Designing Radical Cationic HAT Agents

Group Seminar

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17.04.2020

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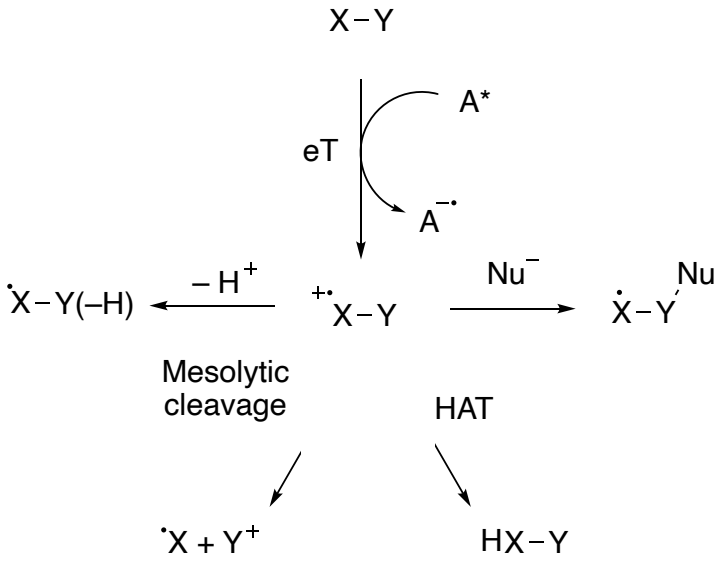
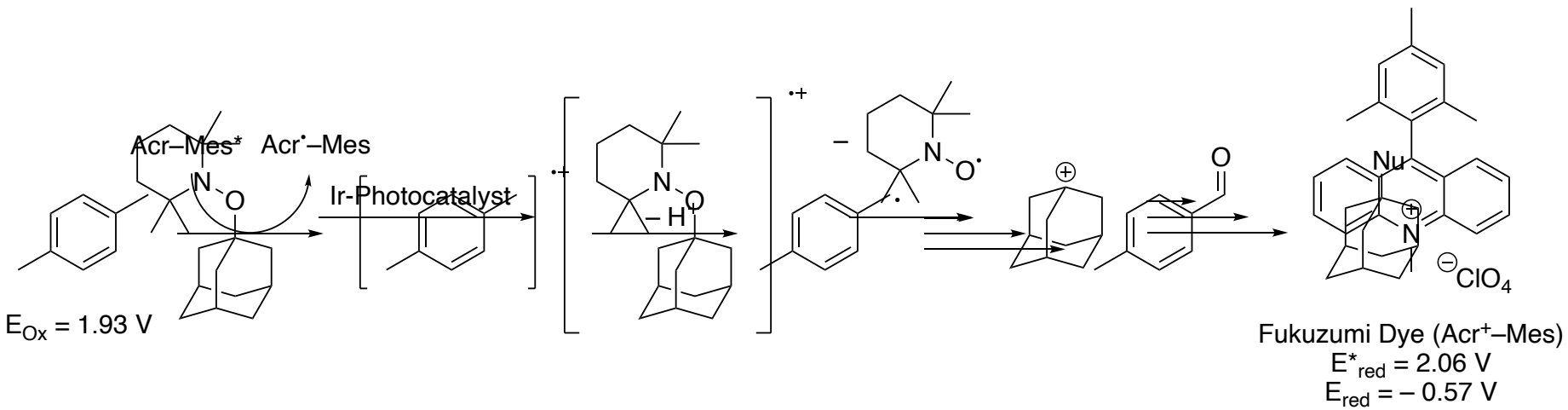
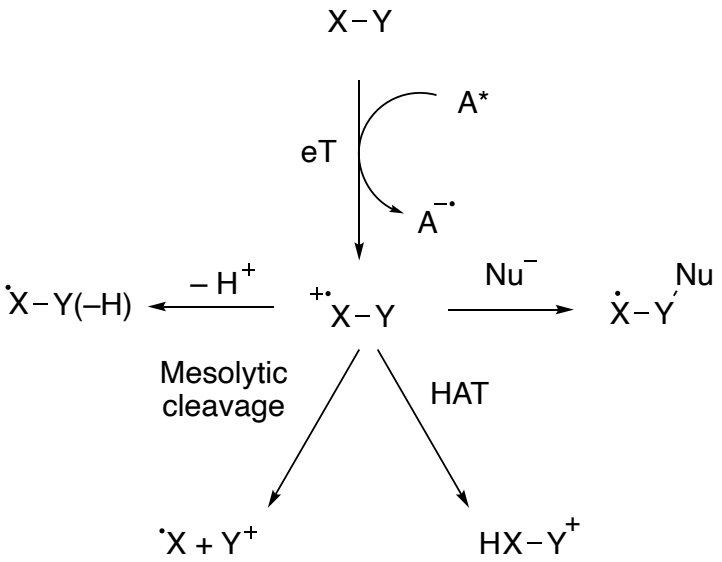
Radical Cations – Basic Concepts





Radical-cation chart: J. Pérez-Prieto and M. A. Miranda in Encycl. Radicals Chem. Biol. Mater. (Eds.: C. Chatgilialoglu, A. Studer), John Wiley & Sons, Ltd, Chichester, UK, 2012, p. 276. Oxidation Xylene: K. Ohkubo, K. Mizushima, R. Iwata, K. Souma, N. Suzuki, S. Fukuzumi, *Chem. Commun.* **2010**, *46*, 601–603. Mesolytic Cleavage Alkoxyamines: Q. Zhu, E. C. Gentry, R. R. Knowles, *Angew. Chem. Int. Ed.* **2016**, *55*, 9969–9973.

Radical Cations – Basic Concepts II

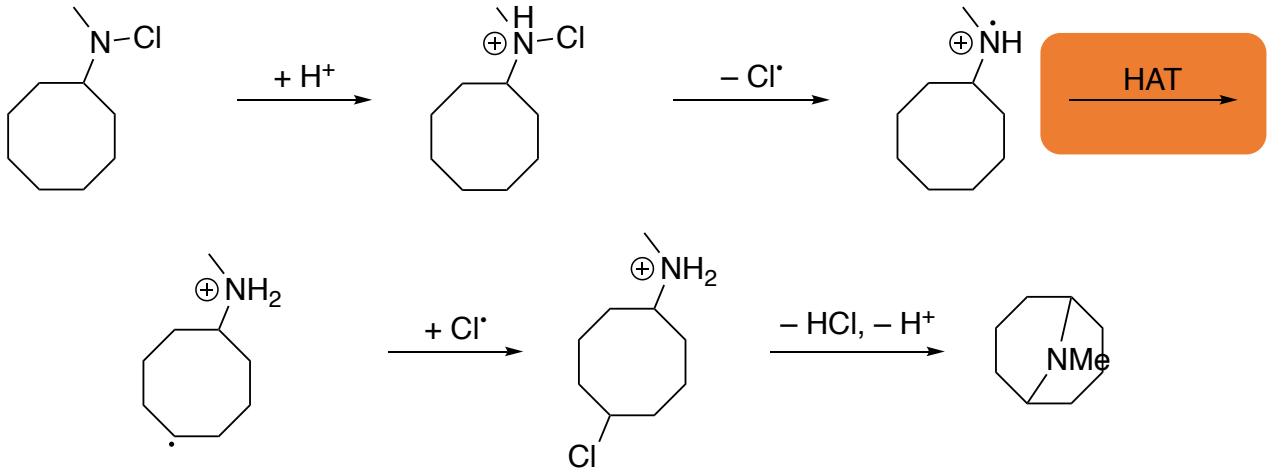


„Radical cations, because of their electron deficient nature, are not likely to participate in HAT; instead, they undergo the analogous radical ion fragmentation, proton transfer.“

S. F. Nelsen, J. T. Ippoliti, *J. Am. Chem. Soc.* **1986**, *108*, 4879–4881.

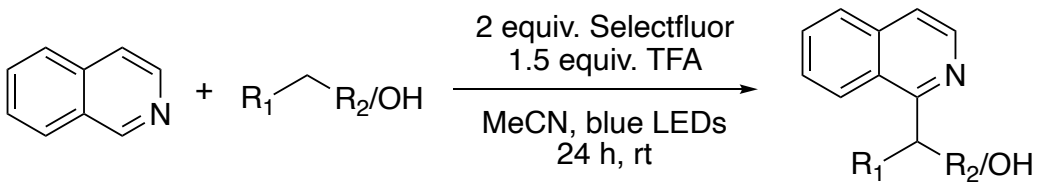
„Hydrogen atom abstraction by $R_3N^{+\bullet}$ is known to be a fast process...“

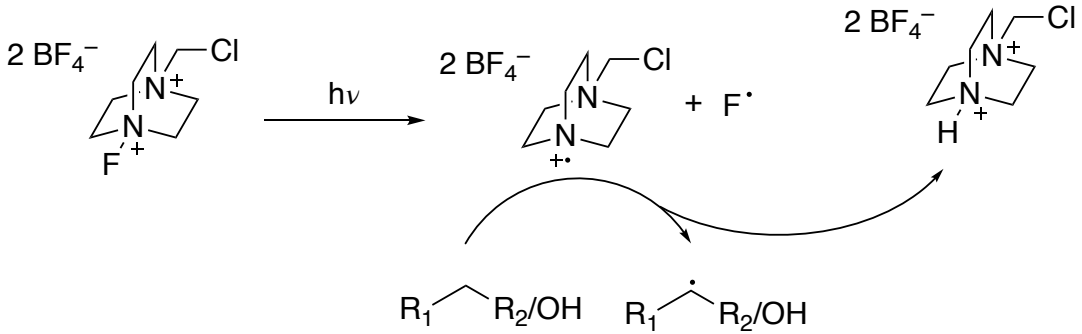
A. N. Hancock and J. M. Tanko in Encycl. Radicals Chem. Biol. Mater. (Eds.: C. Chatgilialoglu, A. Studer), John Wiley & Sons, Ltd, Chichester, UK, 2012, p. 326.



Radical-cation chart: J. Pérez-Prieto and M. A. Miranda in Encycl. Radicals Chem. Biol. Mater. (Eds.: C. Chatgilialoglu, A. Studer), John Wiley & Sons, Ltd, Chichester, UK, 2012, p. 276. Preparation of *N*-Methylgranatanine: S. Wawzonek, P. J. Thelen, *J. Am. Chem. Soc.* **1950**, *72*, 2118–2120. Early Aminium Radical Review: Y. L. Chow, S. F. Nelsen, D. H. Rosenblatt, *Chem. Rev.* **1978**, *78*, 243–274

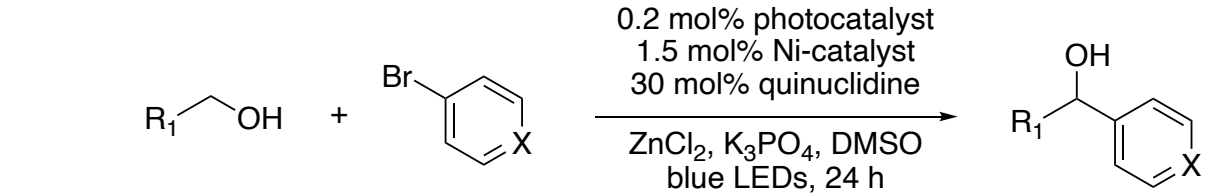
Radical Cation HAT – Recent Examples

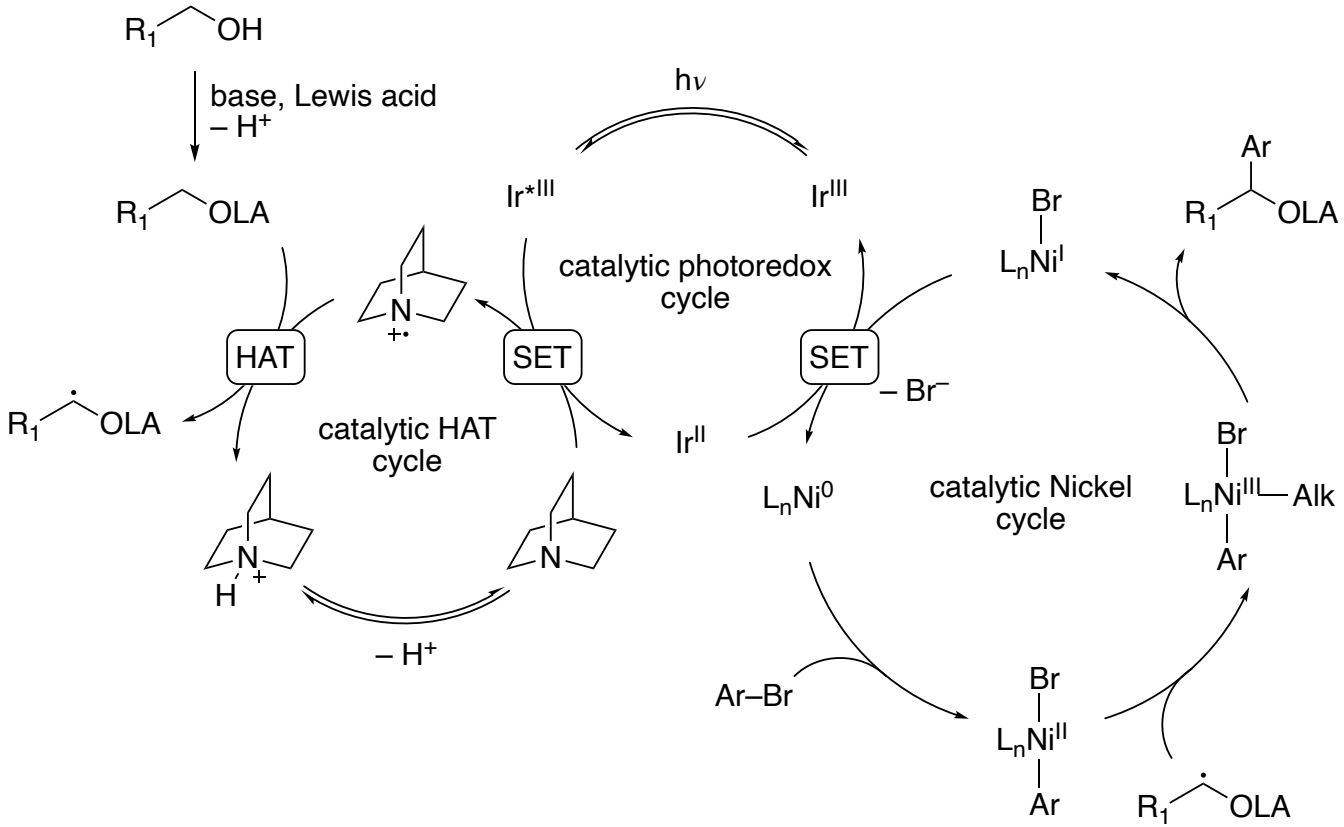




Addition of Alcohols to Heteroarenes: L. Niu, J. Liu, X. A. Liang, S. Wang, A. Lei, *Nat. Commun.* **2019**, *10*, 1–7., Unactivated C(sp^3)–H–Heteroarene coupling: X. A. Liang, L. Niu, S. Wang, J. Liu, A. Lei, *Org. Lett.* **2019**, *21*, 2441–2444.

Radical Cation HAT – Recent Examples II



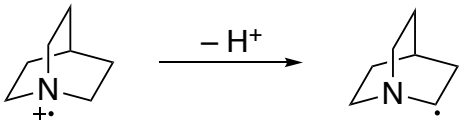


J. Twilton, M. Christensen, D. A. DiRocco, R. T. Ruck, I. W. Davies, D. W. C. MacMillan, *Angew. Chem. Int. Ed.* **2018**, *57*, 5369–5373.

What can be learned from $R_3N^{\bullet+}$?

Deprotonation:

- Radical-cations are stronger acids than neutral counterparts

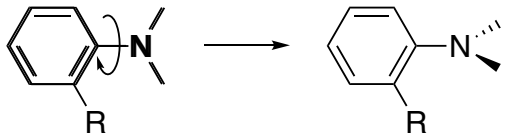


pK_a = 19.5 (in MeCN)

- pK_a–values can be estimated from E_{ox} and the BDE

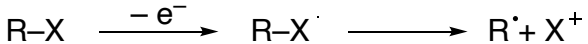
$$pK_a = \frac{-E^{\circ}_{ox}}{0.05916} + \frac{\Delta G^{\circ}_{BDE} - 37.5}{1.36}$$

- Decrease of deprotonation rates by solvation and conjugation



Fragmentation:

- $R_3N^{\bullet+}$ exhibit lower bond breaking energies

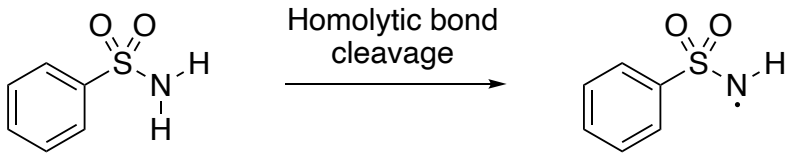


- Effect depends on bond strengh and electrofugacity of leaving cation

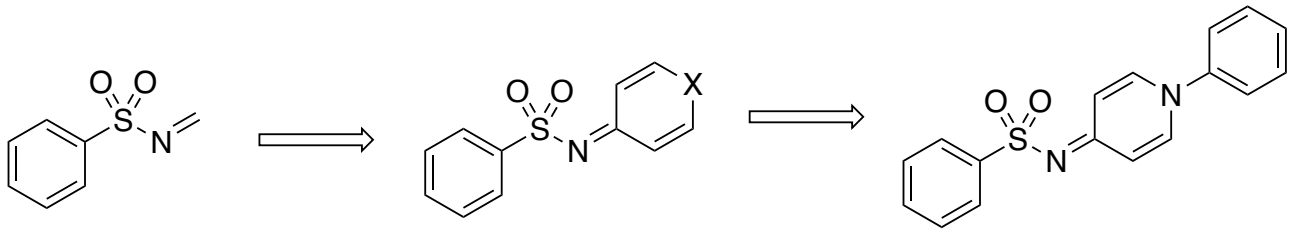
- Decrease of fragmentation rates by solvation and conjugation

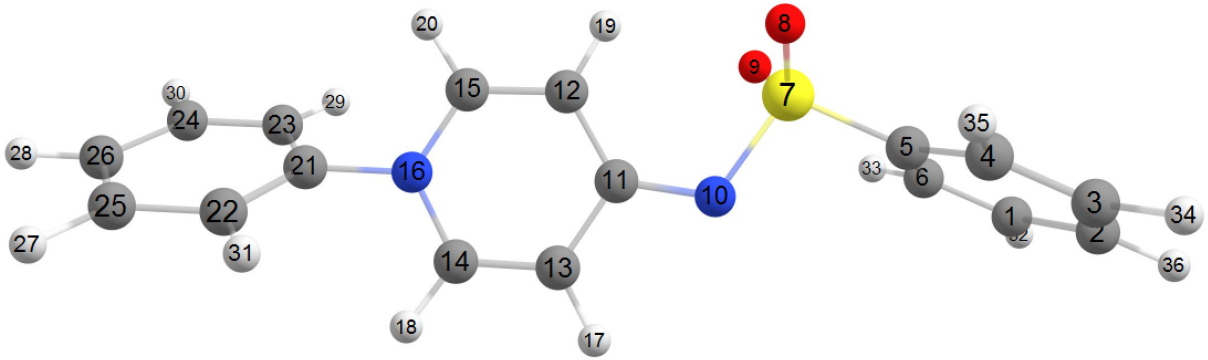
Deprotonation: Y. L. Chow, S. F. Nelsen, D. H. Rosenblatt, *Chem. Rev.* **1978**, *78*, 243–274, A. M. de P. Nicholas, D. R. Arnold, *Can. J. Chem.* **1982**, *60*, 3011–3018, S. F. Nelsen, J. T. Ippoliti, *J. Am. Chem. Soc.* **1986**, *108*, 4879–4881, J. P. Dinnocenzo, T. E. Banach, *J. Am. Chem. Soc.* **1989**, *111*, 8646–8653, G. W. Dombrowski, J. P. Dinnocenzo, P. A. Zielinski, S. Farid, Z. M. Wosinska, I. R. Gould, *J. Org. Chem.* **2005**, *70*, 3791–3800.
Fragmentation: E. R. Gaillard, D. G. Whitten, *Acc. Chem. Res.* **1996**, *29*, 292–297, A. Houmam, *Chem. Rev.* **2008**, *108*, 2180–2237, Z. Su, D. E. Falvey, U. C. Yoon, P. S. Mariano, *J. Am. Chem. Soc.* **1997**, *119*, 5261–5262, Z. Su, P. S. Mariano, D. E. Falvey, U. C. Yoon, S. W. Oh, *J. Am. Chem. Soc.* **1998**, *120*, 10676–10686, M. Mella, M. Fagnoni, M. Freccero, E. Fasani, A. Albini, *Chem. Soc. Rev.* **1998**, *27*, 81–89.

Designing a Radical Cation HAT Agent



BDE ≈ 105 kcal/mol



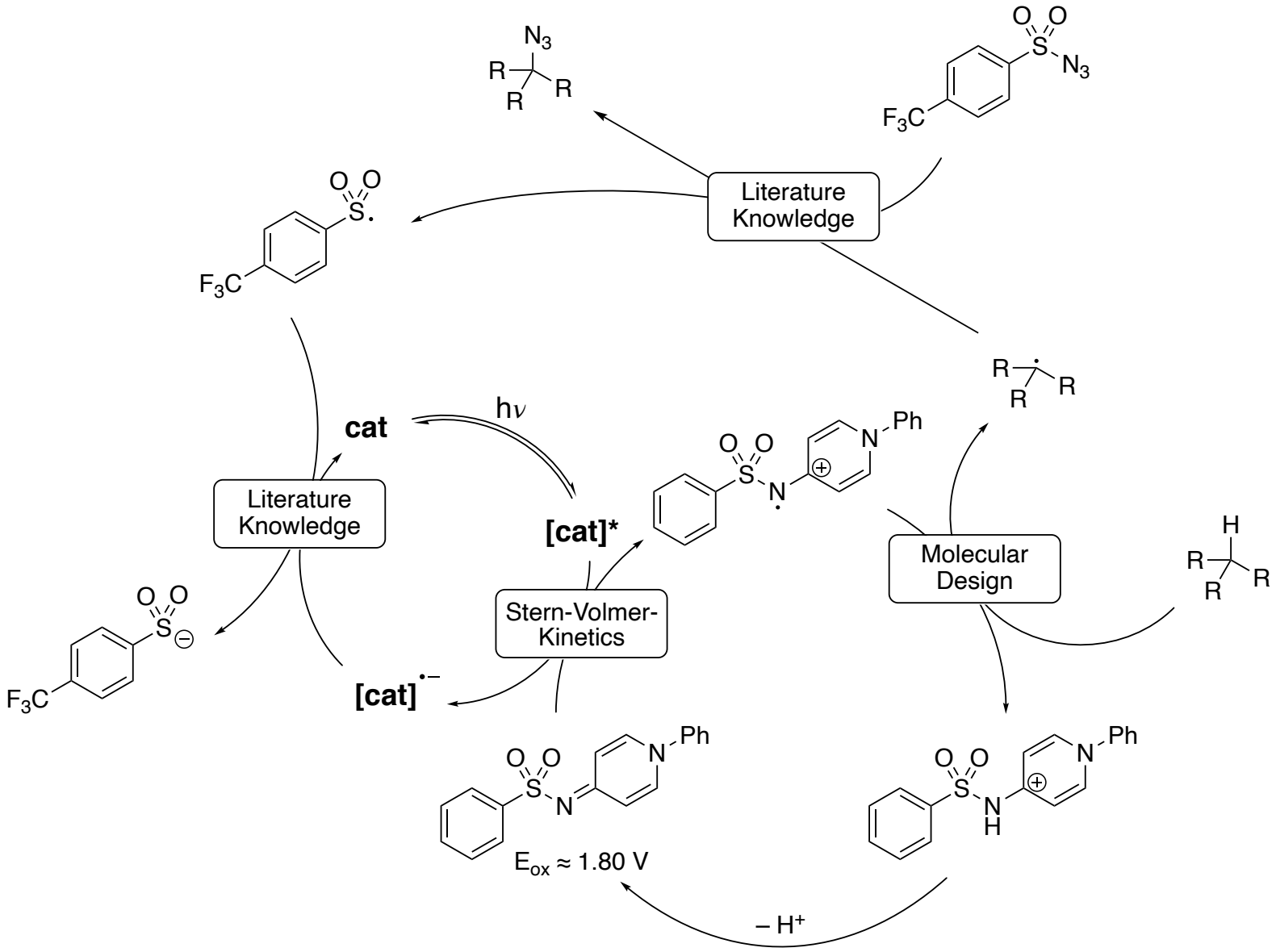


Atomic charges	
C11	0.227
C14	0.217
C15	0.205

Spin densities	
N10	0.763
C14	0.325
C15	0.308

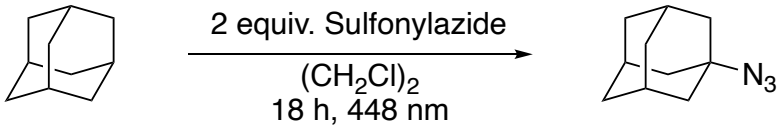
BDE: F. G. Bordwell, J. A. Harrelson, T. Y. Lynch, *J. Org. Chem.* **1990**, *55*, 3337–3341. Alkene Radical cation Reactivity: M. Mella, M. Fagnoni, M. Freccero, E. Fasani, A. Albini, *Chem. Soc. Rev.* **1998**, *27*, 81–89, S. Kuwata, Y. Shigemitsu, Y. Odaira, *J. Org. Chem.* **1973**, *38*, 3803–3805. R. D. Bach, G. J. Wolber, A. Pross, *Isr. J. Chem.* **1983**, *23*, 97–104, R. Torriani, M. Mella, E. Fasani, A. Albini, *Tetrahedron* **1997**, *53*, 2573–2580.

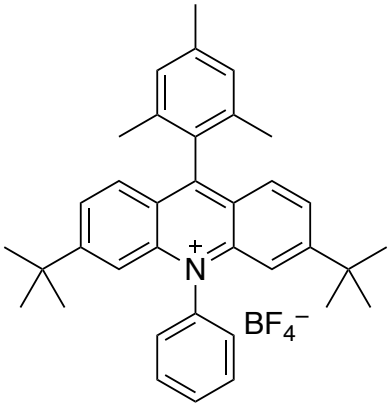
Working Hypothesis



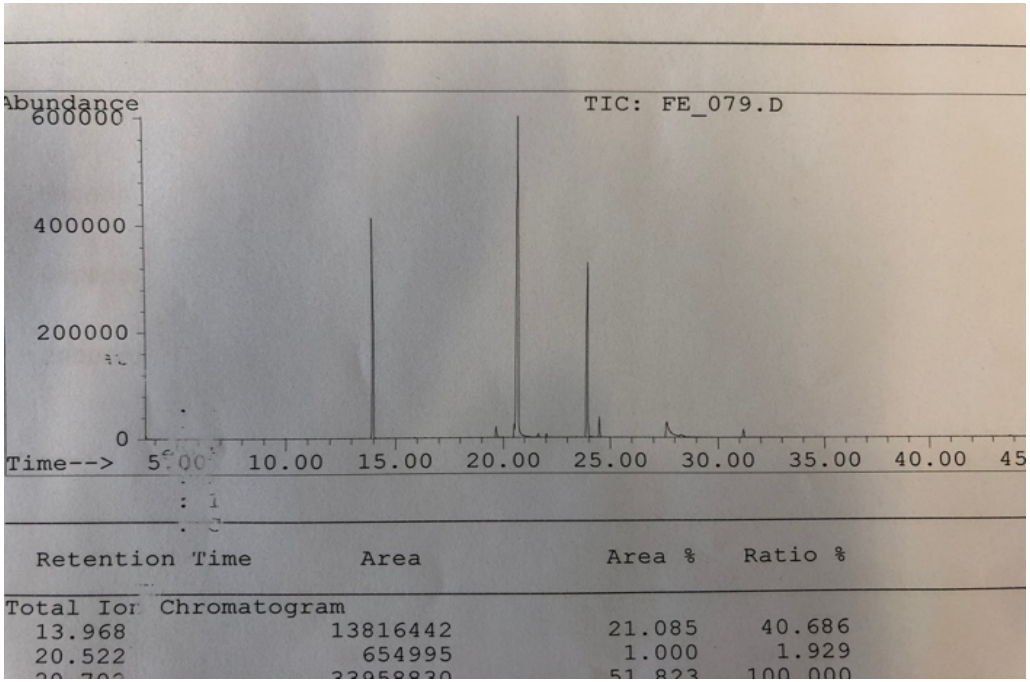
Radical Azidation: X. Huang, J. T. Groves, *ACS Catal.* **2016**, *6*, 751–759. Reduction of sulfonyl radicals by Acridinium catalysts: D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2012**, *134*, 18577–18580, K. A. Margrey, W. L. Czaplyski, D. A. Nicewicz, E. J. Alexanian, *J. Am. Chem. Soc.* **2018**, *140*, 4213–4217.

Initial Experiments





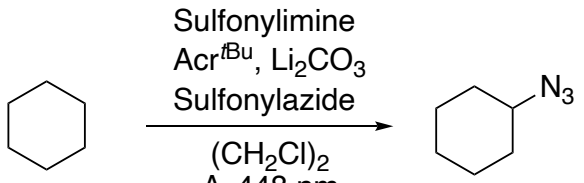
Acr^{tBu}
E^*_{red} = + 2.08 V vs. SCE
E_{red} = – 0.57 V vs. SCE

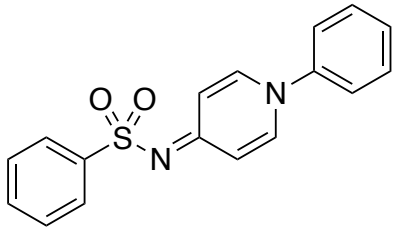


50 °C
1 equiv. Li_2CO_3 added

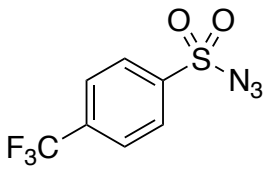
Acridinium catalysts: D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2012**, *134*, 18577–18580, K. A. Margrey, W. L. Czaplyski, D. A. Nicewicz, E. J. Alexanian, *J. Am. Chem. Soc.* **2018**, *140*, 4213–4217, A. White, L. Wang, D. Nicewicz, *Synlett* **2019**, *30*, 827–832.

Design of Experiment – Response Surface Area Model

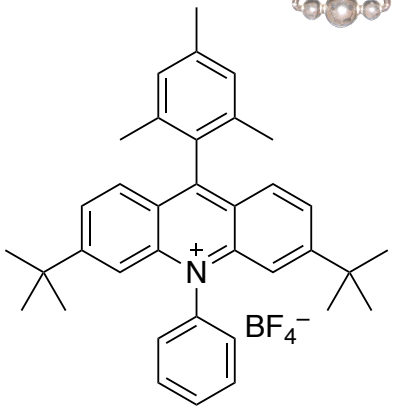




Sulfonylimine



Sulfonylazide



Acr$^{t\mathrm{Bu}}$

E^*_{red} = + 2.08 V vs. SCE

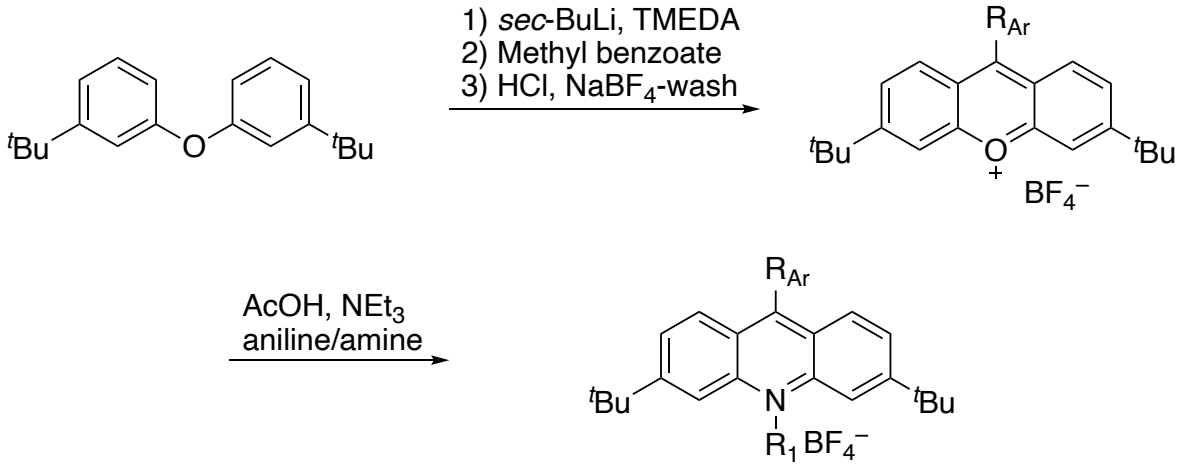
E_{red} = – 0.57 V vs. SCE

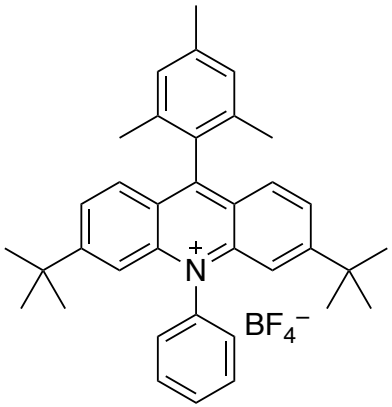
Temperature / °C	PhCat / mol%	TsN_3 / equiv.	HAT / mol%	Time / h	Li_2CO_3 / equiv.	Yield / %[a]
50	2,5	2	20	32	0,5	29.80
50	2,5	2	20	16	2	29.89
50	2,5	2,5	10	32	2	27.21
50*	2,5	2	20	16	1,25	27.67
50	3,75	3	20	32	0,5	31.71
50	5	2	20	32	2	30.42
60	2,5	2,5	20	24	0,5	25.33
60	2,5	2,5	20	24	1,25	24.61
60	3,75	2,5	15	24	1,25	26.69
60	3,75	2,5	15	24	1,25	29.94
70	2,5	3	10	16	2	27.28
70	2,5	3	20	16	0,5	24.86

* Reaction performed in the dark

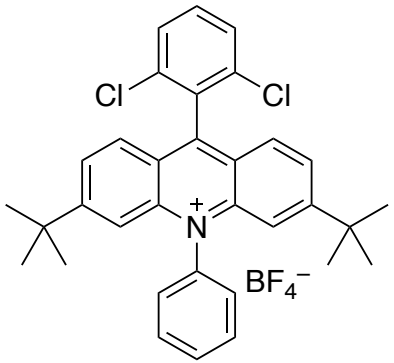
Acridinium catalysts: D. S. Hamilton, D. A. Nicewicz, *J. Am. Chem. Soc.* **2012**, *134*, 18577–18580, K. A. Margrey, W. L. Czaplyski, D. A. Nicewicz, E. J. Alexanian, *J. Am. Chem. Soc.* **2018**, *140*, 4213–4217, A. White, L. Wang, D. Nicewicz, *Synlett* **2019**, *30*, 827–832.

Main effects – Excited State Lifetime Dependency

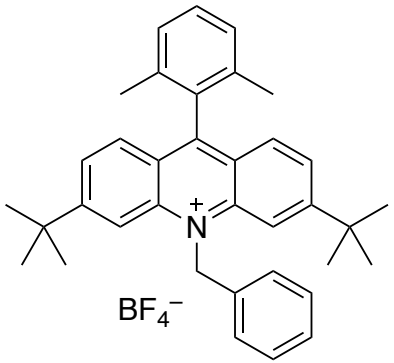




E^*_{red} = + 2.08 V vs. SCE
E_{red} = – 0.57 V vs. SCE
τ = 13.8 ns



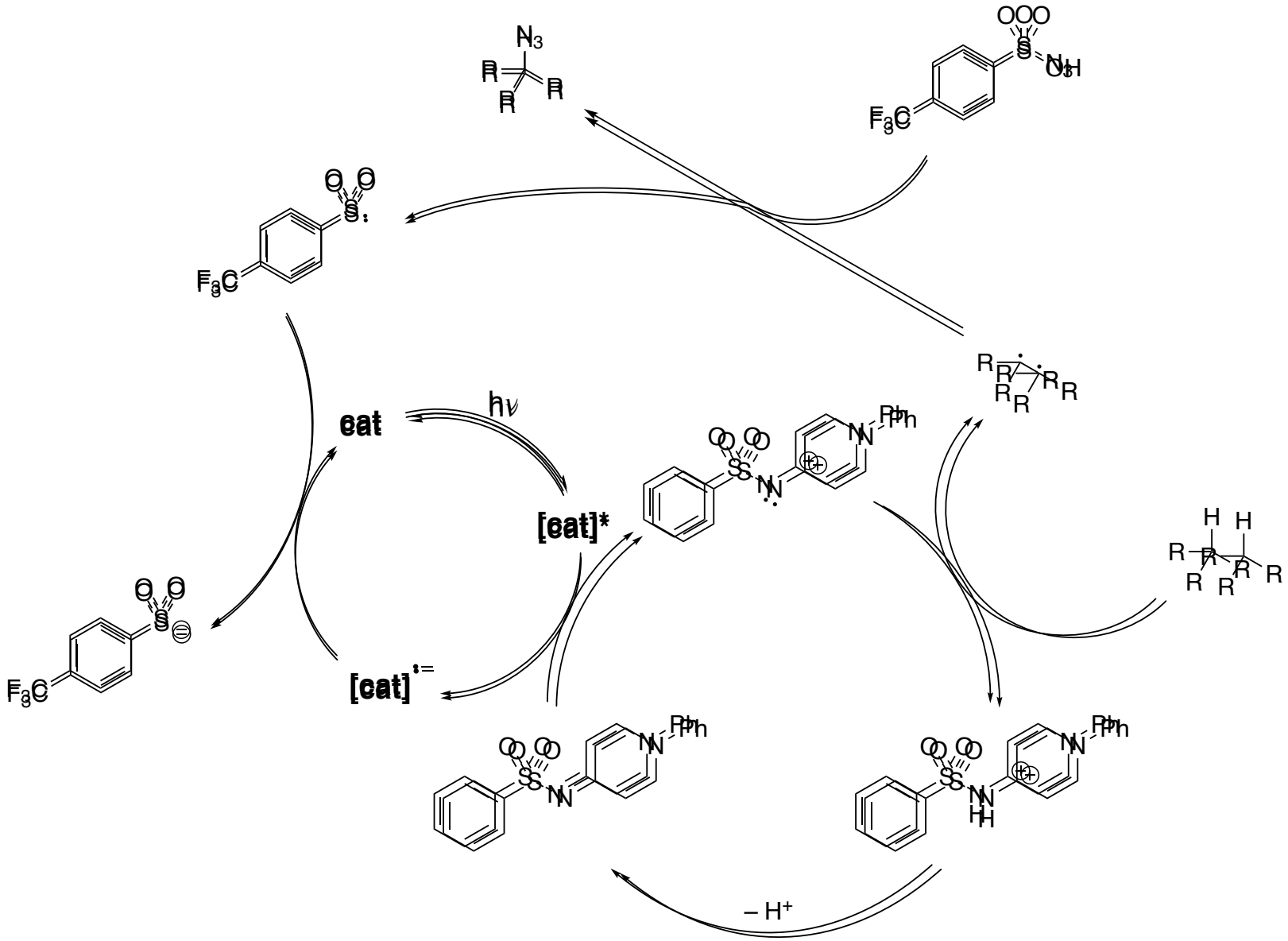
E^*_{red} = + 2.21 V vs. SCE
E_{red} = – 0.43 V vs. SCE
τ = 17.1 ns



E^*_{red} = + 2.13 V vs. SCE
E_{red} = – 0.54 V vs. SCE
τ = 23.7 ns

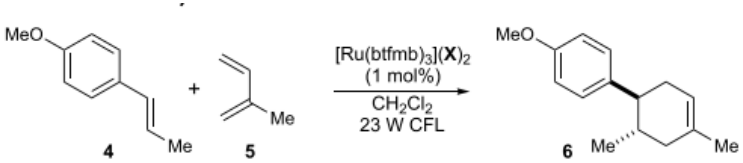
Acridinium catalysts: A. White, L. Wang, D. Nicewicz, *Synlett* **2019**, *30*, 827–832.

Secondary effects – Formation of Sulfinic Acid



Hydrogen transfer reactivity of sulfinic acids: M. Griesser, J. P. R. Chauvin, D. A. Pratt, *Chem. Sci.* **2018**, *9*, 7218–7229.

Secondary effects – Formation of Sulfinate



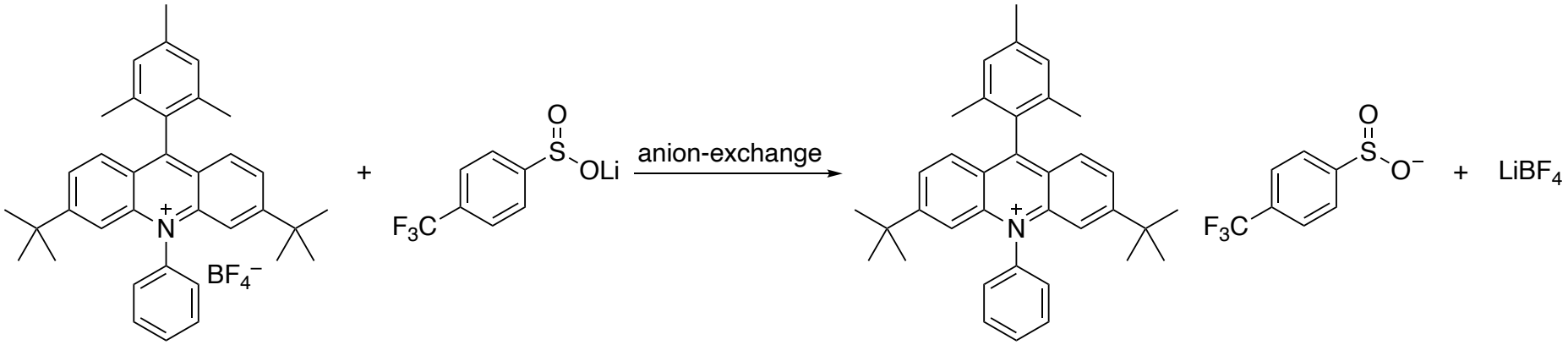
entry	catalyst	time	yield (%) 6[b]	yield (%) unreacted 4[b]
1	**3a** ($BAr^F_4^-$)	20 min	98	0
2	**3b** (TfO^-)	24 h	55	37
3	**3d** ($Ar^FSO_3^-$)	24 h	14	80
4	**3e** (TsO^-)	24 h	2	95
5	**3f** ($Ar^FCO_2^-$)	24 h	0	100

[a]General conditions: anethole (0.06 mmol), isoprene (0.18 mmol), CH_2Cl_2 (0.08 M), [Ru] (1 mol %). Each reaction was subjected to three freeze–pump–thaw cycles prior to irradiation from a 23 W CFL bulb. [b]^{1}H NMR yields referenced to trimethyl(phenyl)silane internal standard.

Table 3. Ground- and Excited-State Redox Potentials for $Ru(btfmb)_3^{2+}$ in CH_2Cl_2[a]

entry	catalyst	ΔG_{ES} (eV)	$E(Ru^{2+/+})$ (V)	$E(Ru^{2+*/+})$ (V)
1	**3a**	2.17	−0.65	+1.52
2	**3c**	2.05	−0.89	+1.16
3	**3d**	2.01	−0.93	+1.08
4	**3e**	1.99	−0.95	+1.04

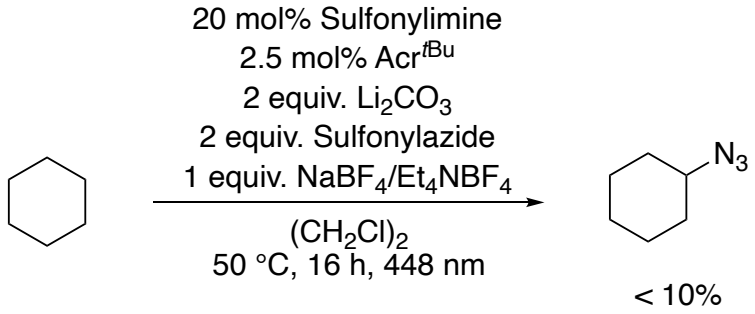
[a]Electrochemical potentials were measured through cyclic voltammetry in a standard three-electrode setup; scan rate = 100 mV/s. A 100 mM solution of a n-$Bu_4N^+X^-$ salt that matched the photocatalyst counteranion was used as a supporting electrolyte. Potentials were corrected to SCE through an external ferrocene reference.



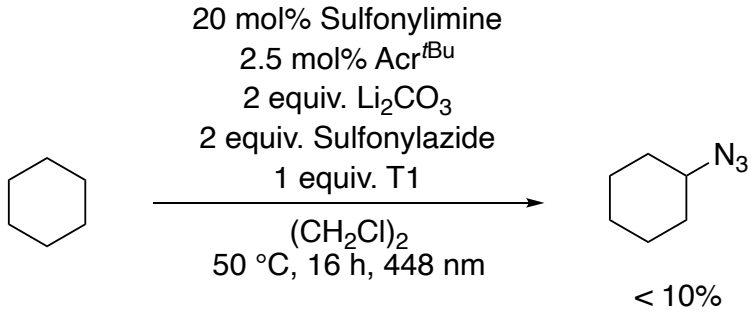
Counteranion dependency: E. P. Farney, S. J. Chapman, W. B. Swords, M. D. Torelli, R. J. Hamers, T. P. Yoon, *J. Am. Chem. Soc.* **2019**, *141*, 6385–6391.

How to omit the problem?

- Addition of BF_4^--anions

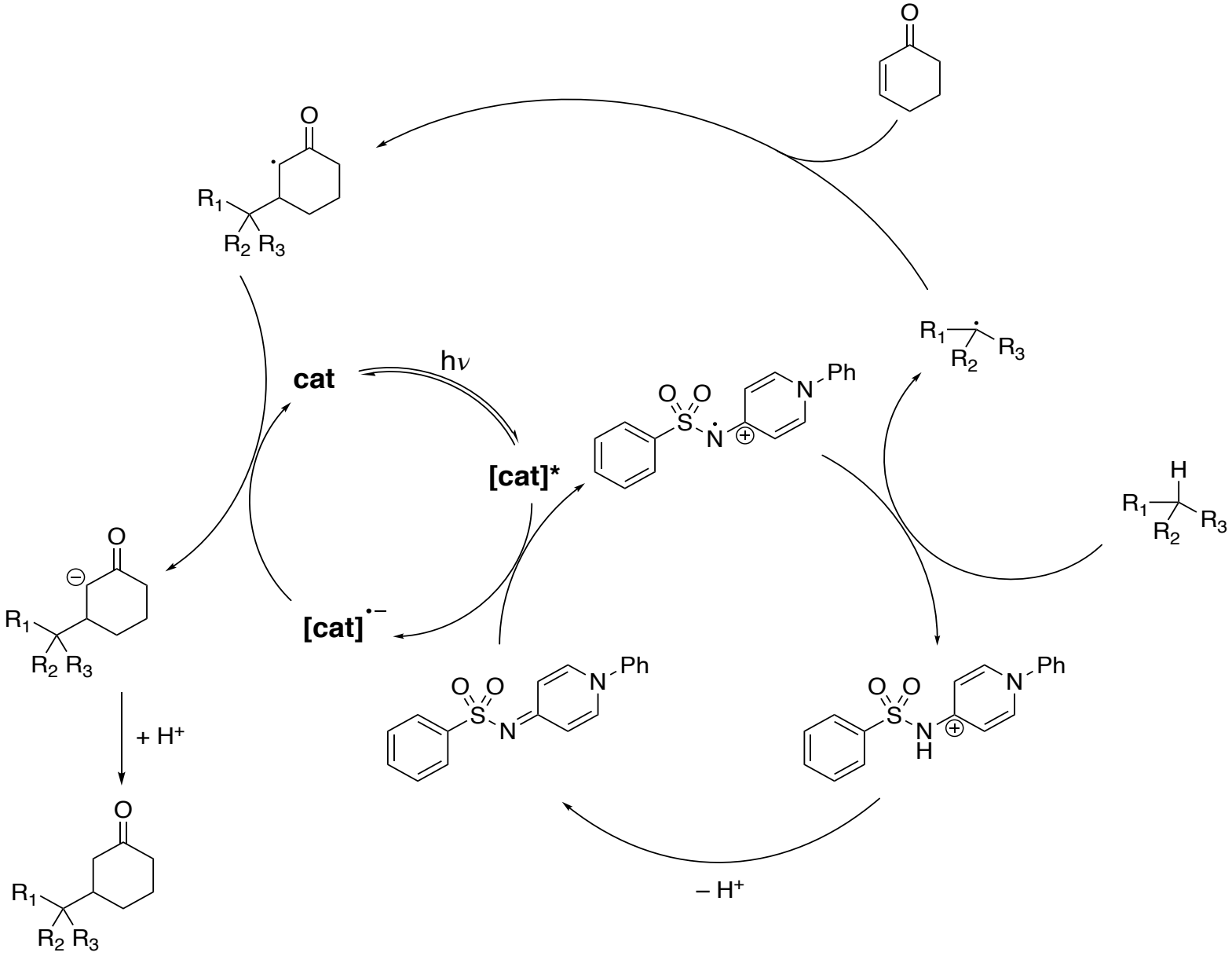


- Addition of anion-binder

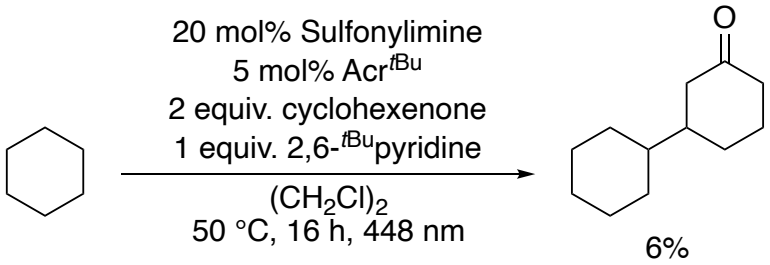


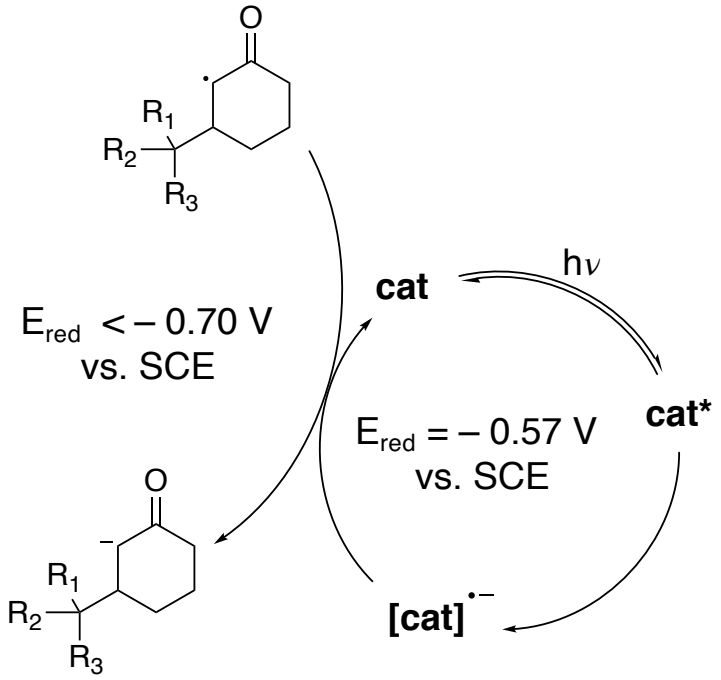
Counteranion dependency: E. P. Farney, S. J. Chapman, W. B. Swords, M. D. Torelli, R. J. Hamers, T. P. Yoon, *J. Am. Chem. Soc.* **2019**, *141*, 6385–6391.

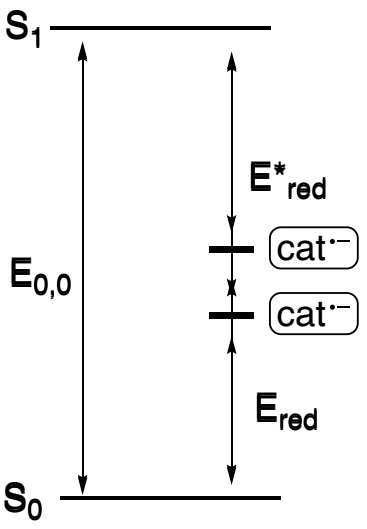
How to omit the problem? – Introducing Electron-Defiecent Double Bonds



How to generate a new problem? – Introducing Electron-Defiecent Double Bonds

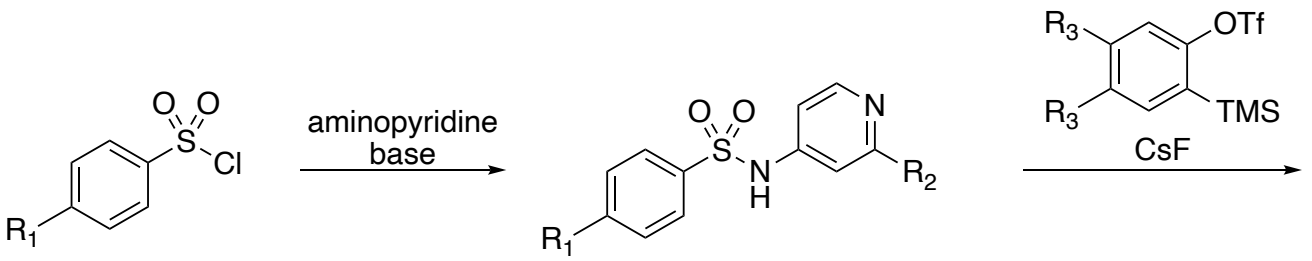




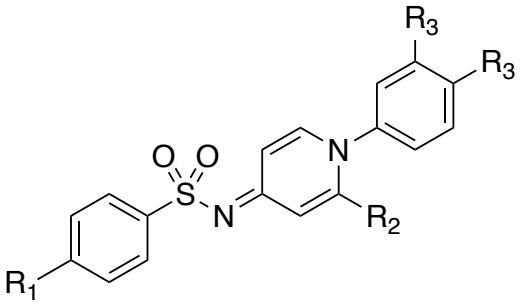


Reduction of α-carbonyl radical: K. A. Margrey, W. L. Czaplyski, D. A. Nicewicz, E. J. Alexanian, *J. Am. Chem. Soc.* **2018**, *140*, 4213–4217, H.-B. Yang, A. Feceu, D. B. C. Martin, *ACS Catal.* **2019**, *9*, 5708–5715, $E_{red} - E^*_{red}$ –Relationship: N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166.

- 50 °C reaction temperature
- Hydrogen transfer ability of sulfinic acids
- Anion dependency of photoredox catalysts
- E_{red} – E^*_{red} –Relationship



- BDE
- UV/Vis
- E_{Ox}



R_1 = H, CF_3, Cl, OMe
R_2 = H, OMe
R_3 = H, F, OMe

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