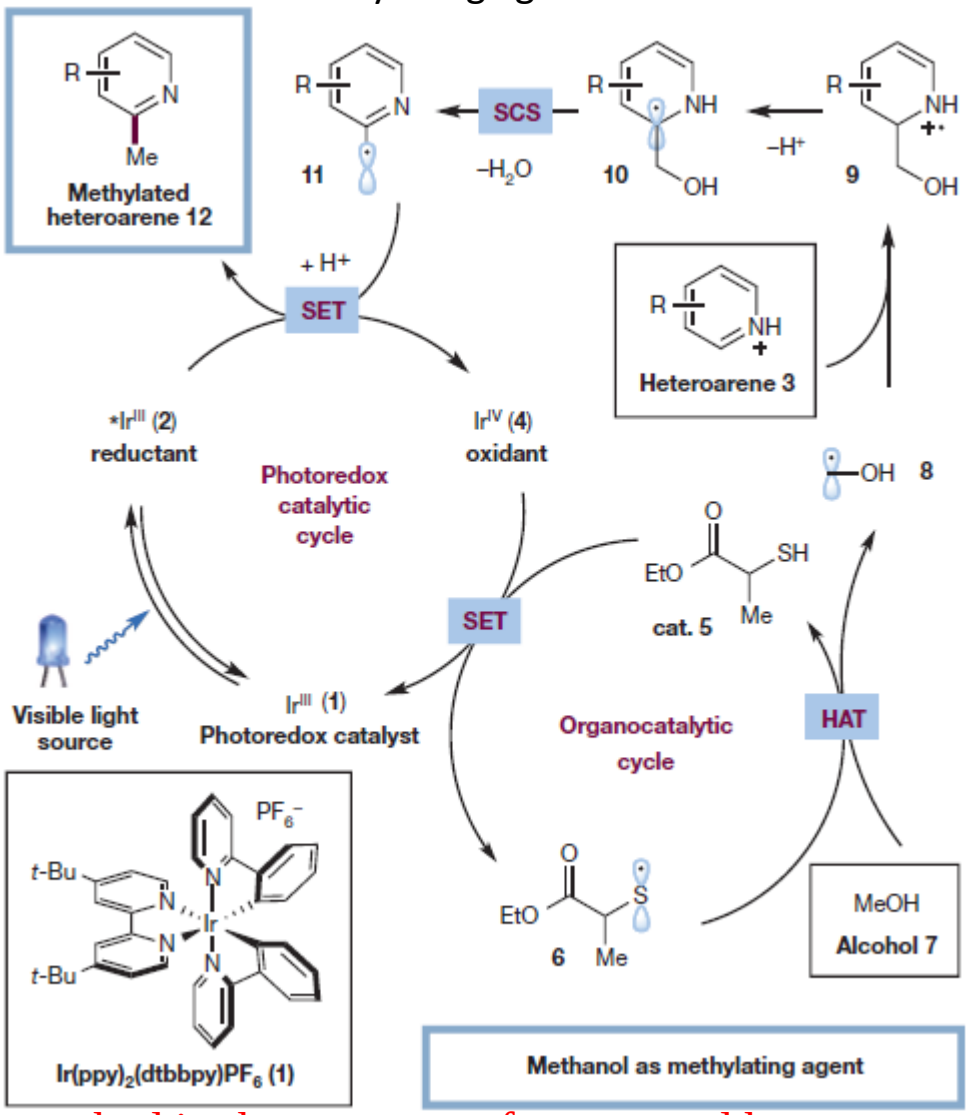


alcohols as alkyl radical precursors formed via high-energy irradiation (ultraviolet light and gamma rays)

Jian Jin, David W. C. MacMillan, *Nature*. **2015**, 525, 87.

2.1. C-C bond formation on aromatic rings

1）Alkylation of heteroarene: **alcohol** as alkylating agent



*Ir^{III} excited state 2 is quenched in the presence of protonated heteroarene 3, but not in the presence of the unprotonated heteroarene or thiol catalyst 5, indicating an oxidative quenching pathway

2.1. C-C bond formation on aromatic rings

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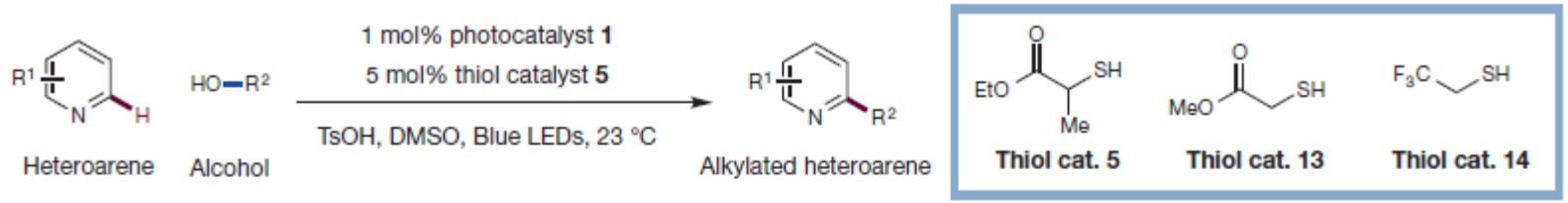
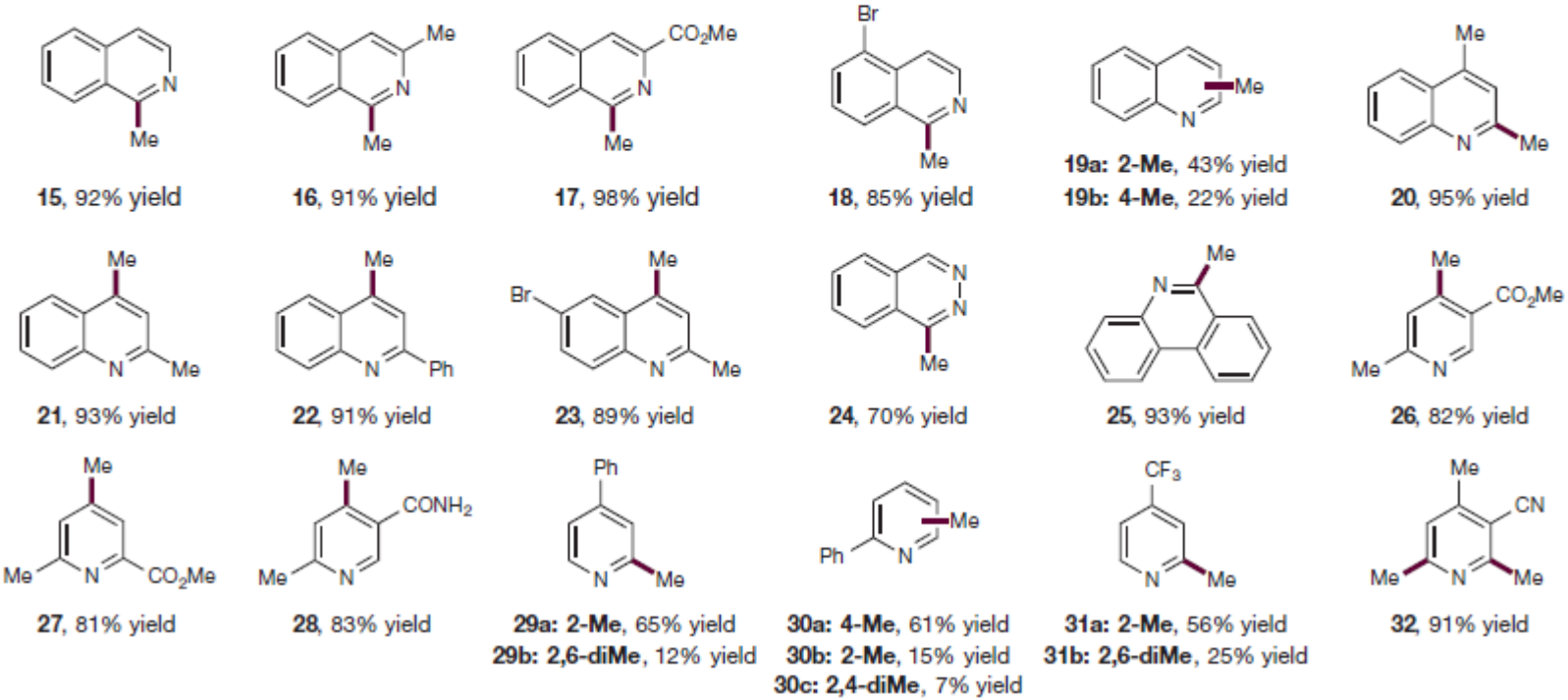


a Heteroarenes



Jian Jin, David W. C. MacMillan, *Nature*. **2015**, 525, 87.

2.1. C-C bond formation on aromatic rings

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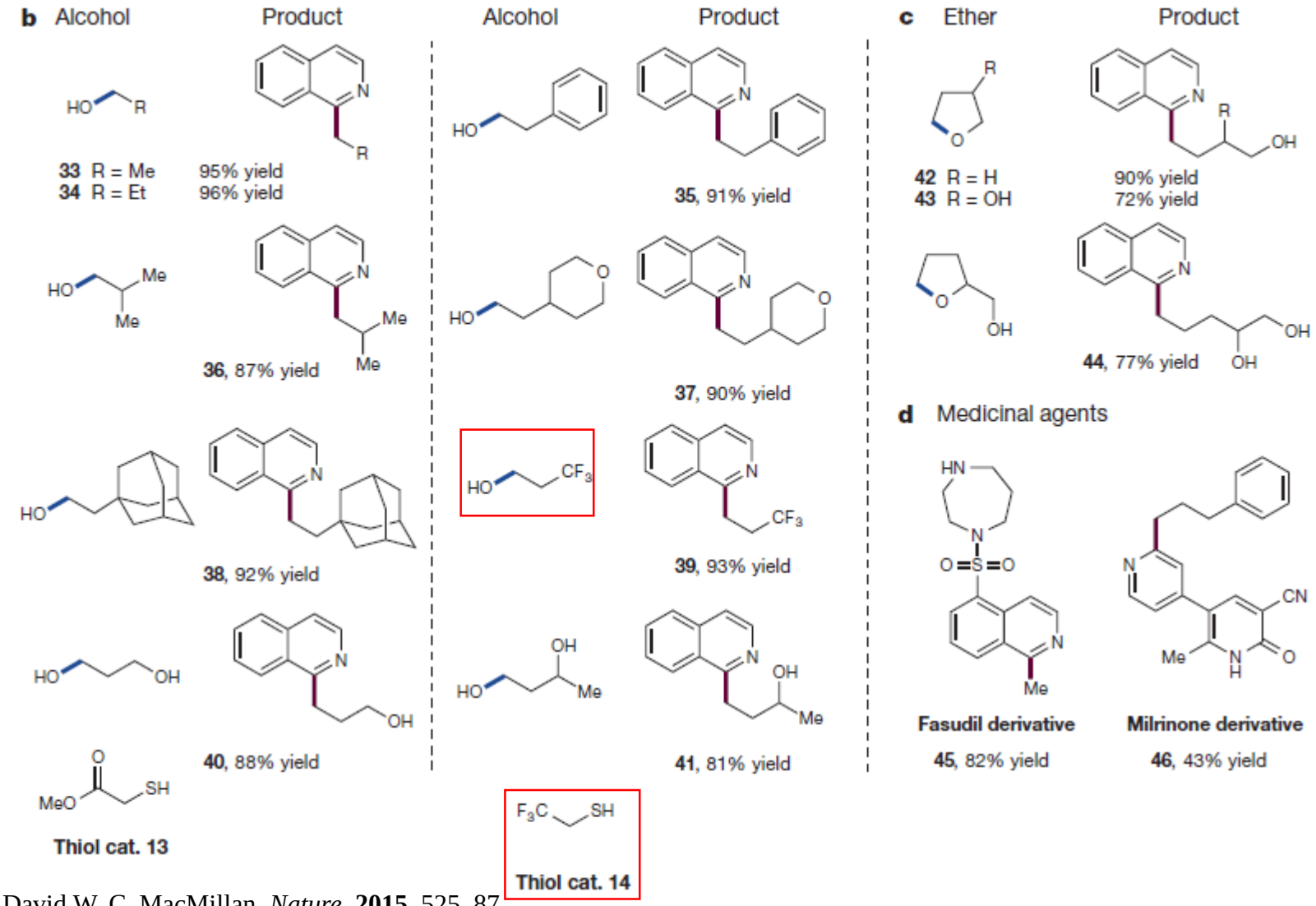
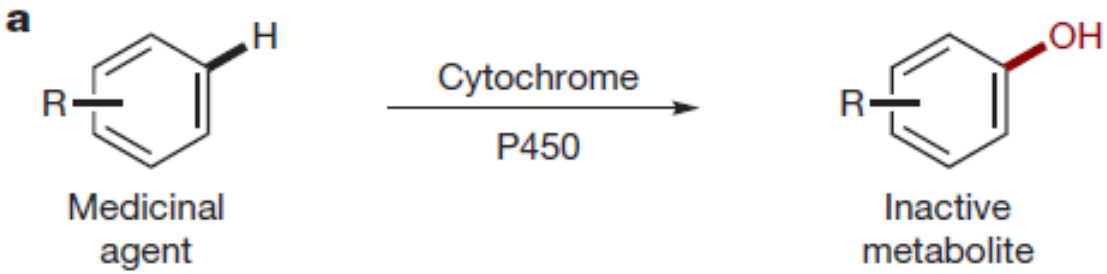


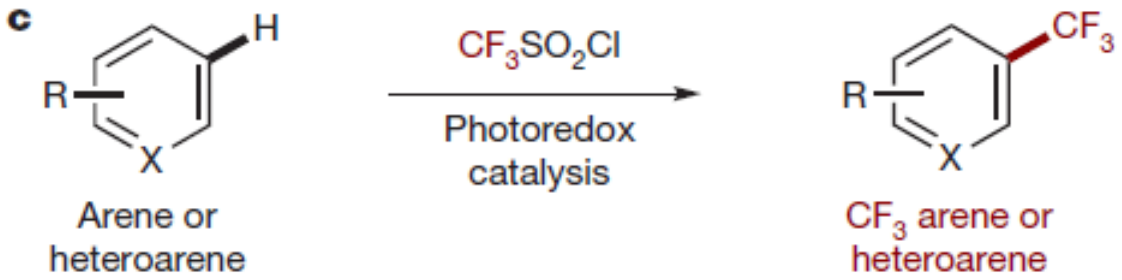
Jian Jin, David W. C. MacMillan, *Nature*. **2015**, 525, 87.

2.1. C-C bond formation on aromatic rings

2）Trifluoromethylation of arenes and heteroarenes



The excretion of medicinal agents is facilitated by remote functionalization of aromatic moieties



★ Site-specific incorporation of electrophilic radicals at metabolically susceptible positions

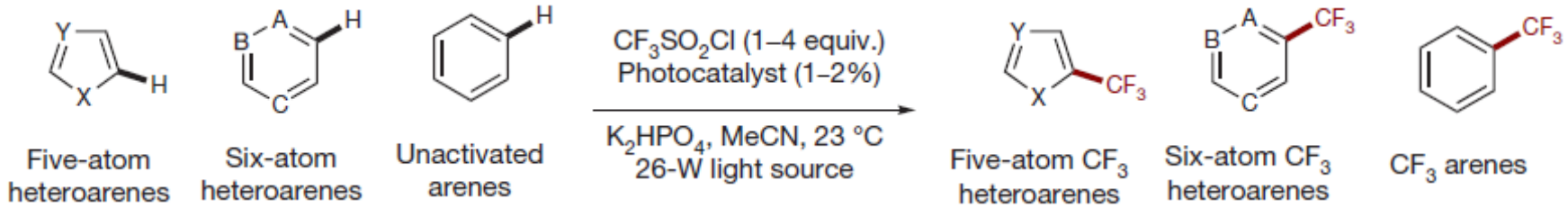
★ Preclude the need for pre-functionalization of arenes

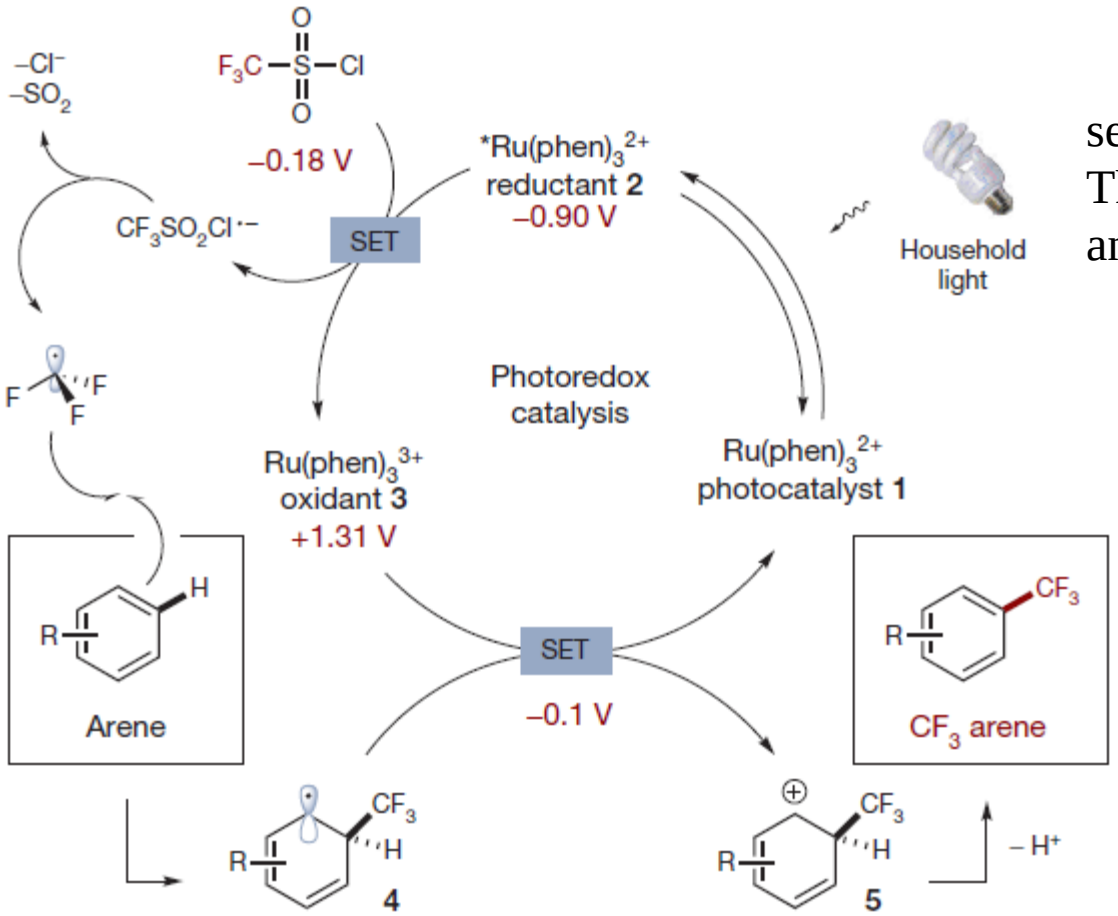
★ complementary method for late-stage synthetic intermediates.

David A. Nagib, David W. C. MacMillan, *Nature*. **2011**, 480, 224.

2.1. C-C bond formation on aromatic rings

2）Trifluoromethylation of arenes and heteroarenes



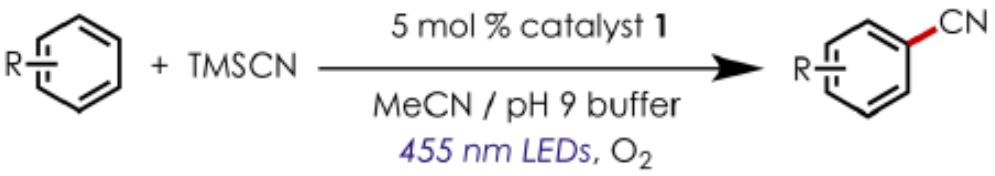


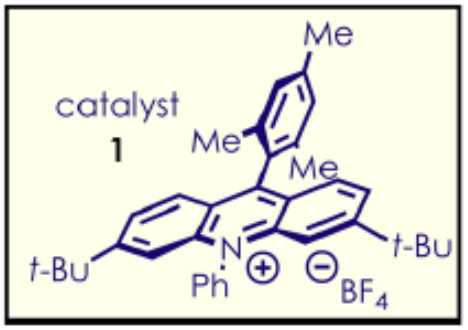
selectivity at the C2 position:
The formation of the conjugated radical and cationic intermediates.

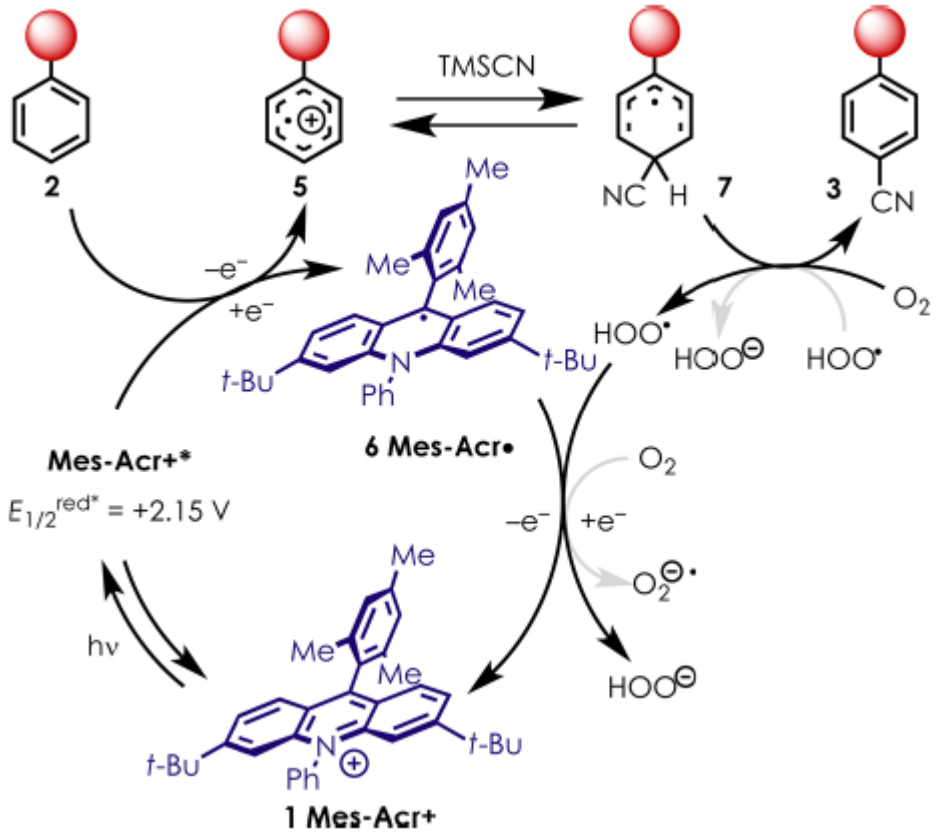
The region selectivity of arenes was not as good as heteroarenes.

2.1. C-C bond formation on aromatic rings

3）Cyanation of arenes and heteroarenes





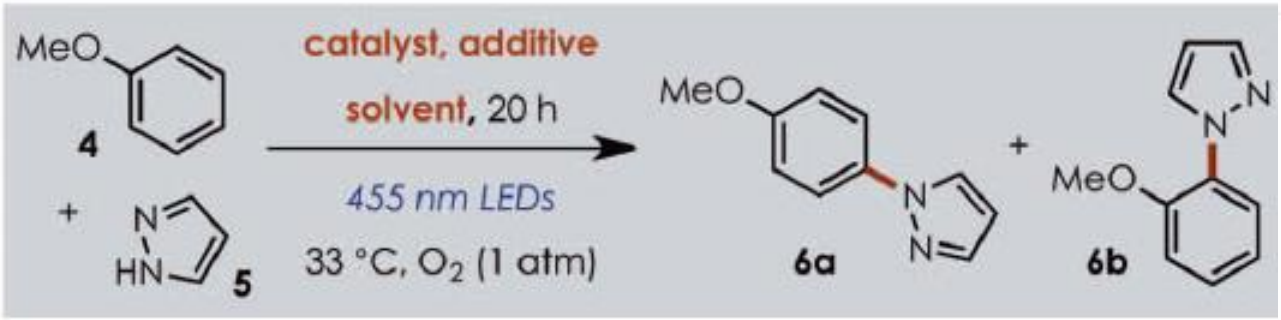


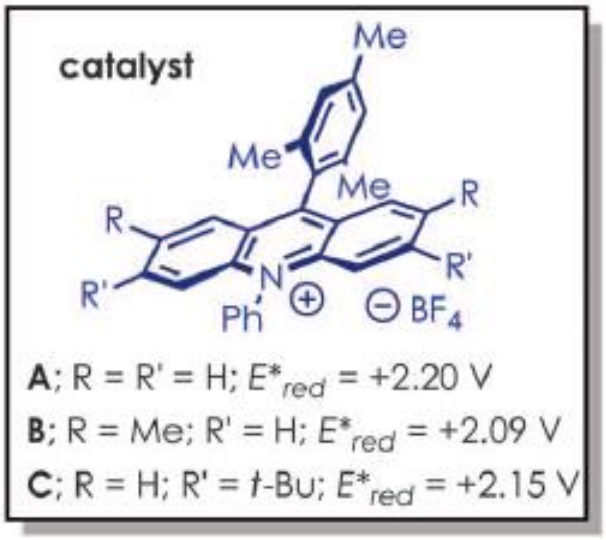
- Electron rich arenes work better;
- Heteroarenes can work;
- Ortho or para regioselectivity

Joshua B. McManus, David A. Nicewicz, *J. Am. Chem. Soc*. **2017**, 139, 2880.

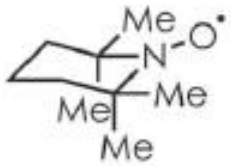
2.2. C-X bond formation on aromatic rings

1）The formation of C-N bond

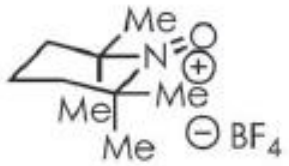




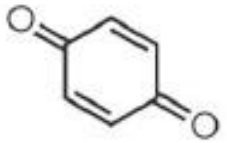
additives:



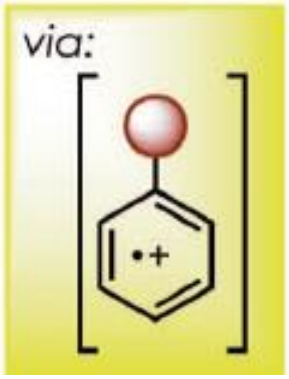
TEMPO



TEMPOniumBF$_4$



BQ



-Arene as limiting reagent

-Diverse amine scope including azoles and ammonia

-Good to excellent site selectivity

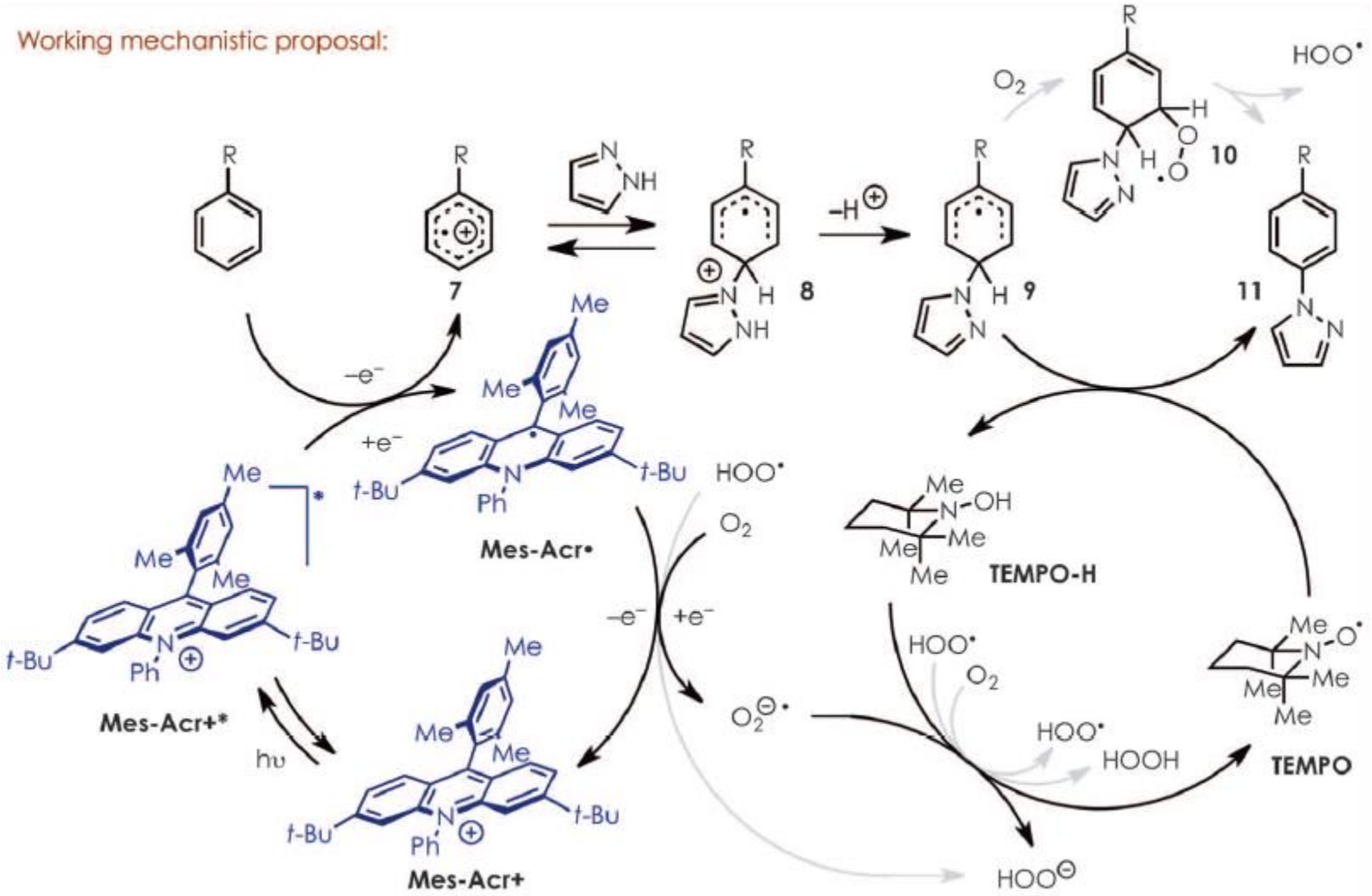
-Easily tunable organic catalyst system

-General method for arene C–*H* functionalization

Nathan A. Romero, Kaila A. Margrey, Nicholas E. Tay, David A. Nicewicz, *Science*. **2015**, 349, 1326.

2.2. C-X bond formation on aromatic rings

1）The formation of C-N bond



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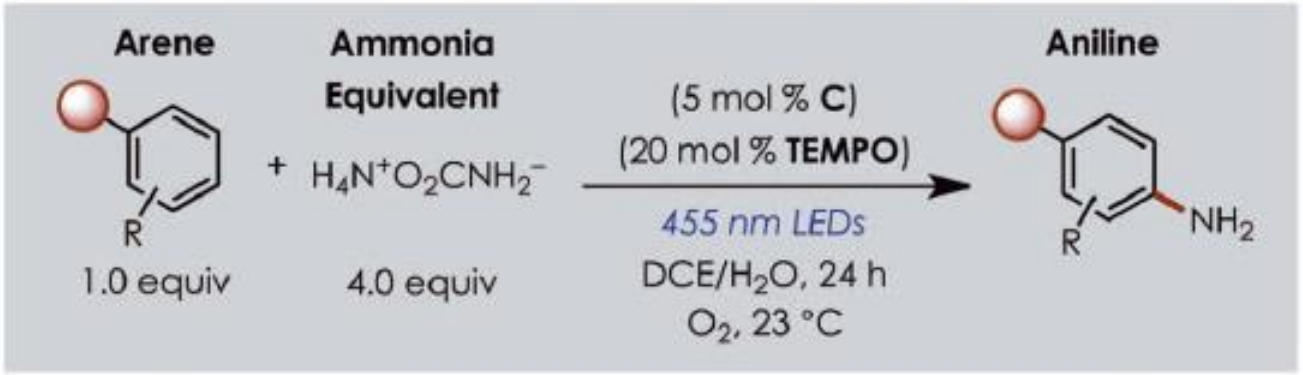
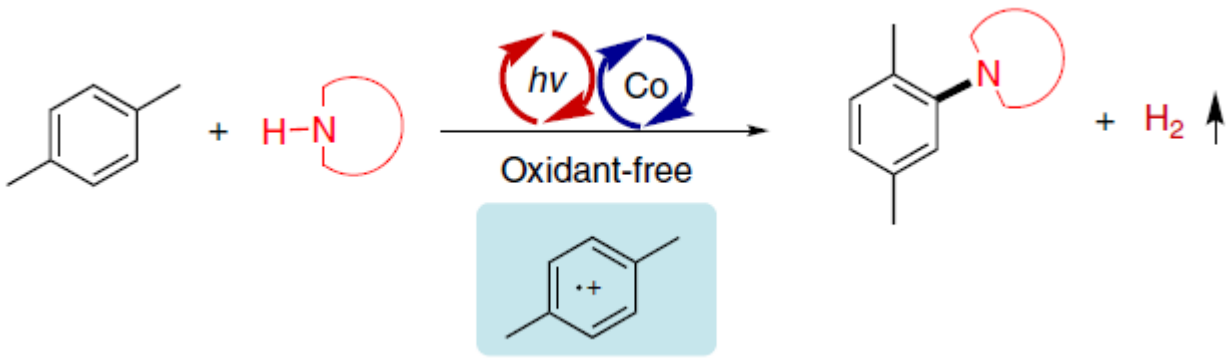


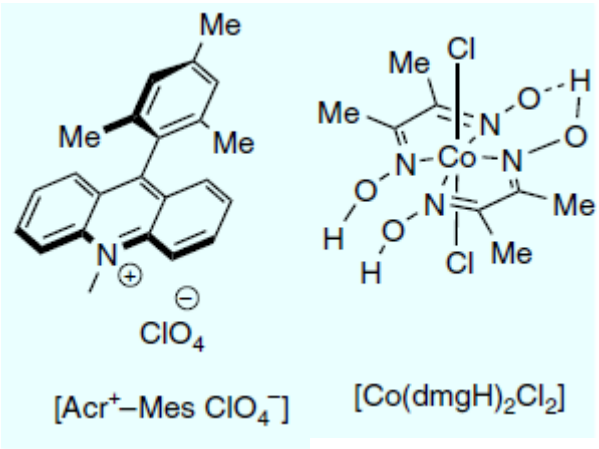
Nathan A. Romero, Kaila A. Margrey, Nicholas E. Tay, David A. Nicewicz, *Science*. **2015**, 349, 1326.

2.2. C-X bond formation on aromatic rings

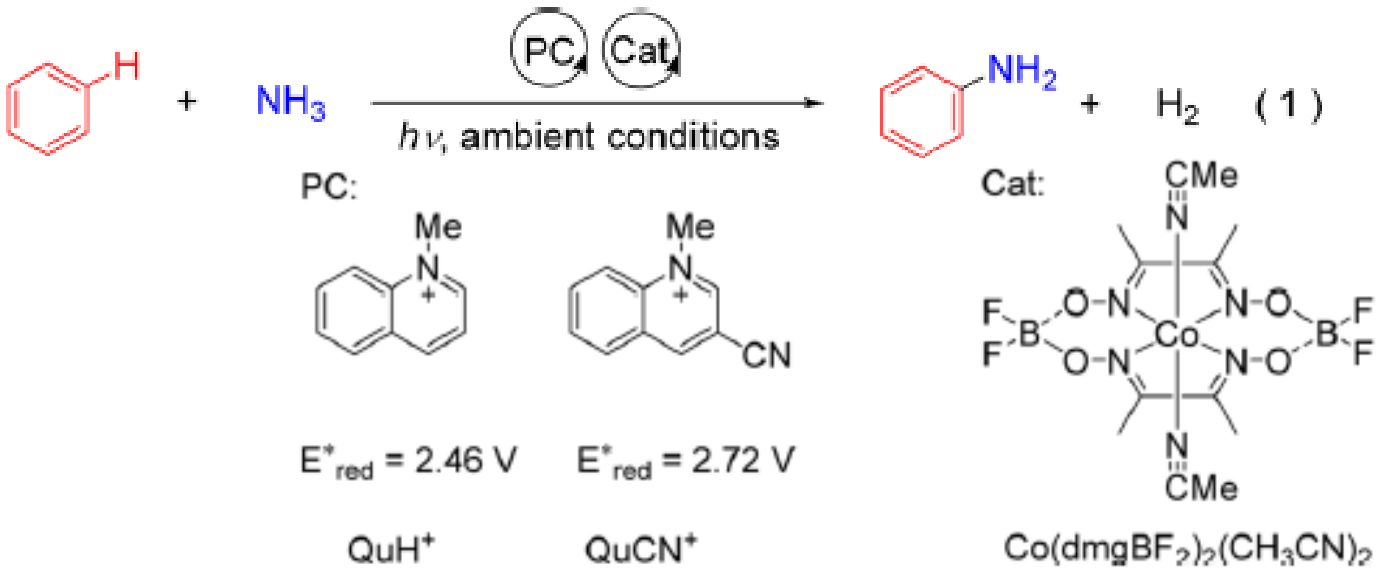
1）The formation of C-N bond

A selective C(sp^2)-H amination of arenes：





Hydrogen-evolution cross-coupling amination：



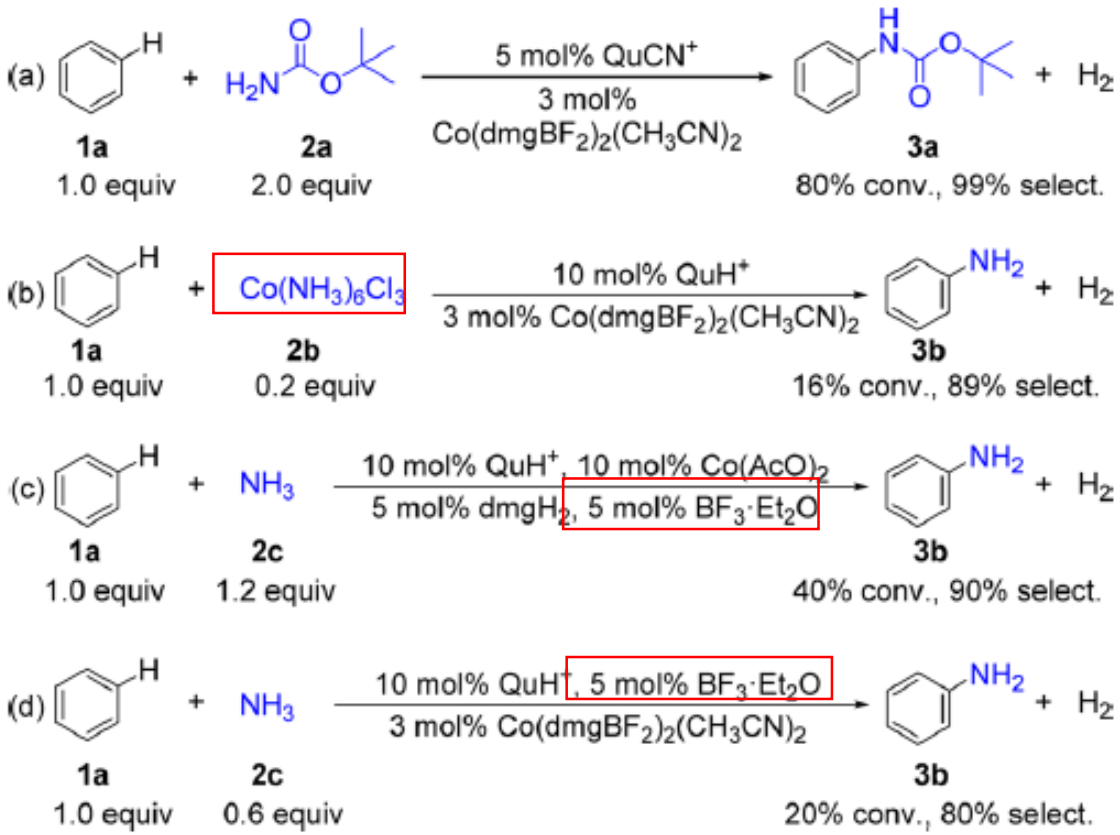
Linbin Niu, Hong Yi, Shengchun Wang, Tianyi Liu, Jiamei Liu, Aiwen Lei, Nature Commun. 2017, 8, 14226.

Yi-Wen Zheng, Bin Chen, Pan Ye, Ke Feng, Wenguang Wang, Qing-Yuan Meng, Li-Zhu Wu, Chen-Ho Tung, *J. Am. Chem. Soc*. **2016**, 138, 10080

2.2. C-X bond formation on aromatic rings

1）The formation of C-N bond

Hydrogen-evolution cross-coupling amination：



[a] λ > 300 nm, in CH_3CN, ambinent conditions. Selectivity = yield/conversion.

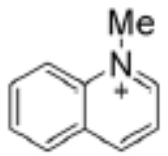
Coordination of ammonia to metal or BF_3 can activate ammonia

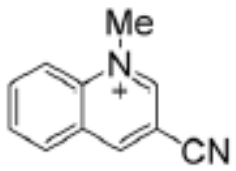
Yi-Wen Zheng, Bin Chen, Pan Ye, Ke Feng, Wenguang Wang, Qing-Yuan Meng, Li-Zhu Wu, Chen-Ho Tung, *J. Am. Chem. Soc*. **2016**, 138, 10080.

2.2. C-X bond formation on aromatic rings

2）The formation of C-O bond

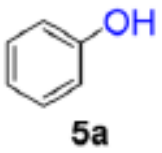
PC:





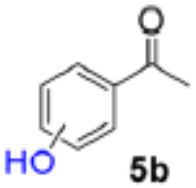
E^*_{red} = 2.46 V E^*_{red} = 2.72 V

QuH^+ $QuCN^+$



5a

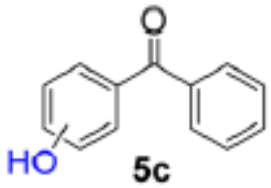
90% conv., 100% select.



5b

58% conv., 100% select.

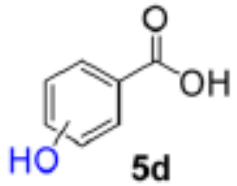
(o : m : p = 65 : 11 : 24)



5c

34% conv., 99% select.

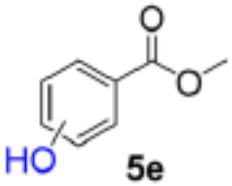
(o : m : p = 57 : 14 : 28)



5d

53% conv., 78% select.

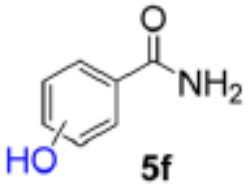
(o : m : p = 55 : 4 : 19)



5e

49% conv., 97% select.

(o : m : p = 57 : 17 : 23)

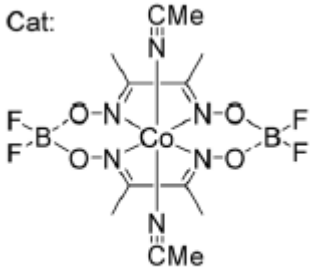


5f

63% conv., 84% select.

(o : m : p = 55 : 12 : 17)

Cat:

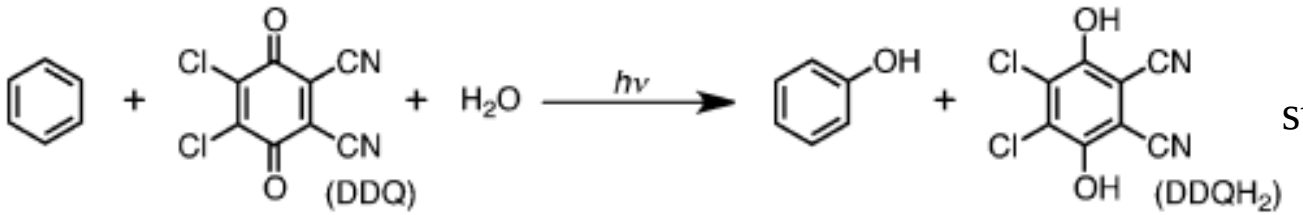


$Co(dmgBF_2)_2(CH_3CN)_2$

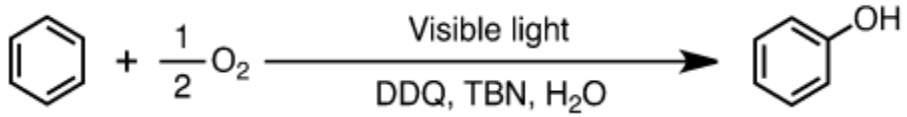
Yi-Wen Zheng, Bin Chen, Pan Ye, Ke Feng, Wenguang Wang, Qing-Yuan Meng, Li-Zhu Wu, Chen-Ho Tung, *J. Am. Chem. Soc*. **2016**, 138, 10080.

2.2. C-X bond formation on aromatic rings

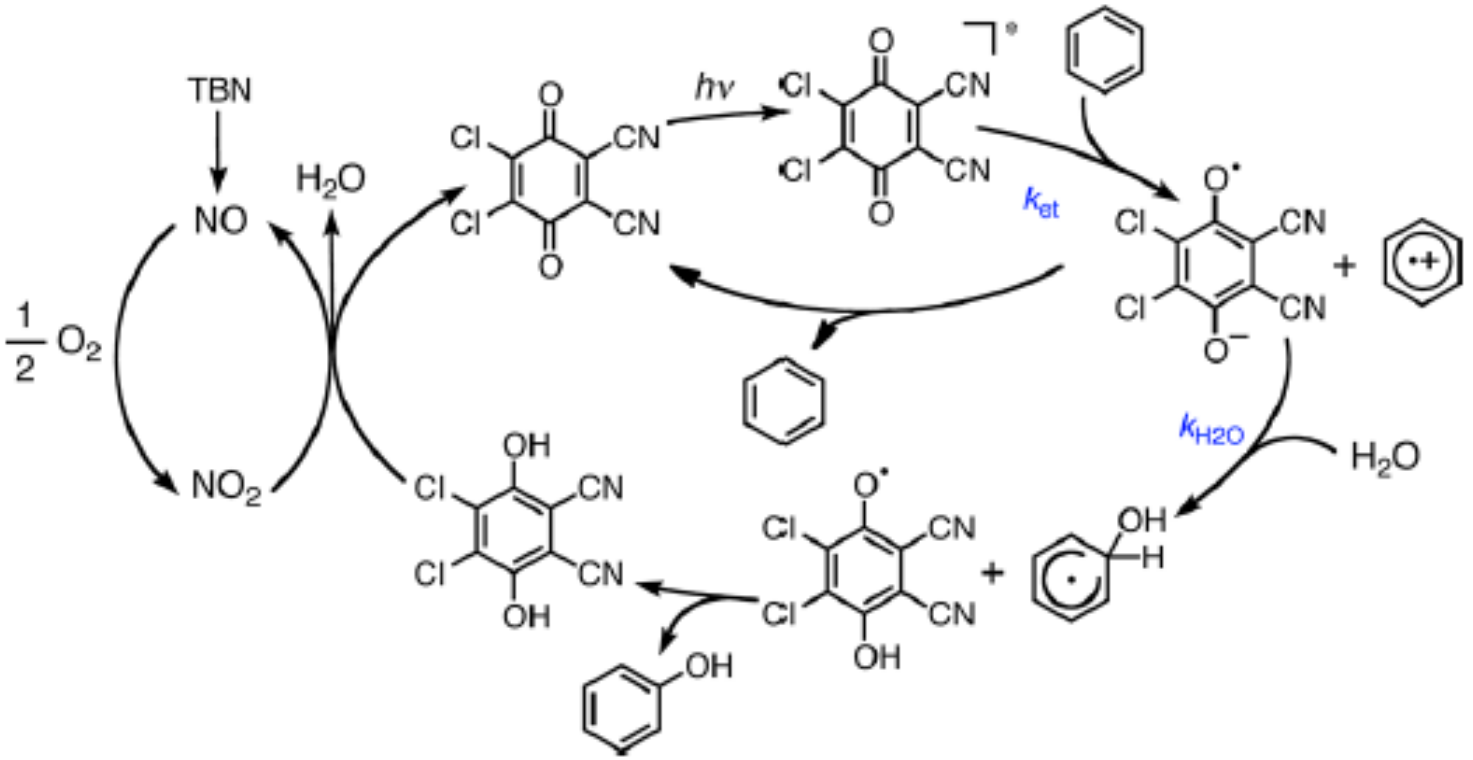
2）The formation of C-O bond



stoichiometric oxidant---DDQ



catalytic oxygenation

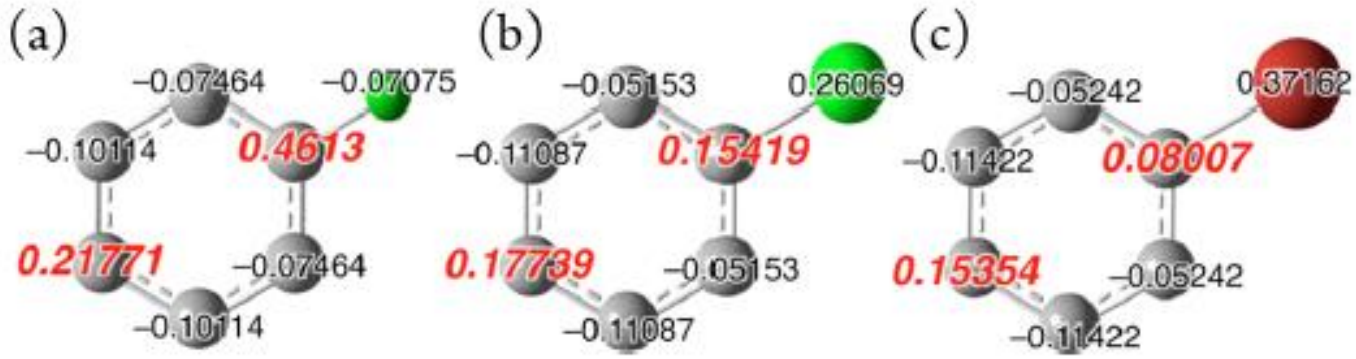


Kei Ohkubo, Atsushi Fujimoto, Shunichi Fukuzumi, *J. Am. Chem. Soc.* **2013**, 135, 5368.

2.2. C-X bond formation on aromatic rings

2）The formation of C-O bond

substrate (conversion, %)	product: yield, % (selectivity, %)
fluorobenzene (44)	phenol: 14 (32)
	p-fluorophenol: 24 (55)
	o-fluorophenol: 5.7 (13)
chlorobenzene (34)	phenol: 0 (0)
	p-chlorophenol: 28 (82)
	o-chlorophenol: 6.1 (18)
bromobenzene (14)	phenol: 0 (0)
	p-bromophenol: 11 (80)
	o-bromophenol: 2.8 (20)

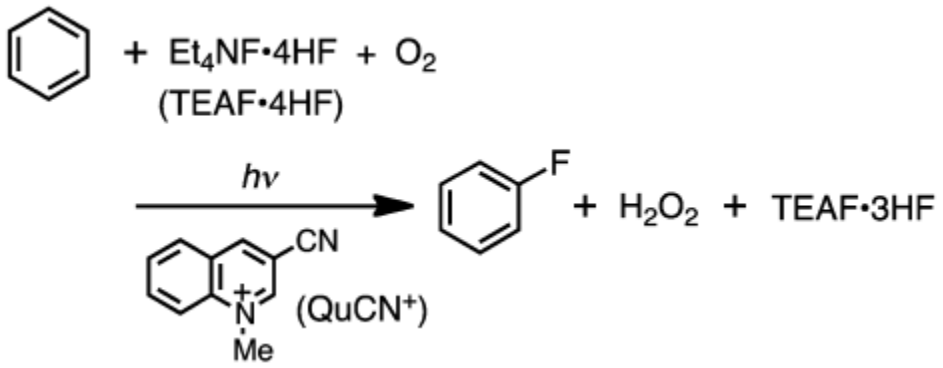


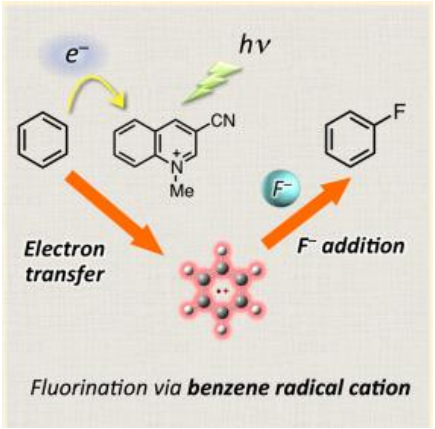
fluorobenzene chlorobenzene bromobenzene

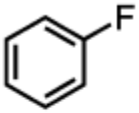
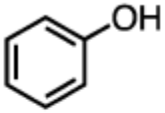
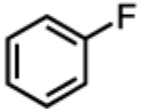
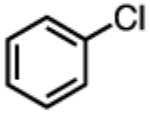
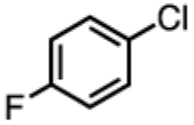
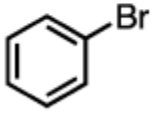
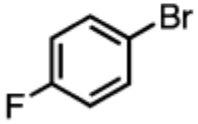
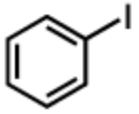
Kei Ohkubo, Atsushi Fujimoto, Shunichi Fukuzumi, *J. Am. Chem. Soc*. **2013**, 135, 5368.

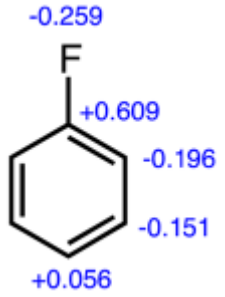
2.2. C-X bond formation on aromatic rings

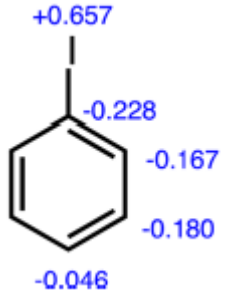
3）The formation of C-F bond





substrate	conv., %	product	yield, %	k_q, M^{-1} s^{-1}	k_F, M^{-1} s^{-1}
	40	 20	 4	1.1×10^{10}	9.4×10^{9}
	39	no fluorination		1.0×10^{10}	7.7×10^{9}
	34		7	1.1×10^{10}	7.0×10^{9}
	25		6	1.2×10^{10}	3.4×10^{9}
	trace	no fluorination		1.3×10^{10}	—

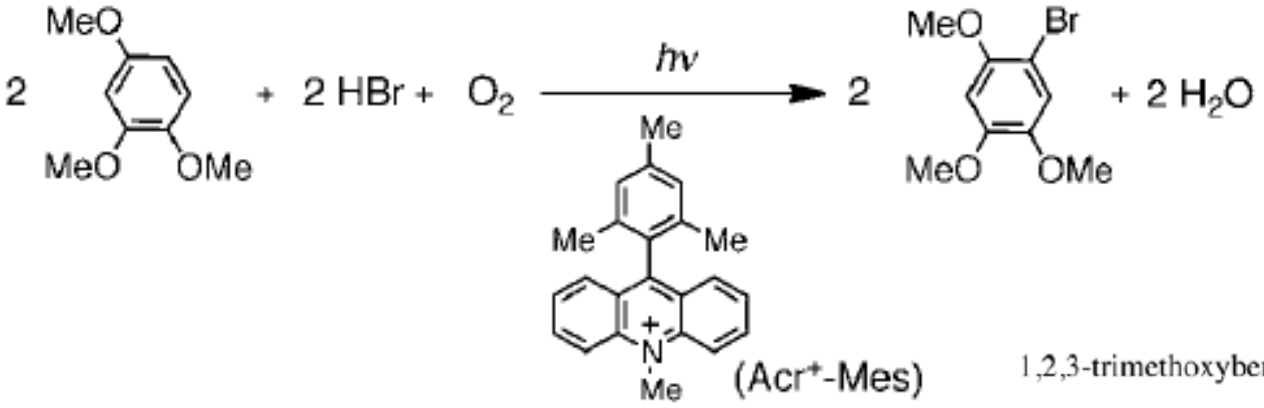




Kei Ohkubo, Atsushi Fujimoto, Shunichi Fukuzumi, *J. Phys. Chem. A.* **2013**, 117, 10719.

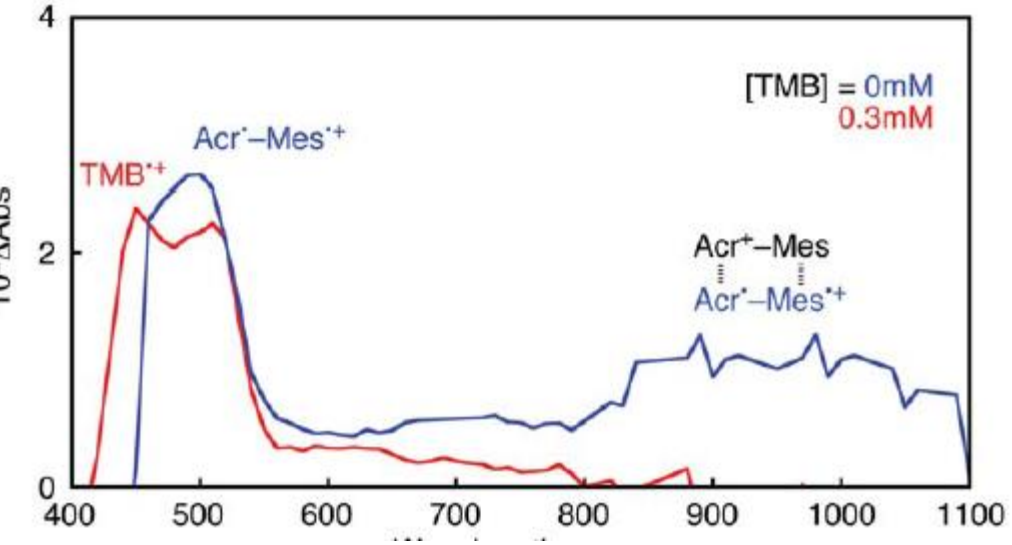
2.2. C-X bond formation on aromatic rings

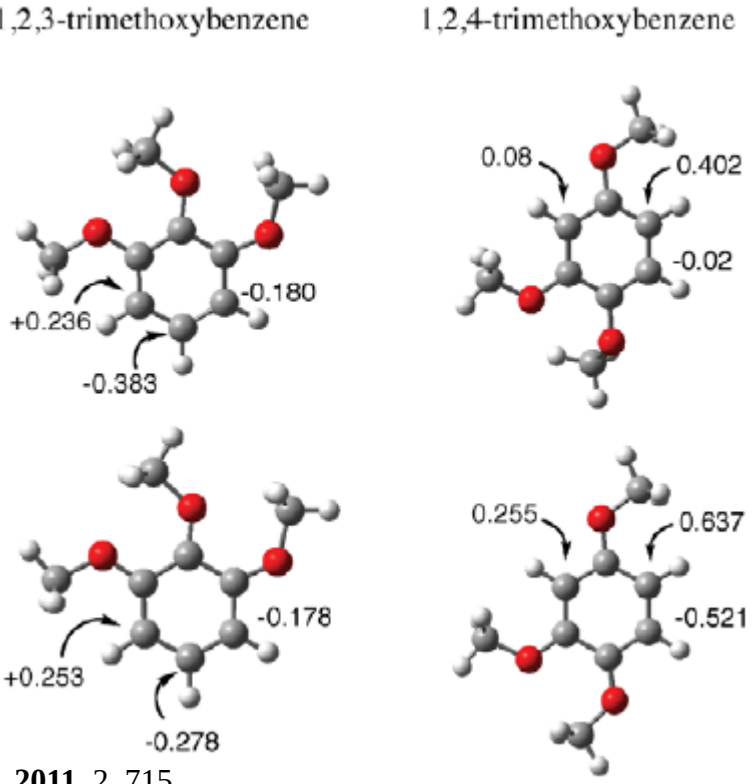
3）The formation of C-Br bond



Monobromination

Regioselectivity

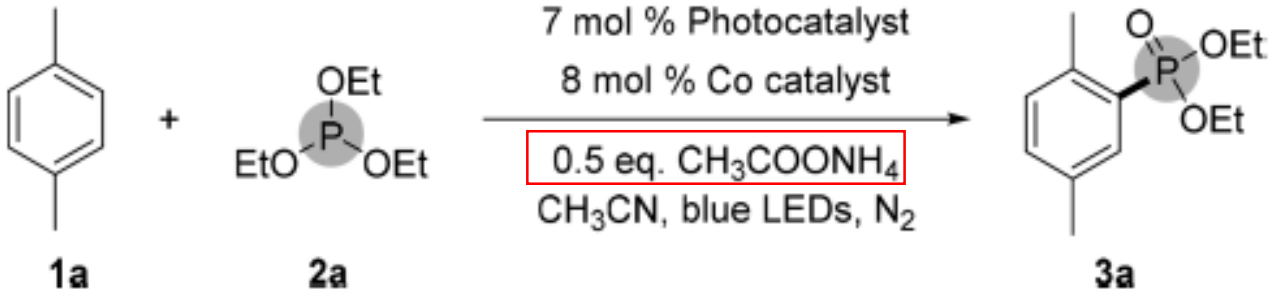


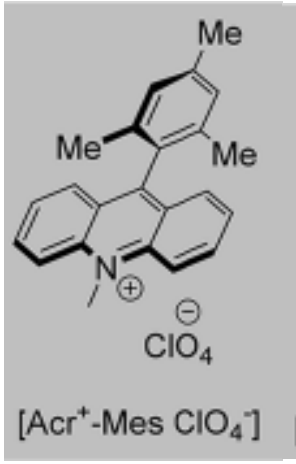


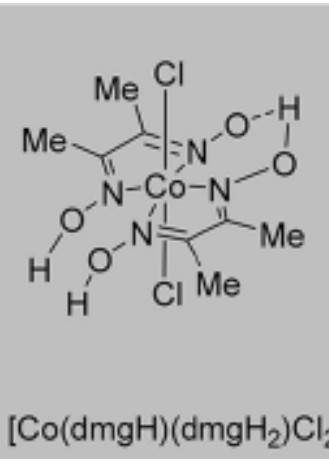
Kei Ohkubo, Kentaro Mizushima, Ryosuke Iwata,, Shunichi Fukuzumi, *Chem. Sci*. **2011**, 2, 715.

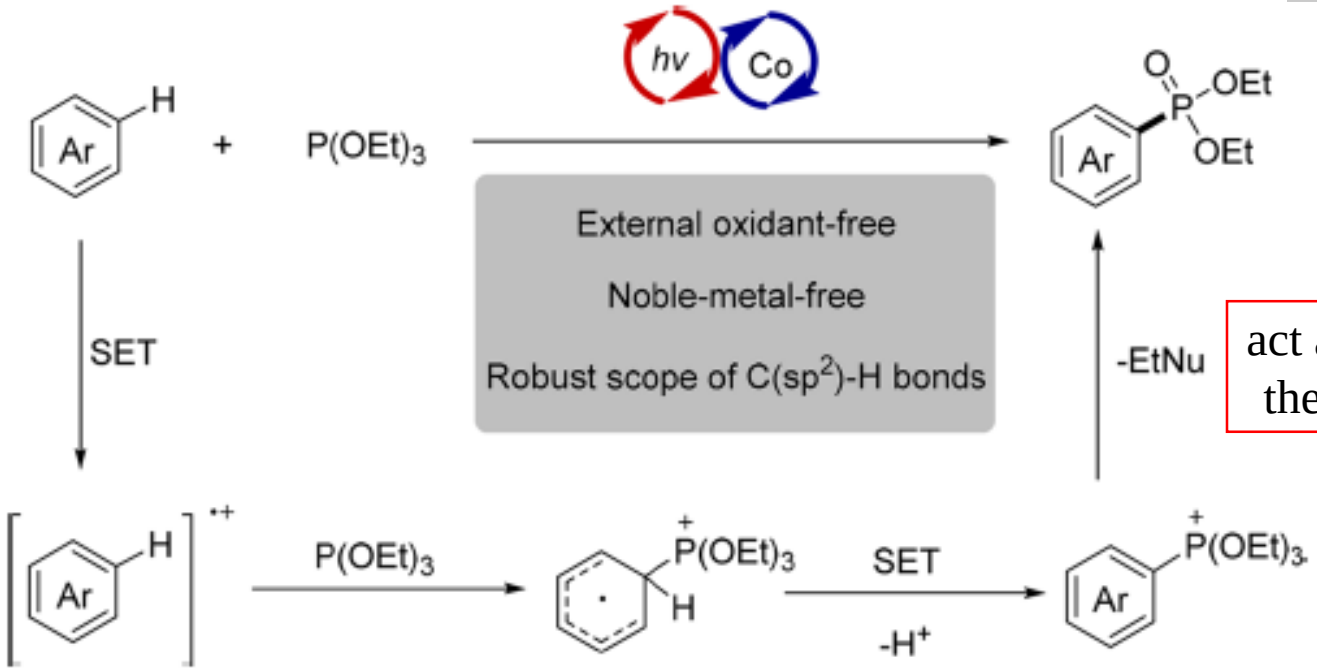
2.2. C-X bond formation on aromatic rings

4）The formation of C-P bond





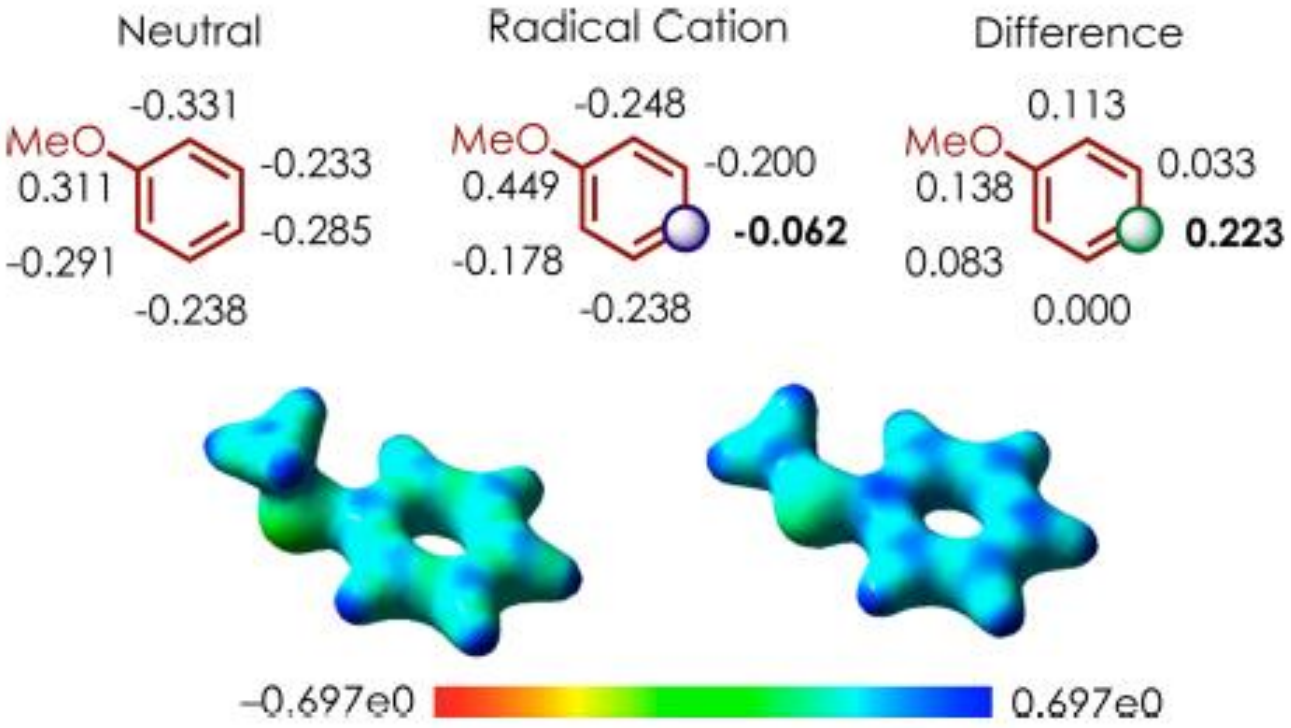




Linbin Niu, Jiamei Liu, Hong Yi, Shengchun Wang, Xing-An Liang, Atul K. Singh, Chien-Wei Chiang, Aiwen Lei, *ACS Catal*. **2017**, 7, 7412.

3. Predictive model for site-selective functionalization

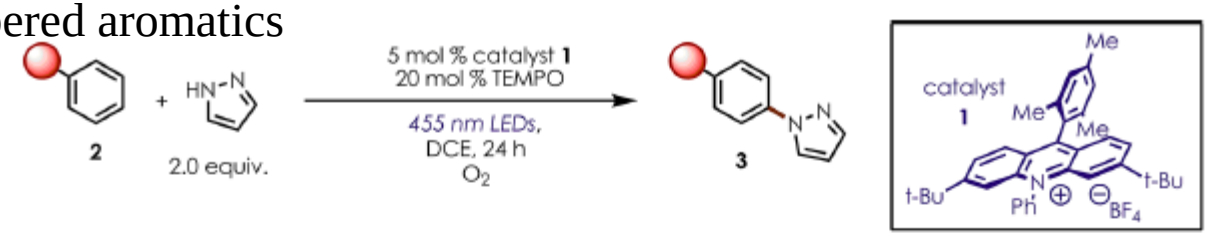
Natural population analysis: the analysis of the electron density in molecular system based on the orthonormal natural atomic orbitals.

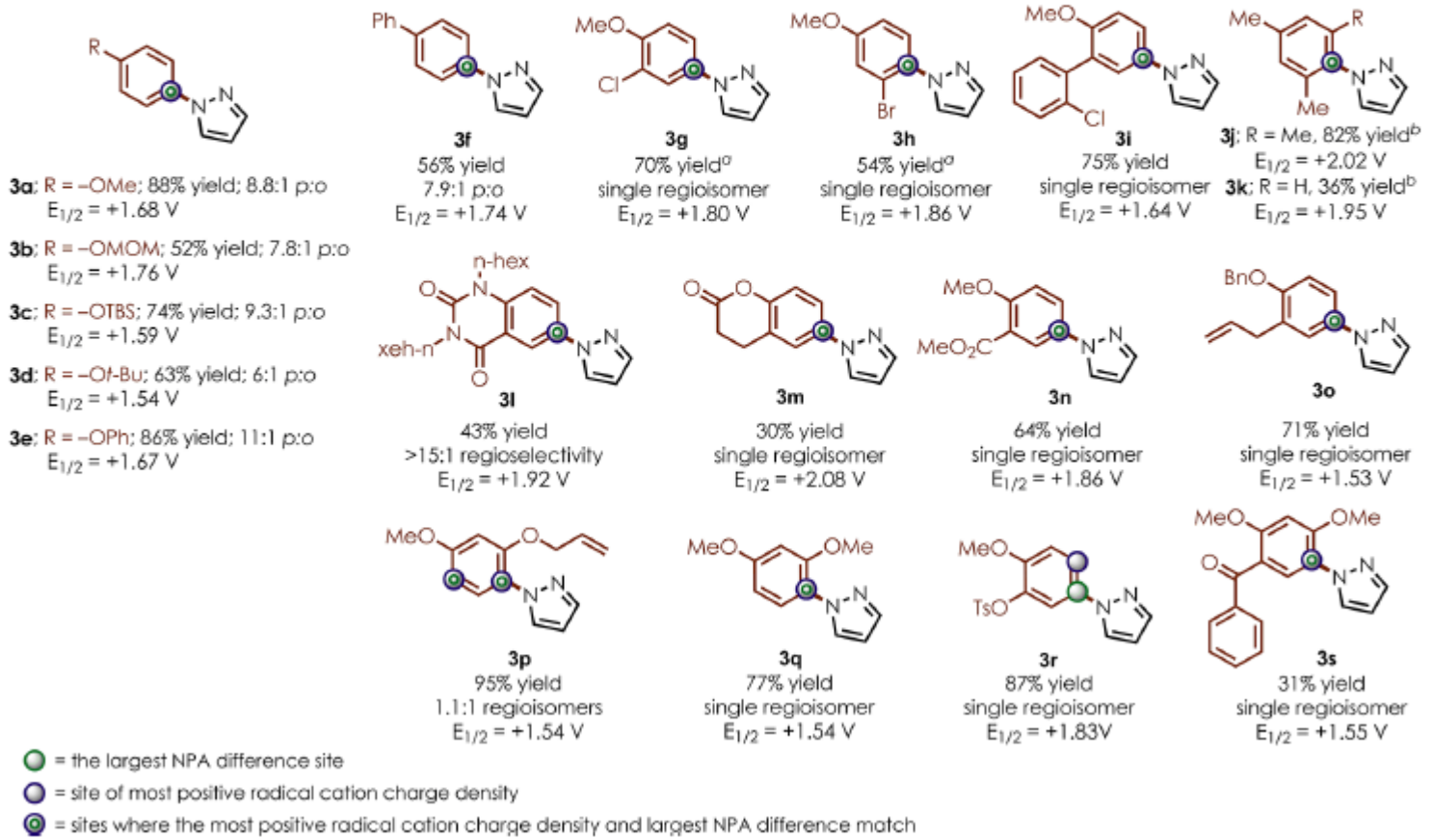


Kaila A. Margrey, Joshua B. McManus, Simone Bonazzi, Frederic Zecri, David A. Nicewicz, *J. Am. Chem. Soc*. **2017**, 139, 11288.

3. Predictive model for site-selective functionalization

1）Six-membered aromatics



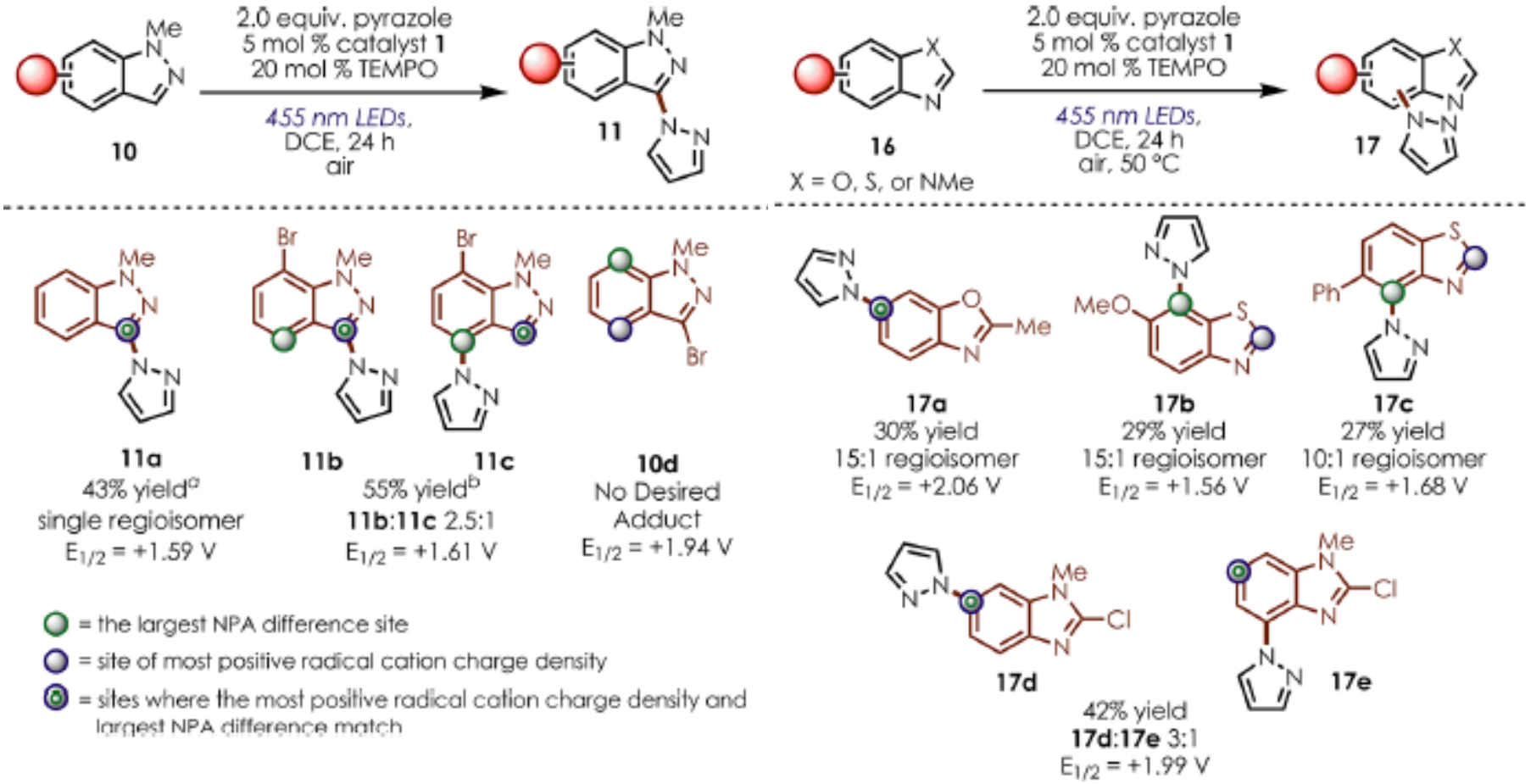


For benzenoid including pyridines and quinolines, the experimental selectivity matched the computationally predicted site of largest NPA value difference

Kaila A. Margrey, Joshua B. McManus, Simone Bonazzi, Frederic Zecri, David A. Nicewicz, *J. Am. Chem. Soc*. **2017**, 139, 11288.

3. Predictive model for site-selective functionalization

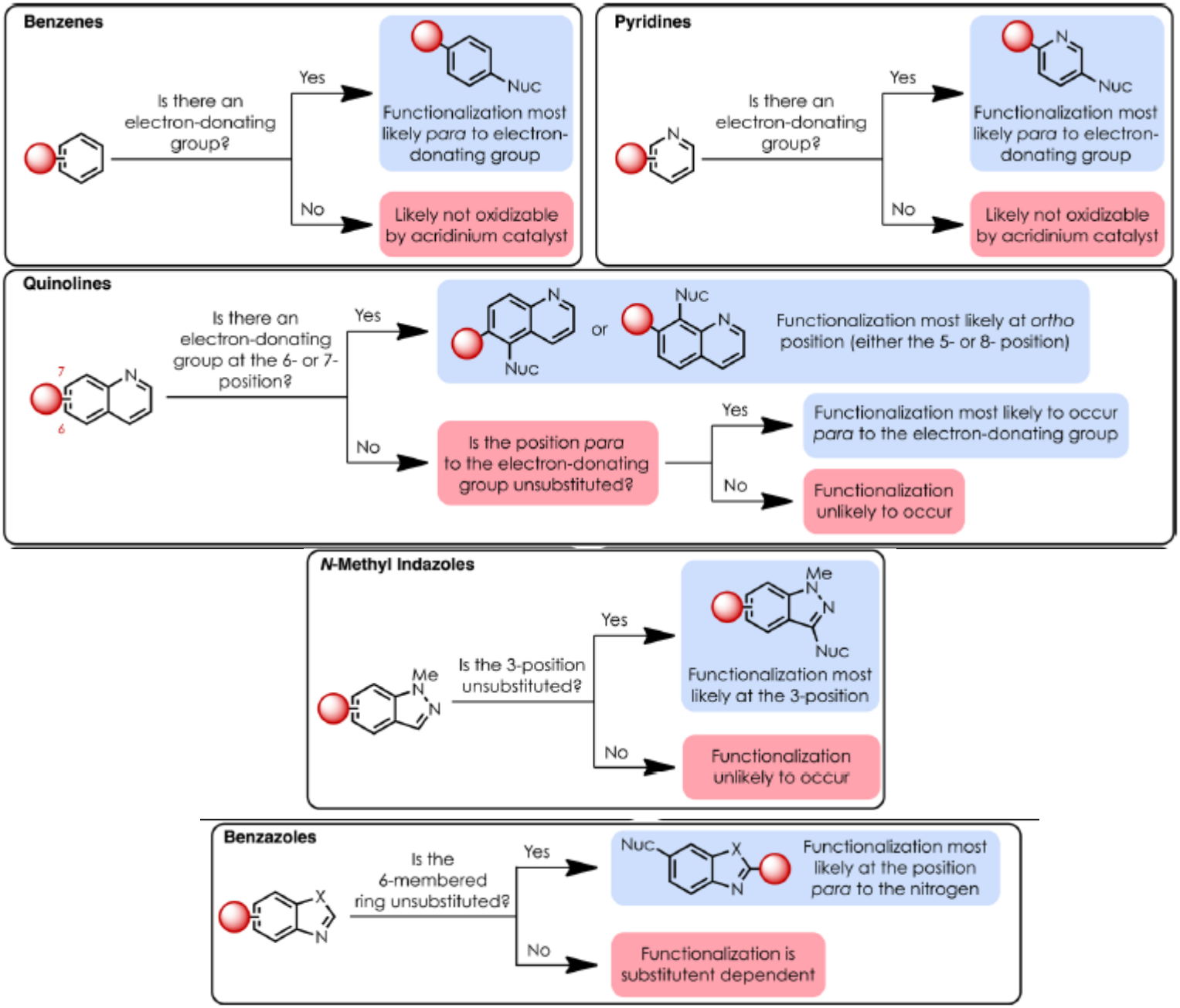
2）Indazoles, benzazoles



the experimental selectivity matched the computationally predicted site of largest NPA value difference

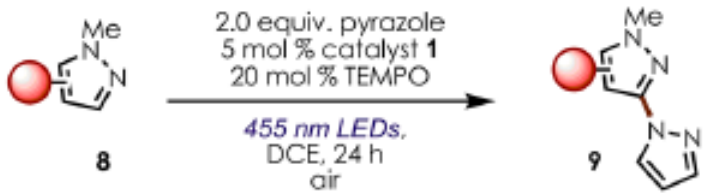
Kaila A. Margrey, Joshua B. McManus, Simone Bonazzi, Frederic Zecri, David A. Nicewicz, *J. Am. Chem. Soc*. **2017**, 139, 11288.

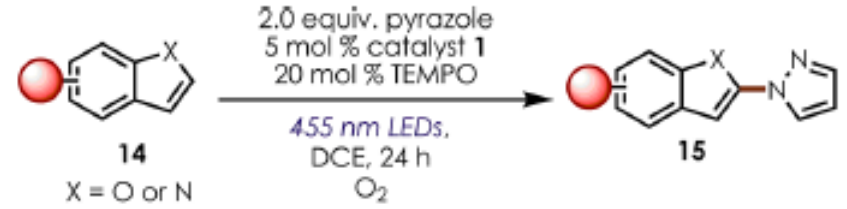
3. Predictive model for site-selective functionalization

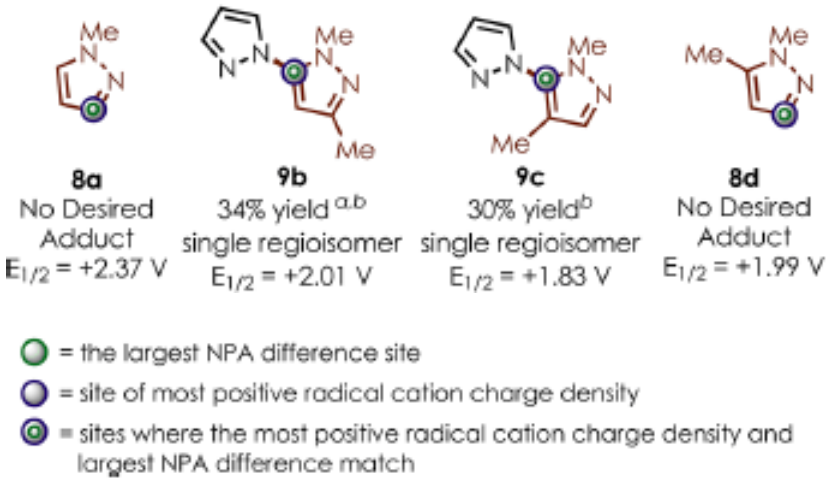


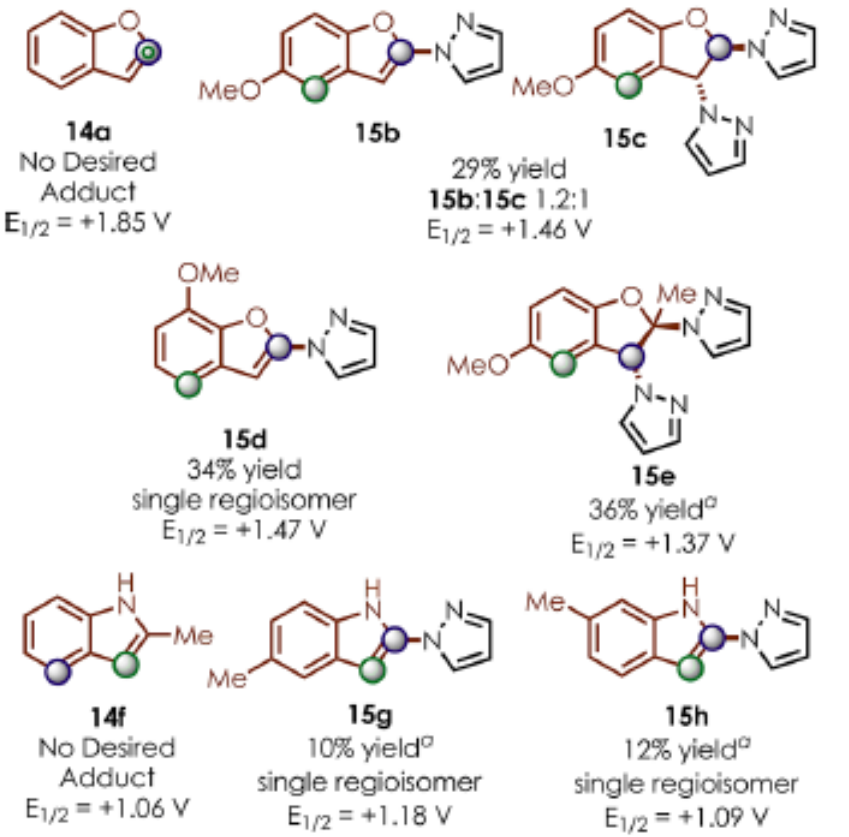
3. Predictive model for site-selective functionalization

3）Pyrazoles, benzofurans, indoles









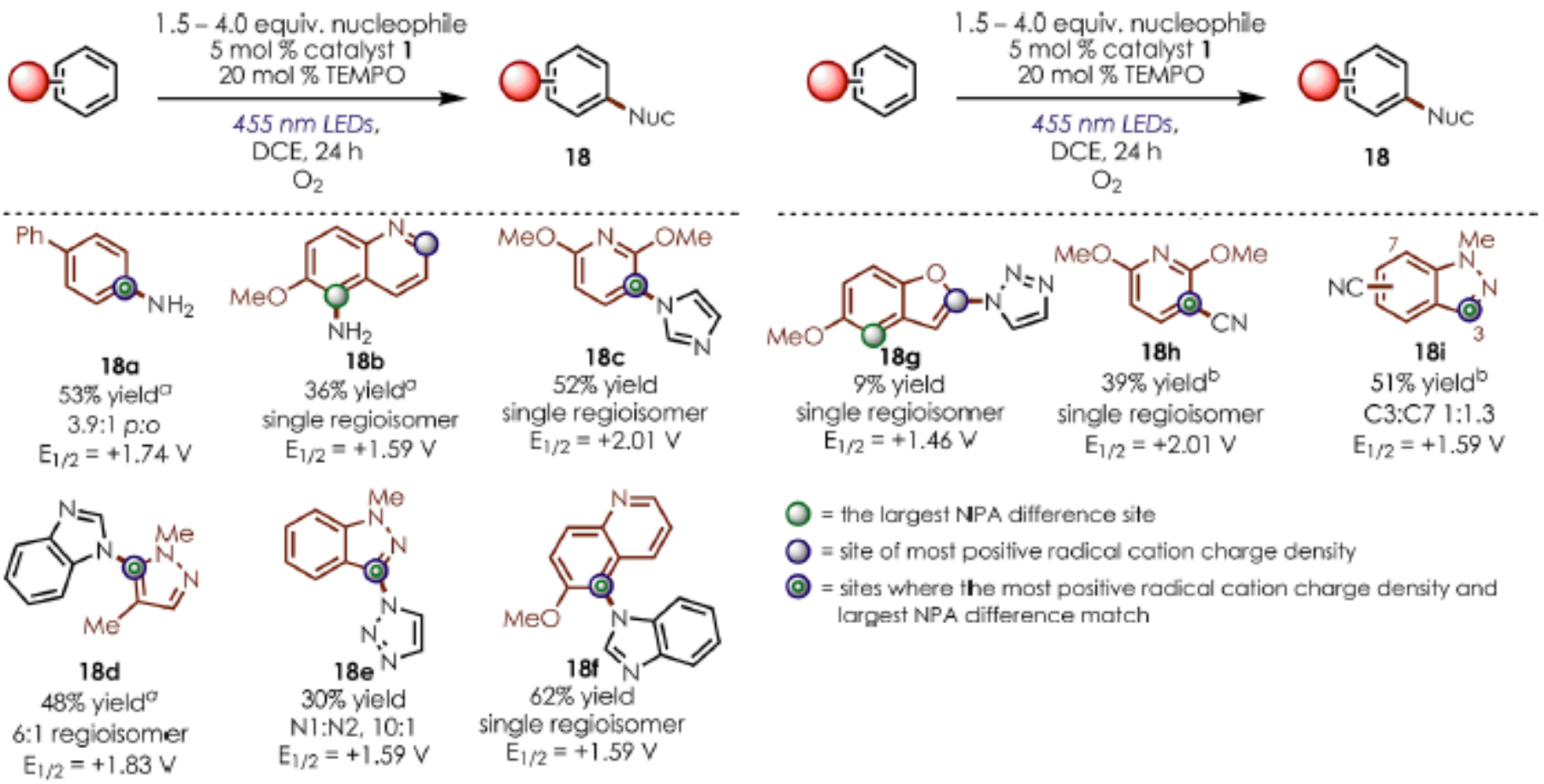
They behave as a distonic iminium radical or oxocarbenium radical instead of a delocalized arene cation radical.

Benzofurans and indoles react as electron-rich styrene derivatives.

Kaila A. Margrey, Joshua B. McManus, Simone Bonazzi, Frederic Zecri, David A. Nicewicz, *J. Am. Chem. Soc.* **2017**, 139, 11288.

3. Predictive model for site-selective functionalization

4）Other nucleophiles



Other nucleophiles exhibit the same site selectivities for a variety of heterocyclic classes as previously discussed, allowing the predictive model to be generalized to include a range of nucleophiles.

Kaila A. Margrey, Joshua B. McManus, Simone Bonazzi, Frederic Zecri, David A. Nicewicz, *J. Am. Chem. Soc*. **2017**, 139, 11288.

4. Conclusion

1. Functionalization of arenes and heteroarenes is important for LSF.
2. Direct C-H functionalizaition can be realized via photocatalysis.
3. Many limitation need solving, such as regioseliectivty, tolerance of substrates
4. Predict model for regioselectivity can desicide major product only.

Acknowledgement

Prof. Huang

All members in E201

Everyone here

Thank you!