

Pyridinium Salts as Carbon Radical Precursors in Organic Synthesis

Ai Yuyang

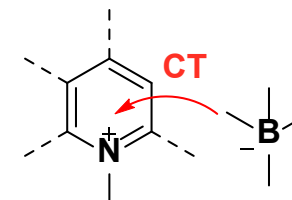
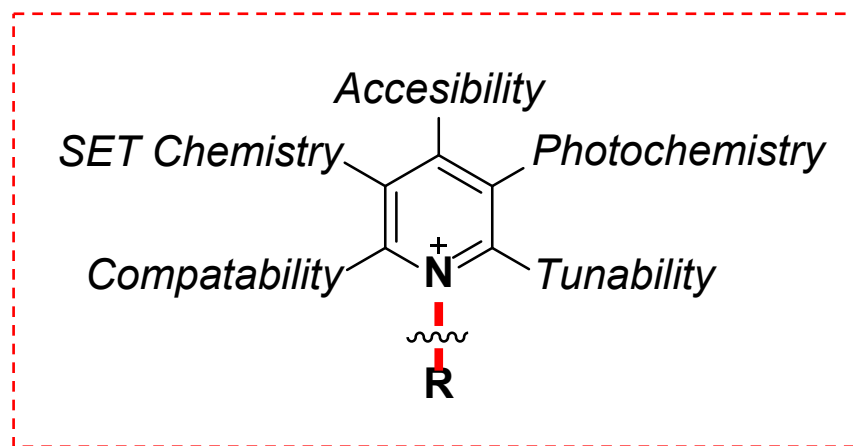
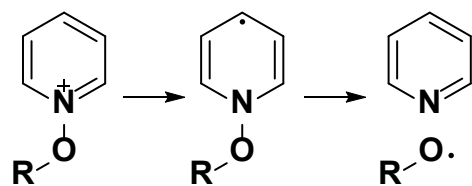
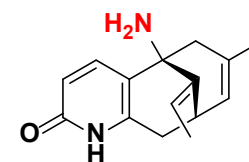
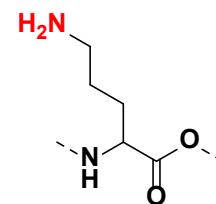
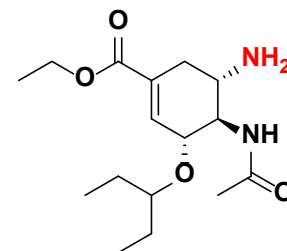
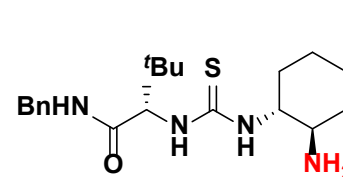
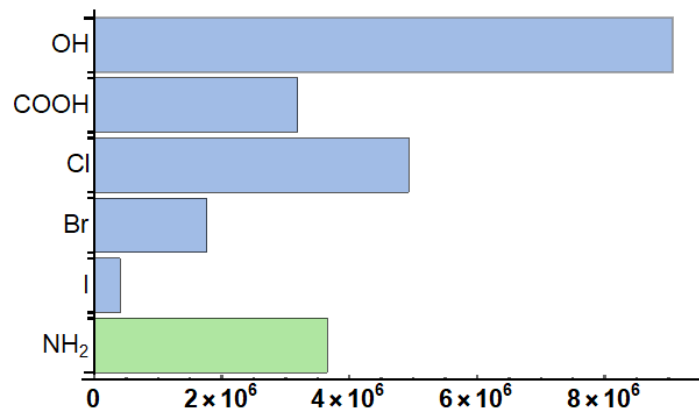
College of Chemistry and Molecular Engineering, PKU

April 16th 2022

Outline

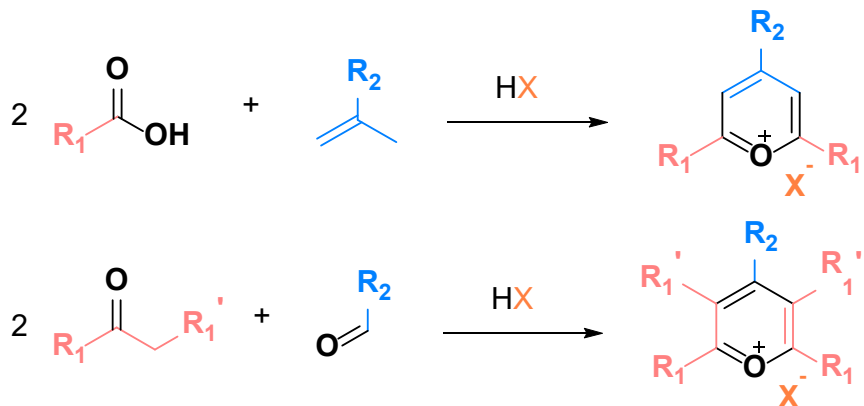
- Introduction
- Katritzky salt
 - History of development
 - Methodologies
 - Structure-property relationships
- Pyridinium ylide
 - Ground and excited state properties
- Summary

Pyridinium Salts

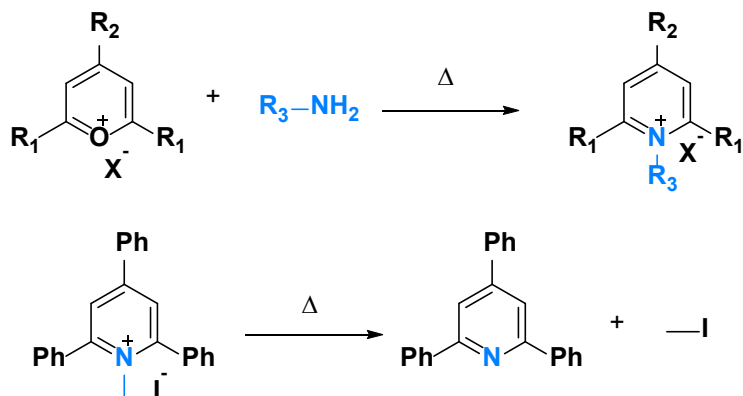


Katritzky Salts

Pyridiniums synthesis from pyryliums

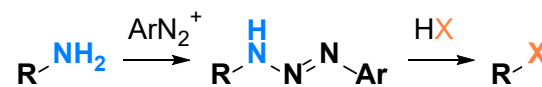
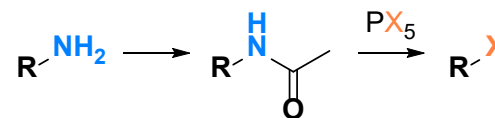


Balaban-Nenitzescu-Prail reaction, 1959

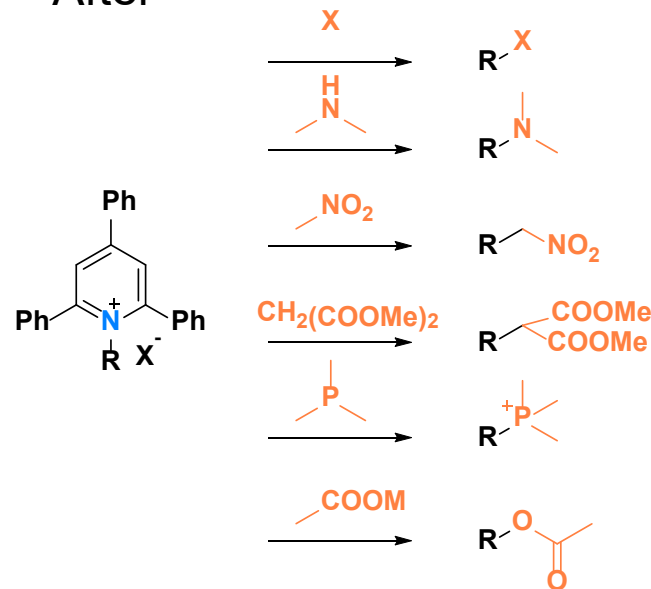


Substitution reactions of pyridinium salts

Before 1970s:



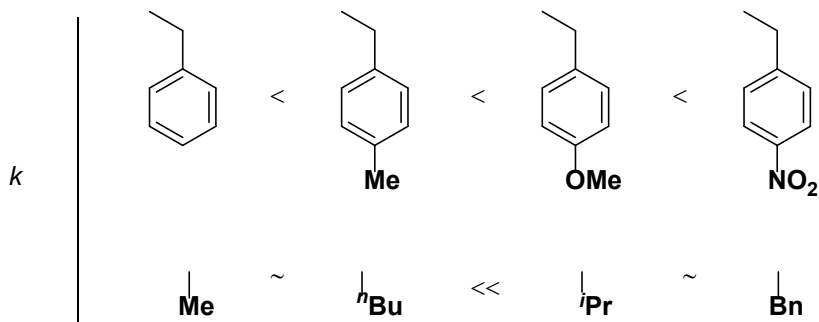
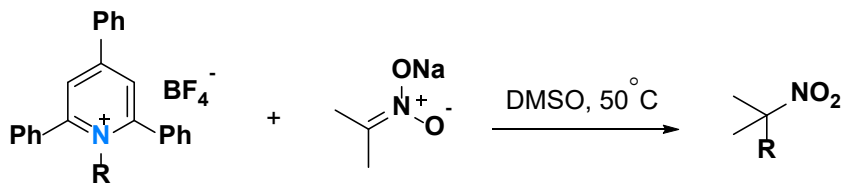
After



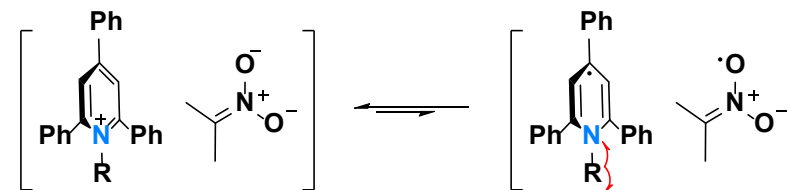
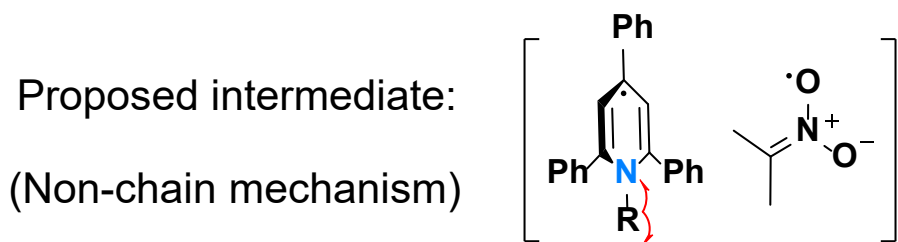
Alan Roy Katritzky
1928-2014

Evidence of Open-shell Mechanisms

□ Nitroalkane

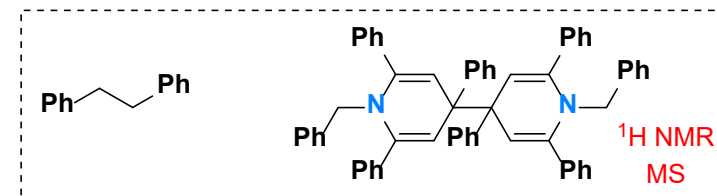
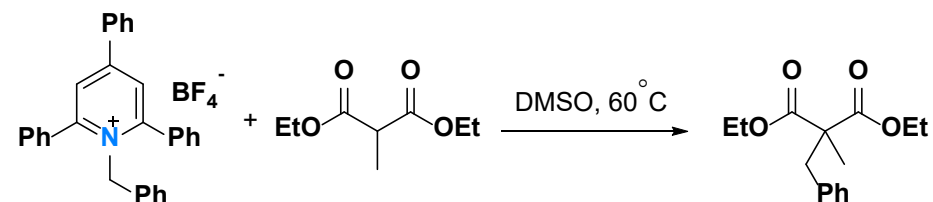


Aromatic H signal broadening & ESR signal detected



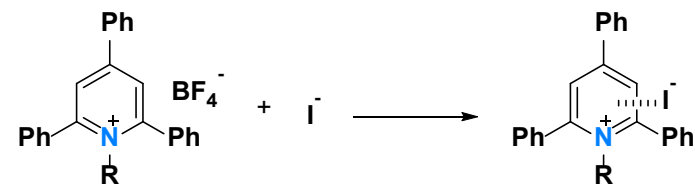
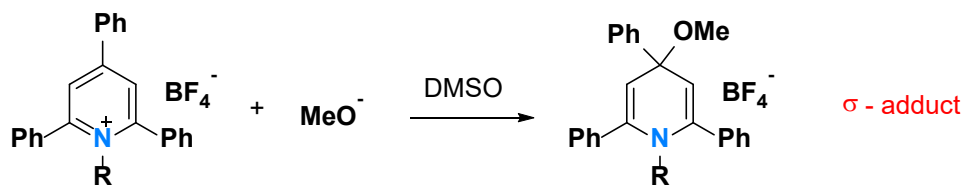
ΔG estimated to be 5 kcal mol⁻¹ based on
 $E_{\text{red}}(\text{py}^+) = -0.79 \text{ V}$, $E_{\text{ox}}(\text{NA}^-) = 0.59 \text{ V}$

□ Malonate

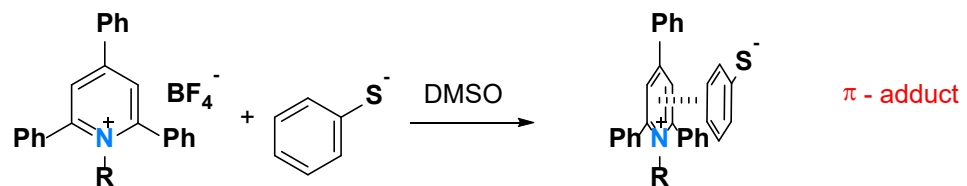


Charge-transfer Complexes

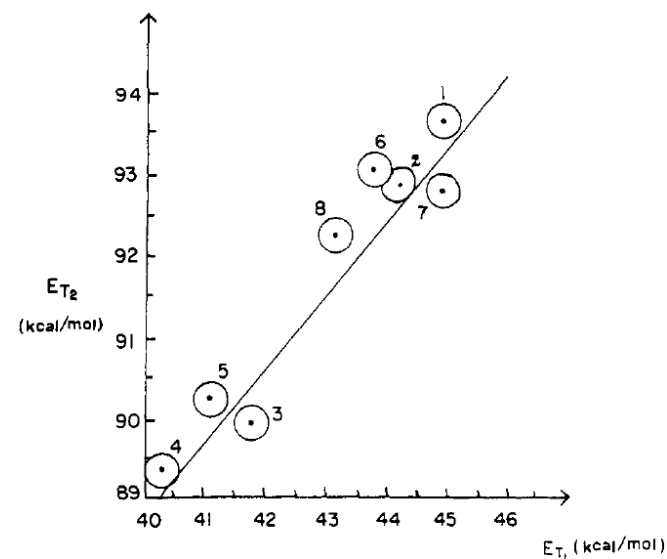
□ With nitroalkane and thiophenolate



CT band dependent on solvent polarity

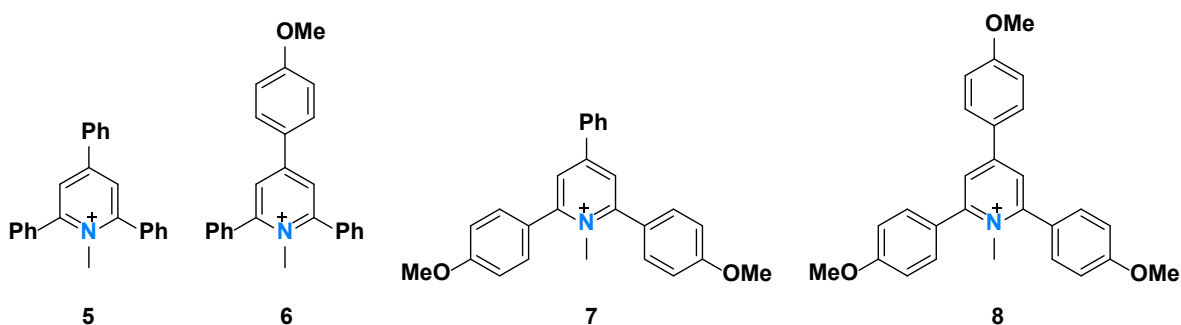


supported by ^1H , ^{13}C , UV-vis



Photochemical Studies

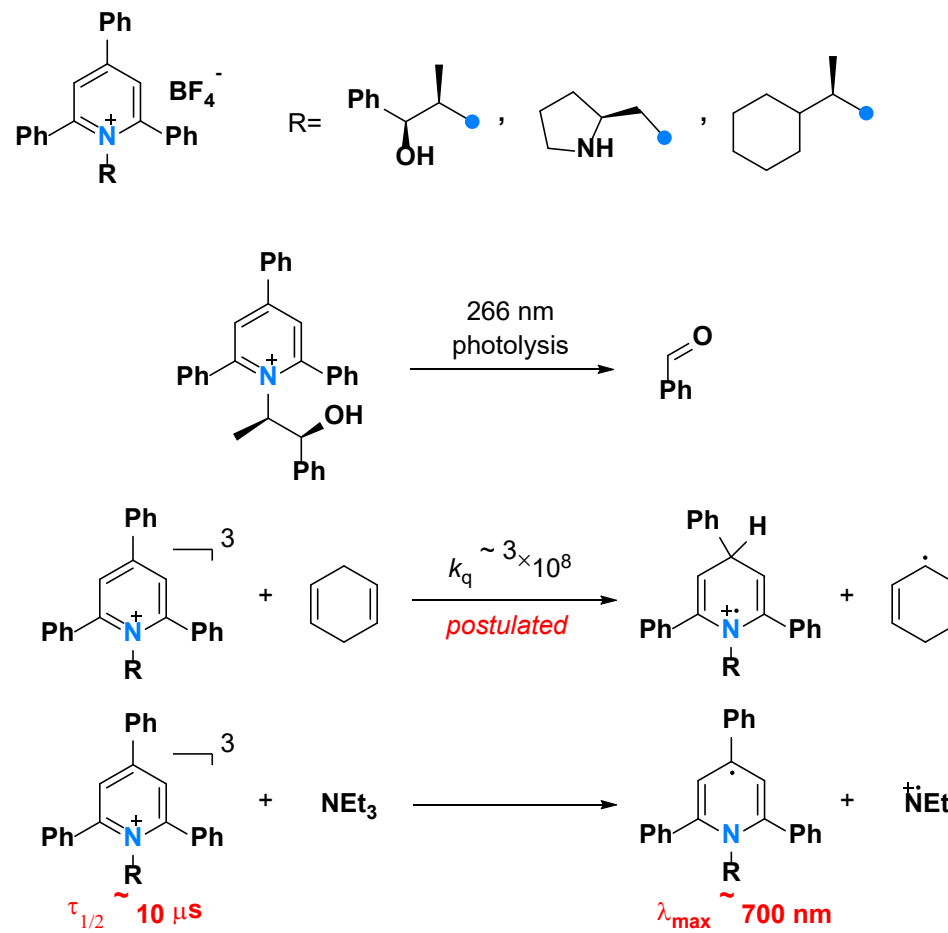
EDA complex between Katritzky salt and Et₃N



Constant	Compound			
	5	6	7	8
K_q (10^9 l mol ⁻¹)	5.2	3.0	2.16	1.93
K (l mol ⁻¹)	2.8	—	—	—

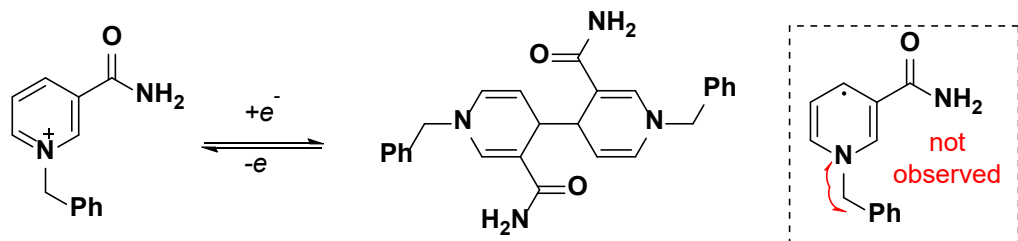
Such EDA complex is unobservable in UV-vis

Asymmetric triplet sensitizer

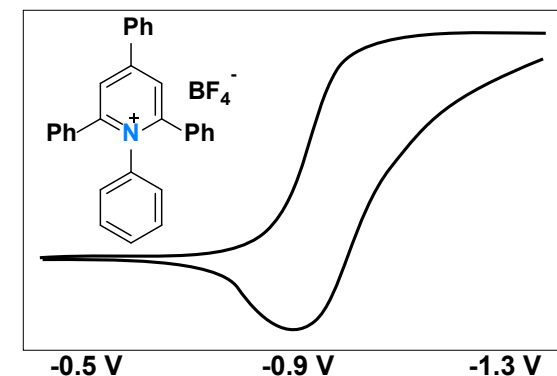
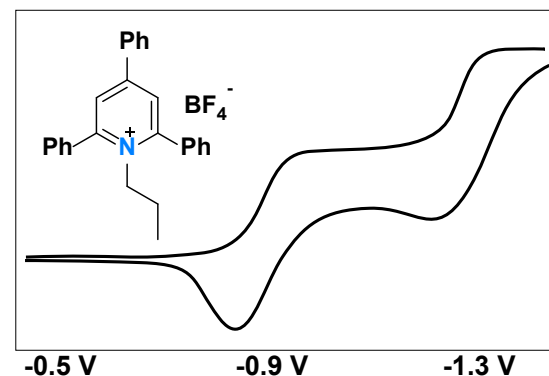


Electrochemical Studies

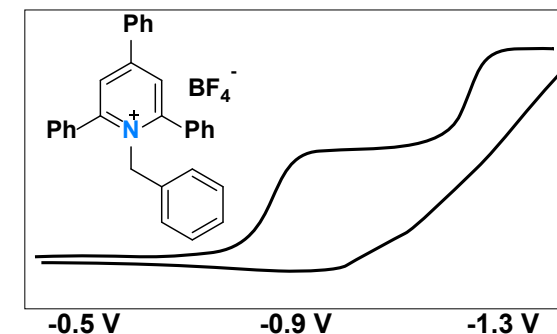
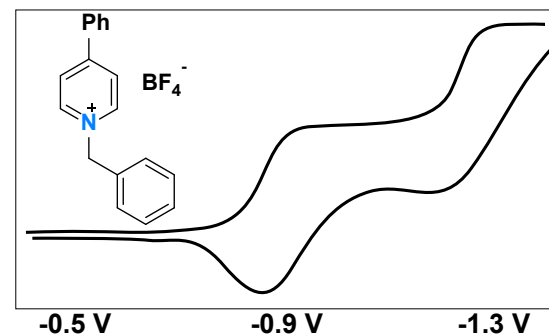
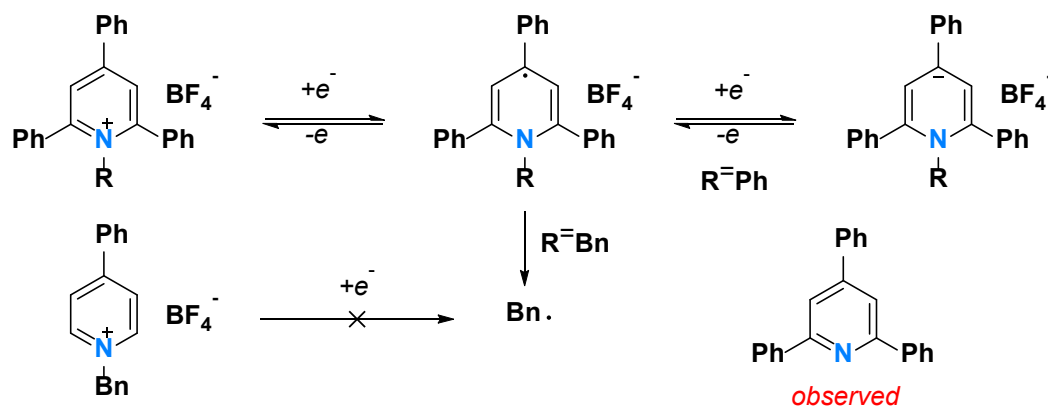
Reduction of 1-alkyl pyridinium salts



Cyclic Voltammetry



Plausible mechanism

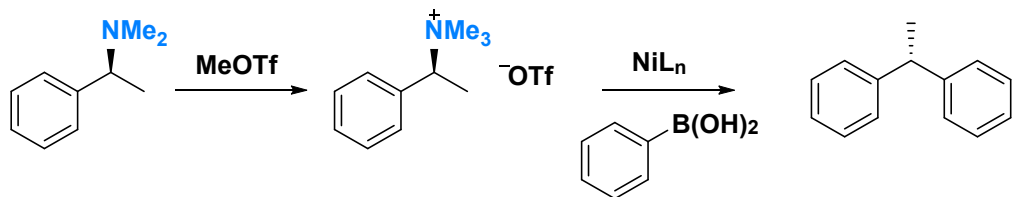


(Qualitatively simulated CV data)

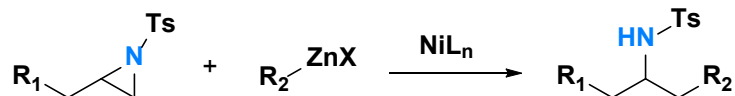
Blank until 2017

□ C-N bond cleavage for cross coupling

■ Before: activated C-N bond

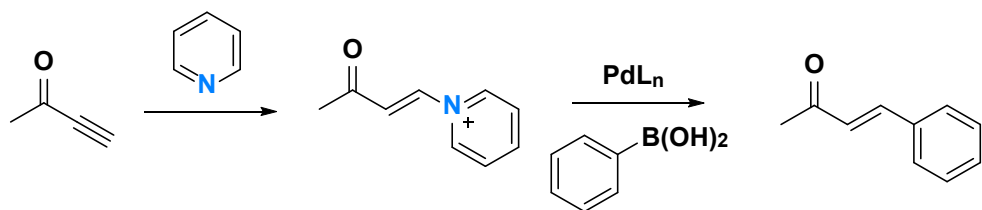


Watson 2013



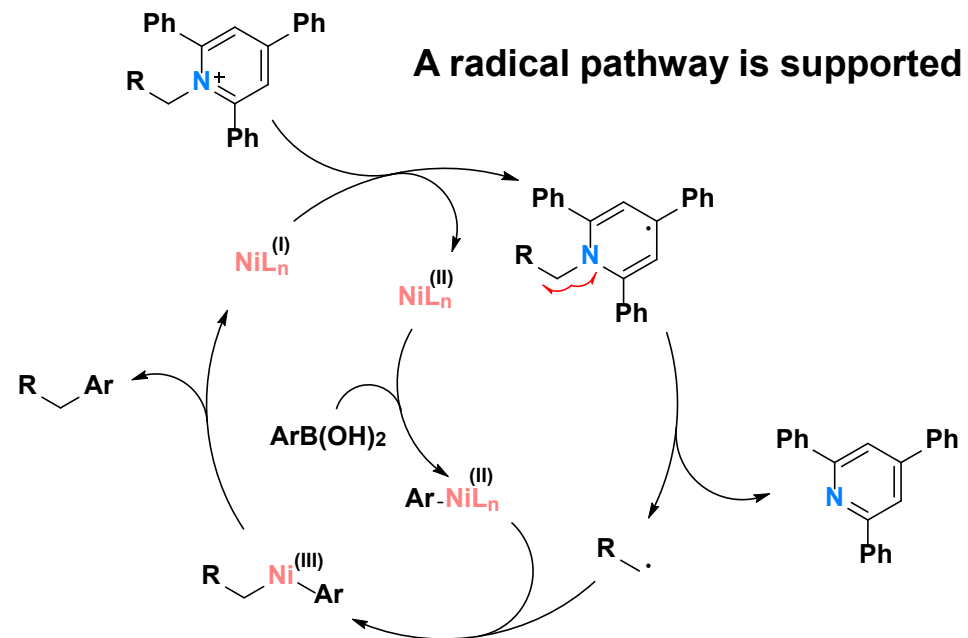
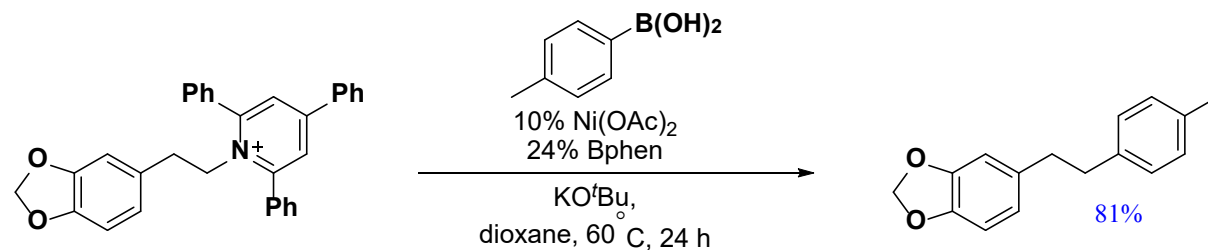
Jamison 2014

■ Before:



Brown 2007

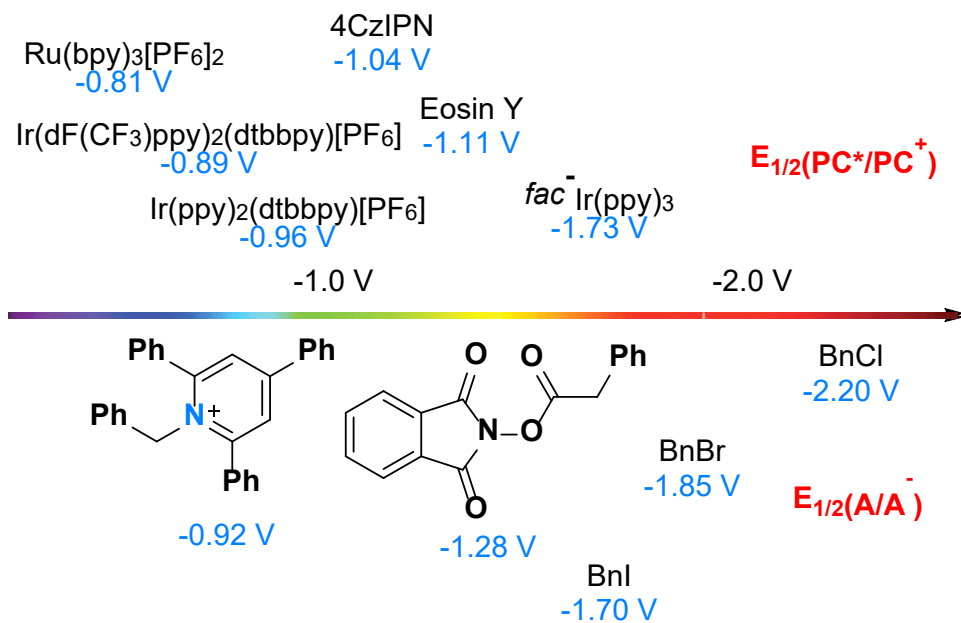
□ Primary amines activation



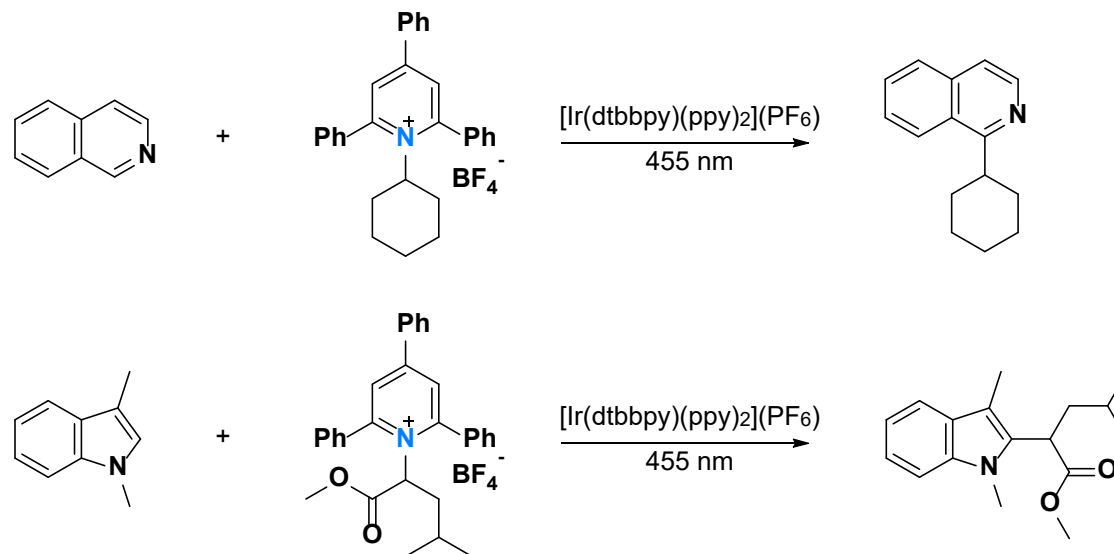
Photoredox with Katritzky Salt

□ Simple and mild radical generation

Photocatalyst	Quenching percentage
[Ru(bpy) ₃](PF ₆) ₂	16 %
[Ir(dtbbpy)(ppy) ₂](PF ₆)	83 %
<i>fac</i> -Ir(ppy) ₃	>99 %
[Ir(dF(CF ₃)ppy) ₂ (dtbbpy)](PF ₆)	73 %



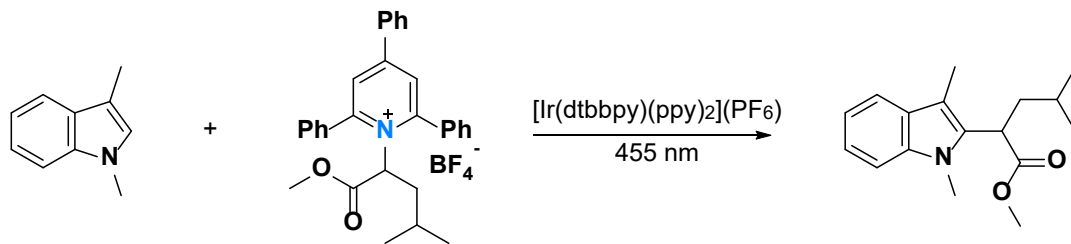
■ Minisci reactions



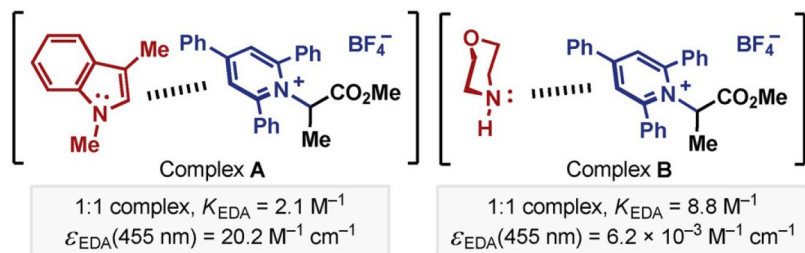
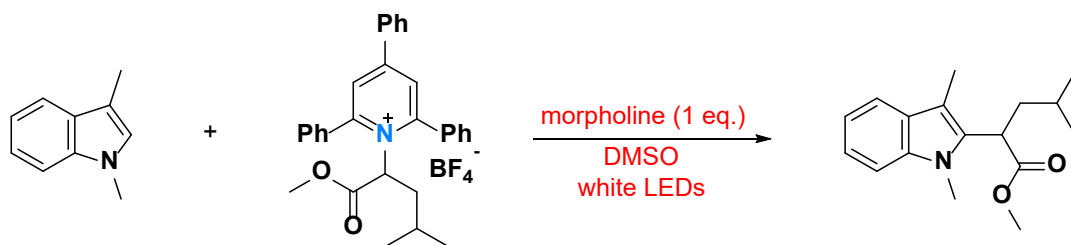
DMA (0.2 M)	<i>fac</i> -Ir(ppy) ₃	16	Traces
DMA (0.2 M)	[Ru(bpy) ₃](PF ₆) ₂	16	9
DMA (0.2 M)	[Ru(phen) ₃](PF ₆) ₂	16	5
DMA (0.2 M)	[Ir(dtbbpy)(ppy) ₂](PF ₆)	48	88 (83)
DMA (0.2 M)	-	48	9
DMA (0.2 M)	[Ir(dtbbpy)(ppy) ₂](PF ₆)	48	^b

Photoinduced Electron Transfer with Katritzky Salt

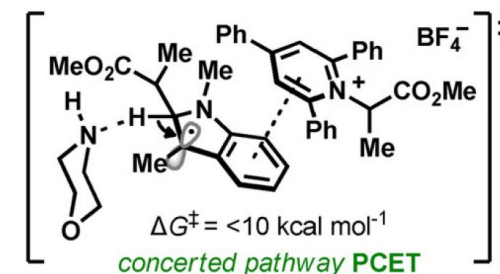
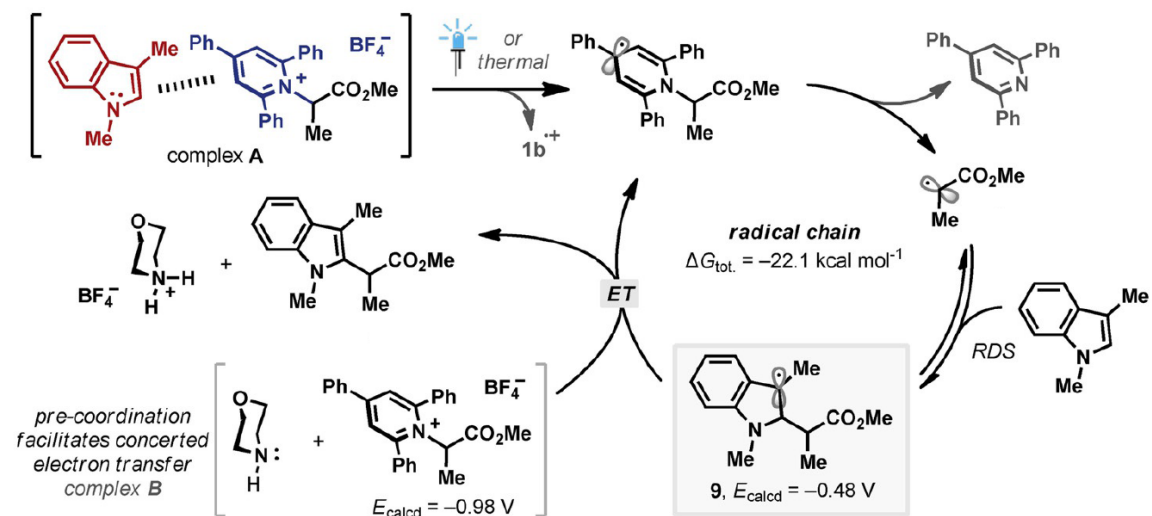
□ photocatalyst-free reaction



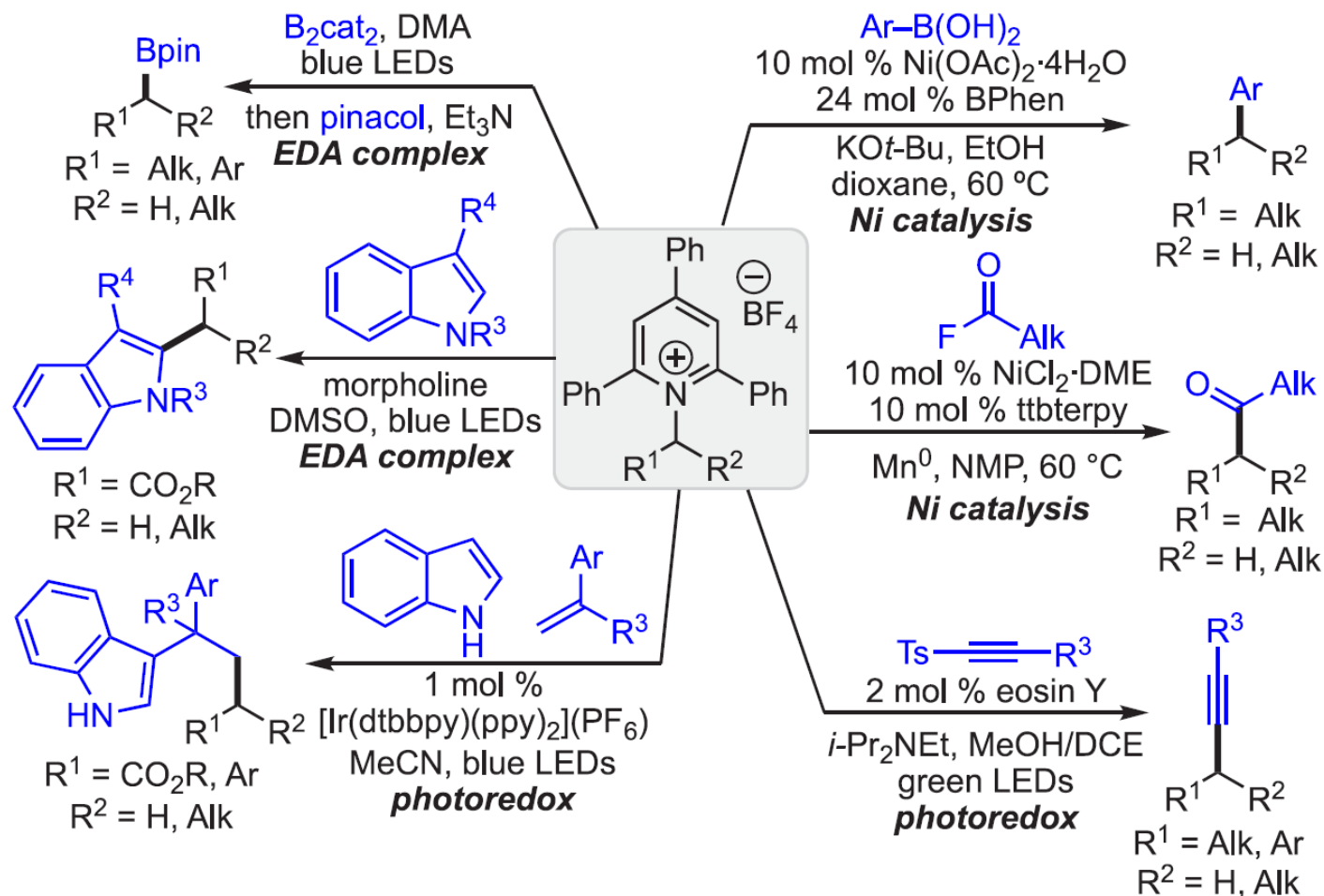
[Base]	Yield
none	0%
imidazole	12%
Et_3N	57%
morpholine	70%



■ Mechanism elucidation

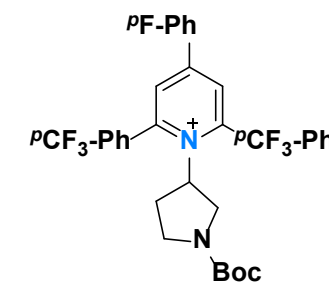
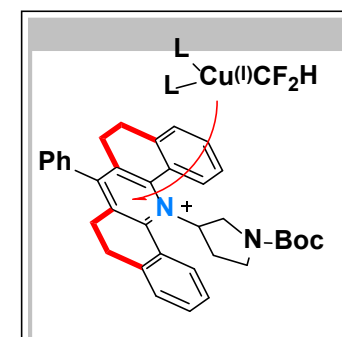
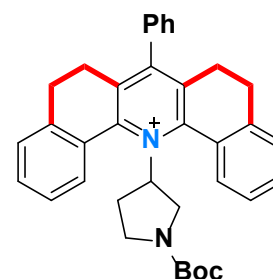
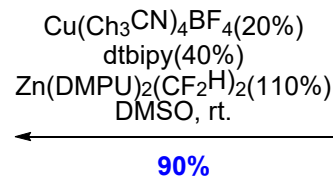
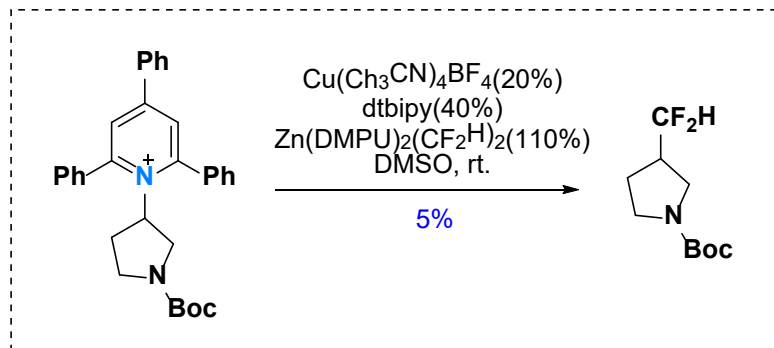
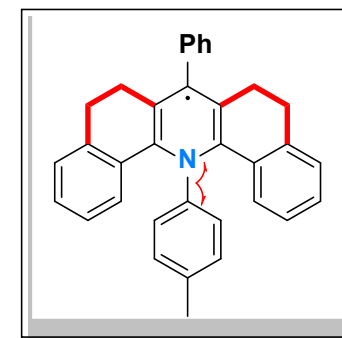
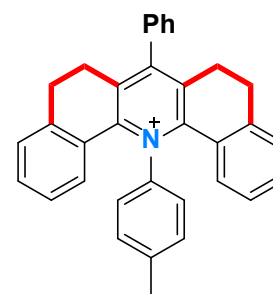
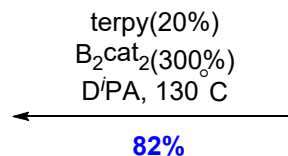
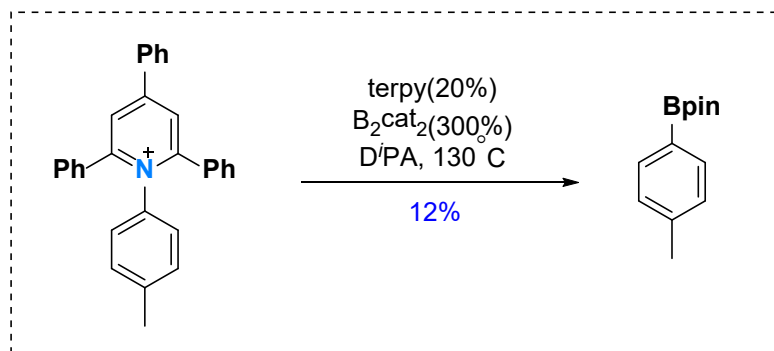


Related Methodologies



Unsuccessful Cases

- Structural modification benefits the reaction



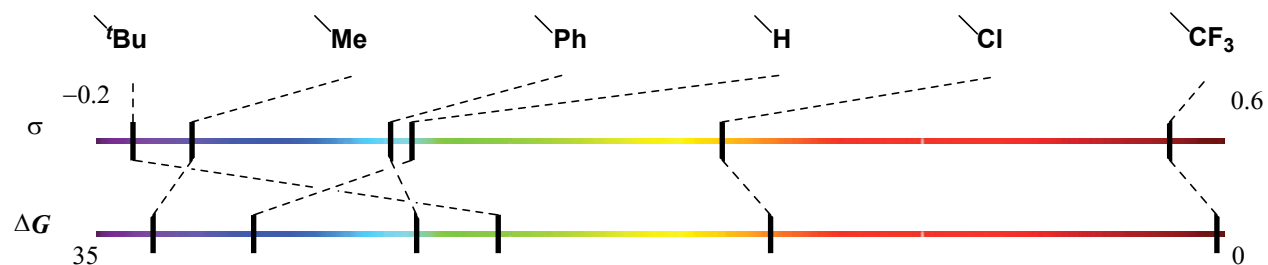
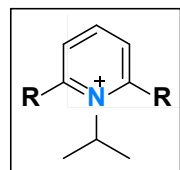
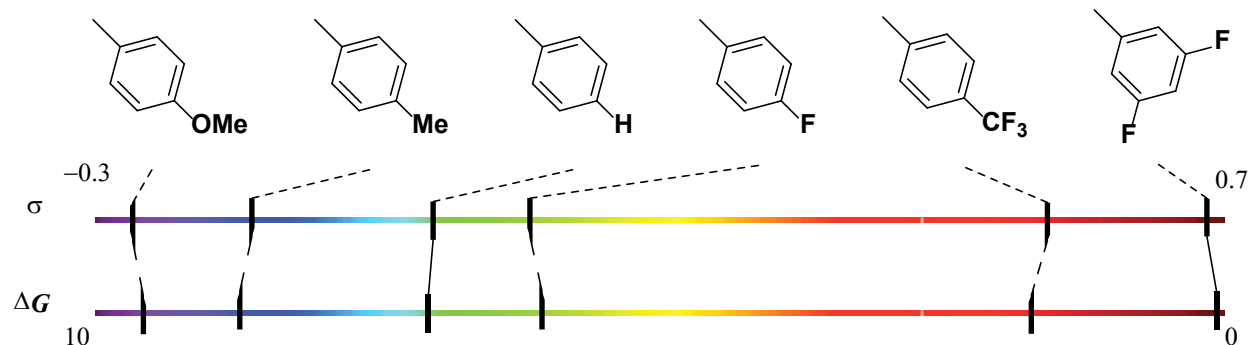
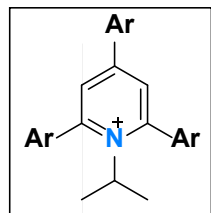
-0.77 V

-0.57 V

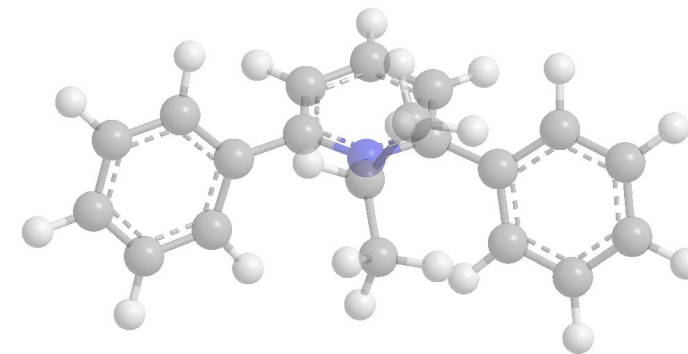
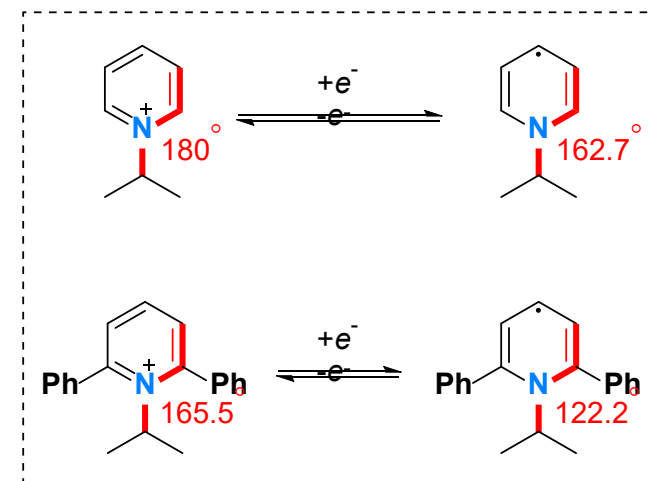
-0.70 V
42%

Structure-property Relationships

Reduction potential

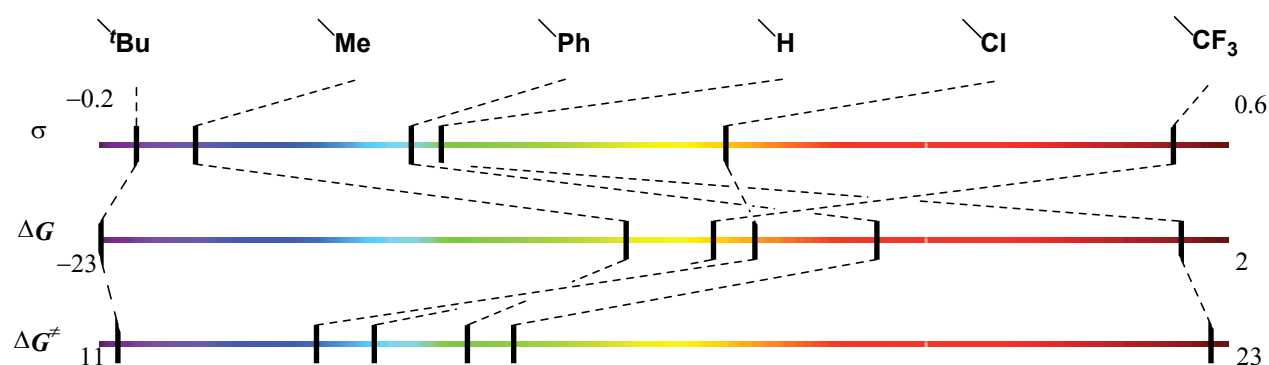
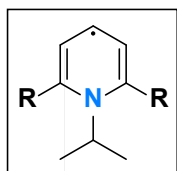
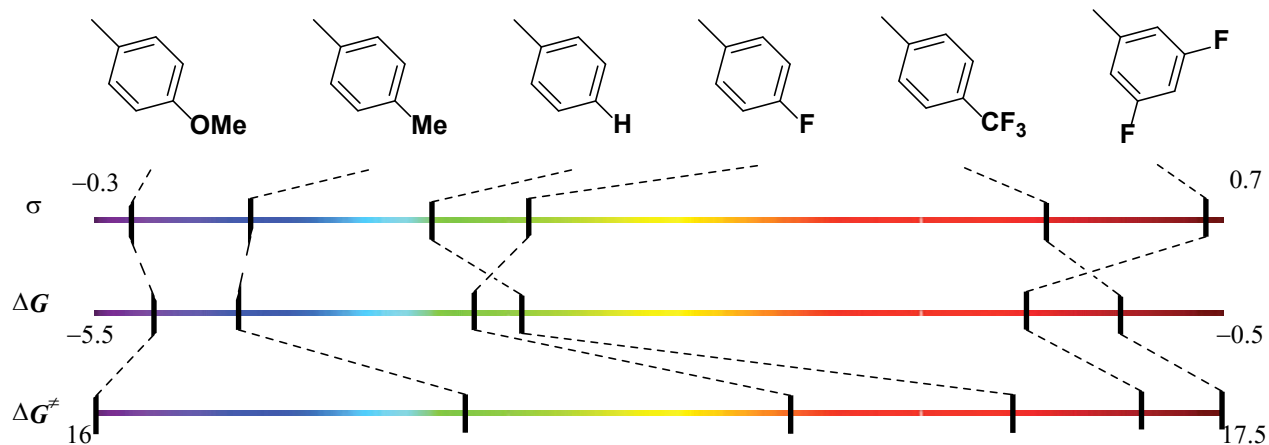
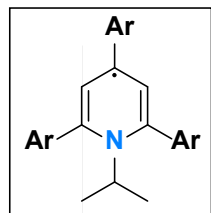


$$\Delta G_{\text{red}}^0 = -35.87\sigma_p - 15.03\nu + 32.48$$

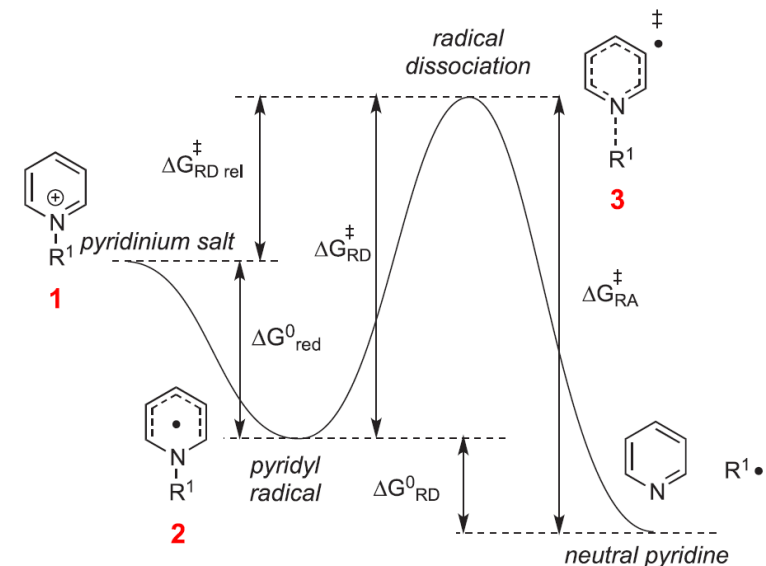
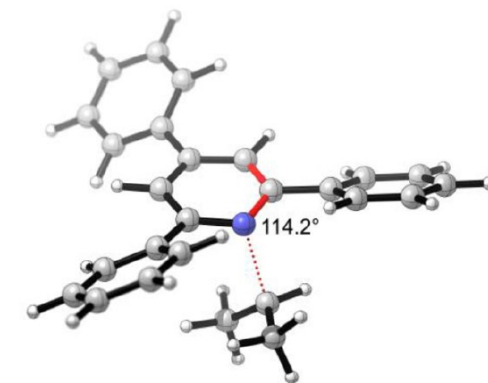


Structure-property Relationships

□ N-C bond fragmentation rate

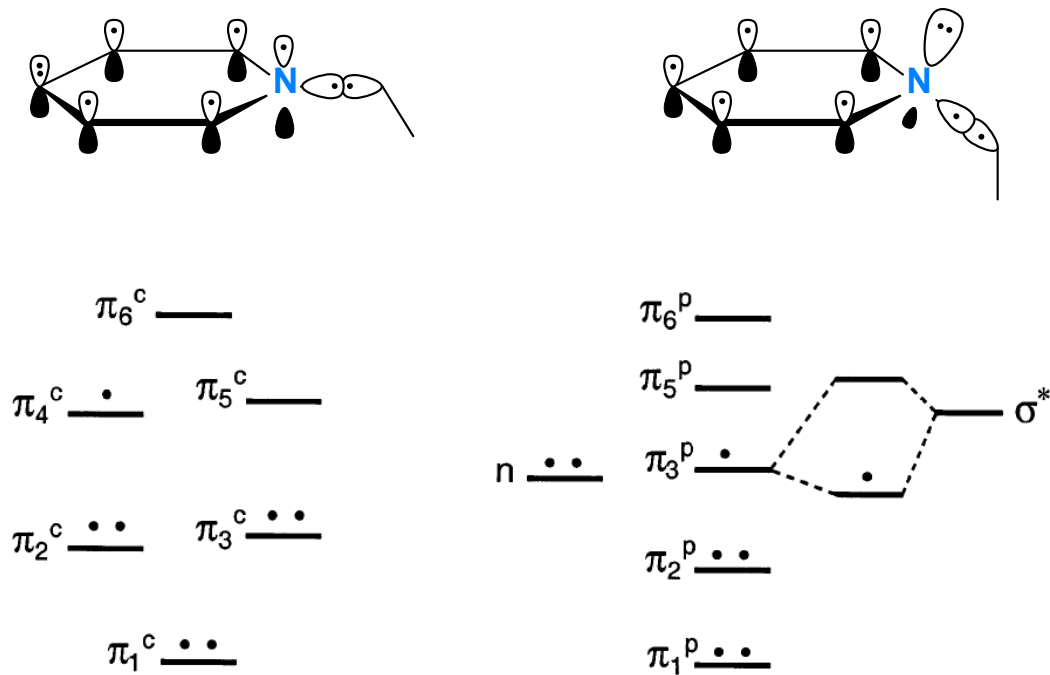


$$\Delta G_{RD}^\ddagger = -0.79\sigma_p - 6.54\nu + 18.91$$



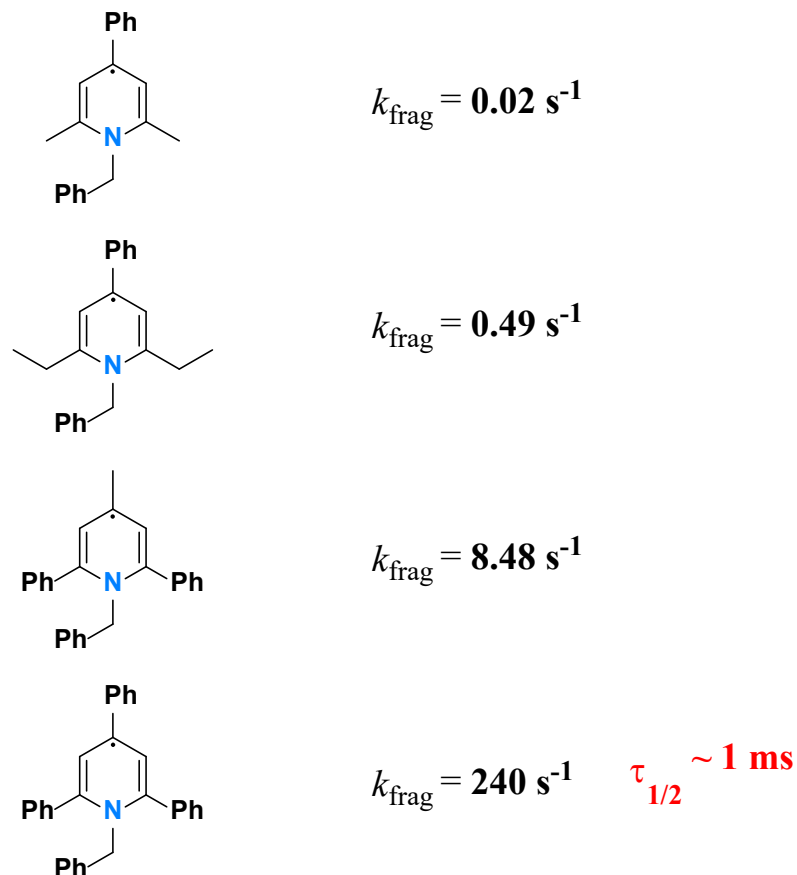
Conical Intersection in N-C Fragmentation

□ Molecular orbital depiction



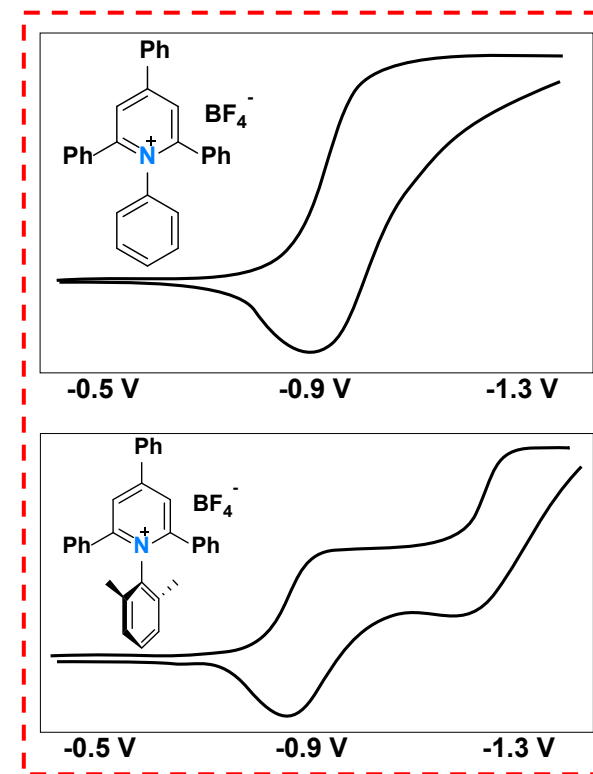
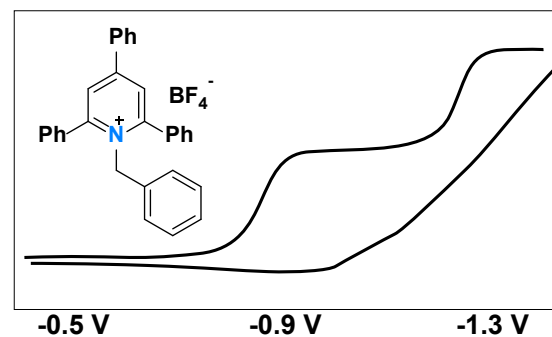
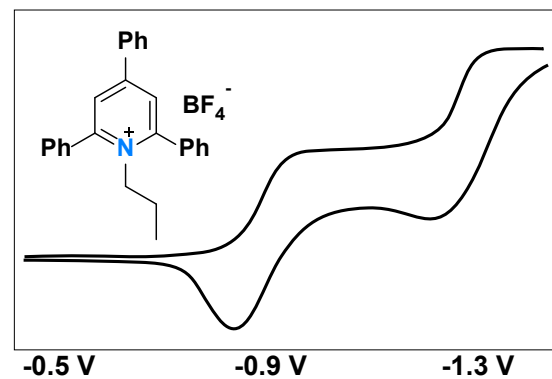
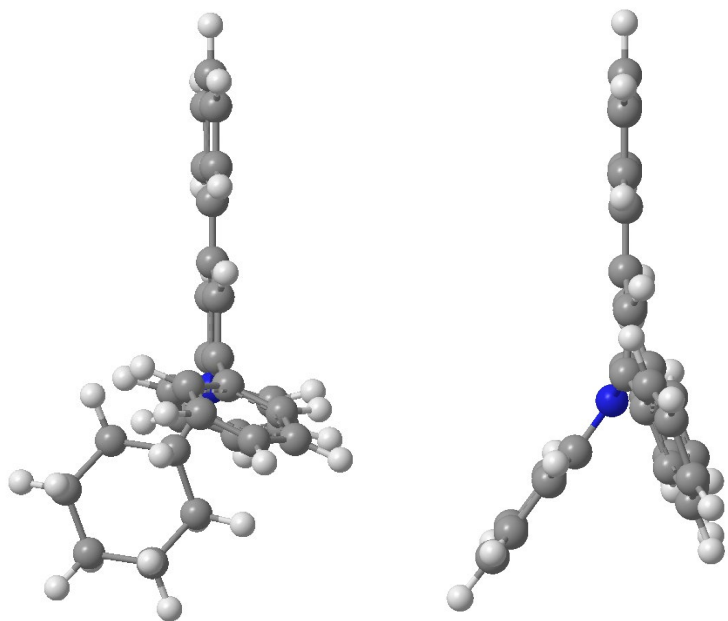
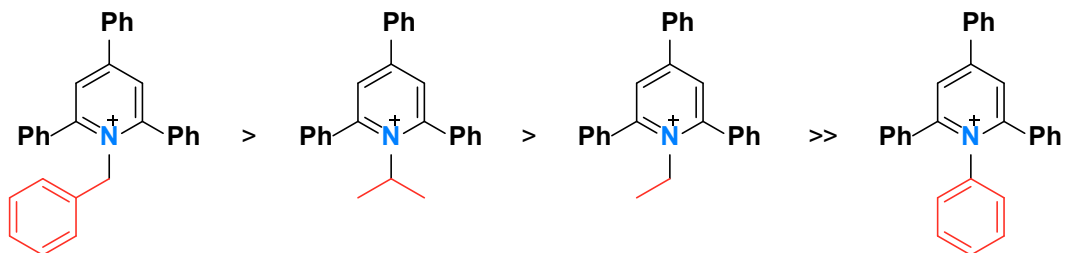
■ EWG stabilize the π -radical more

■ Rate constant of N-C fragmentation



Structure-property Relationships

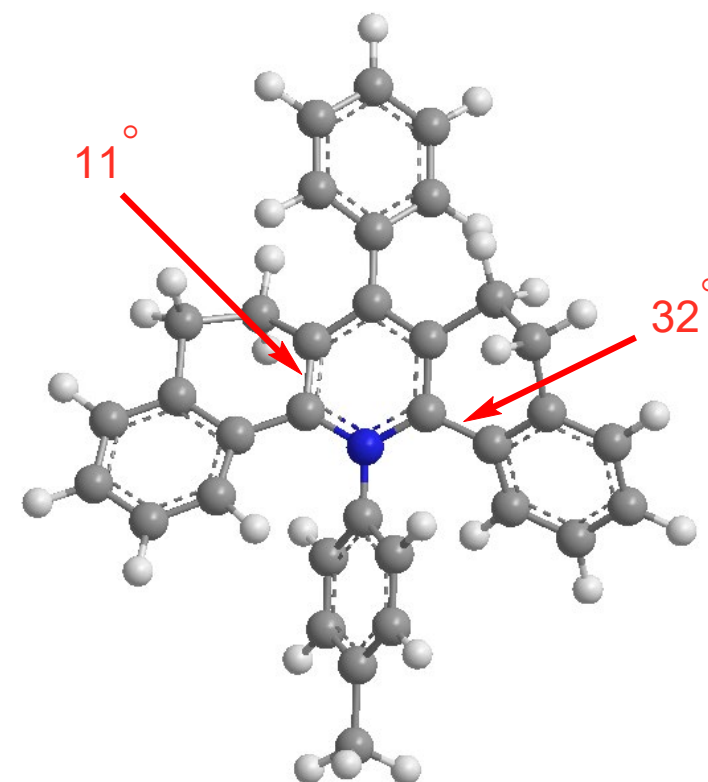
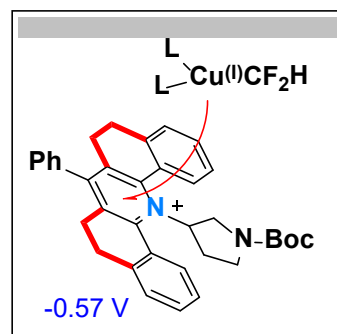
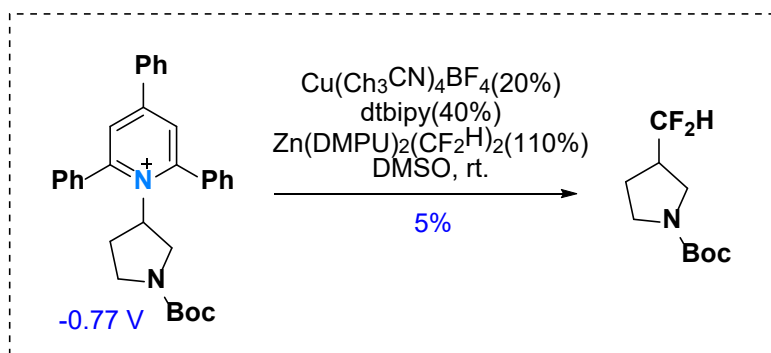
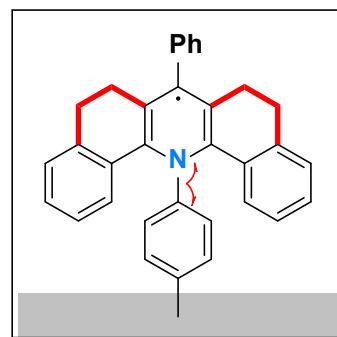
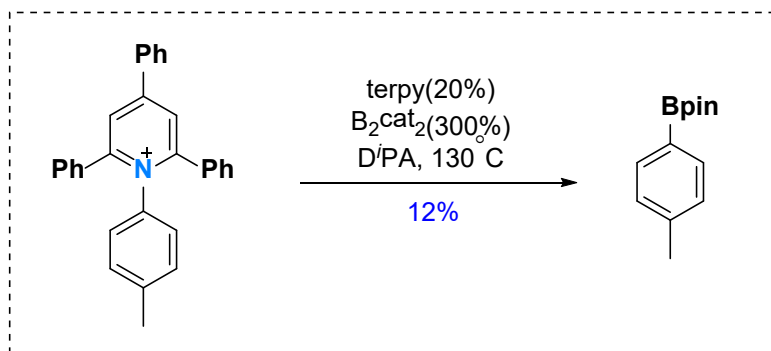
□ Variation of N-substituents



(Qualitatively simulated)

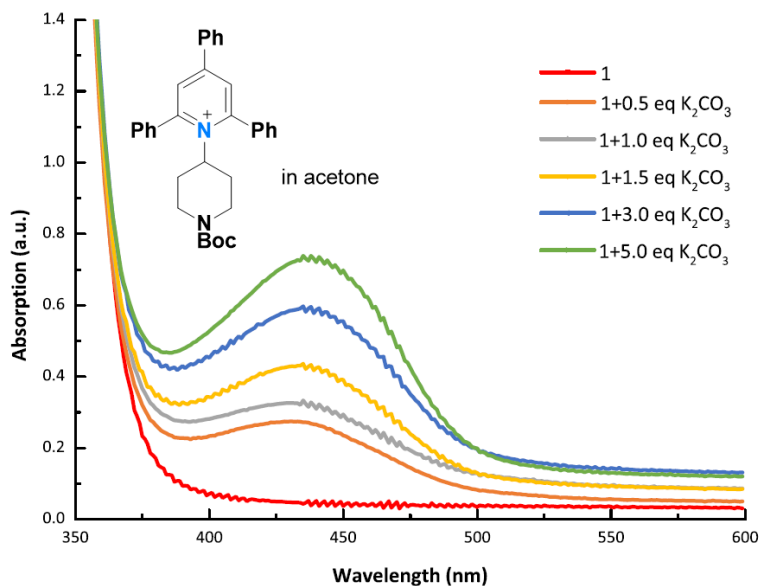
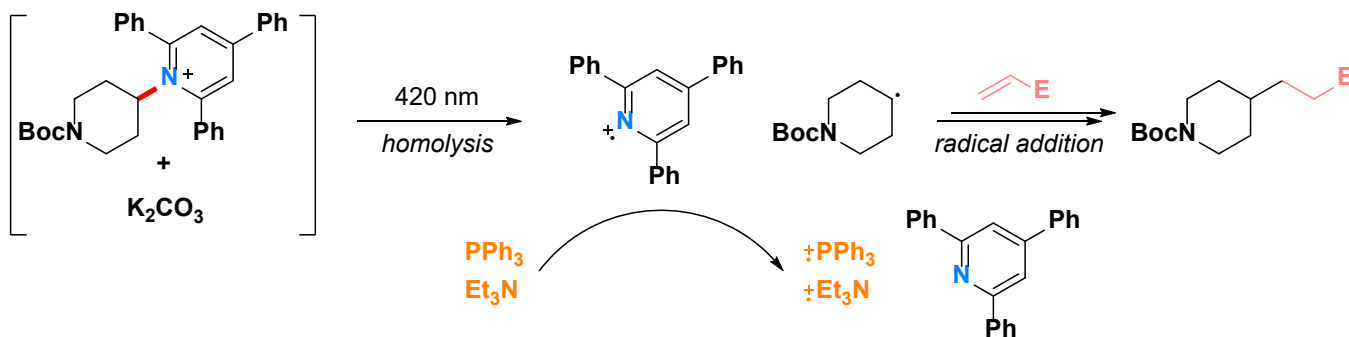
Revisit to Unsuccessful Cases

- Structural modification benefits the reaction

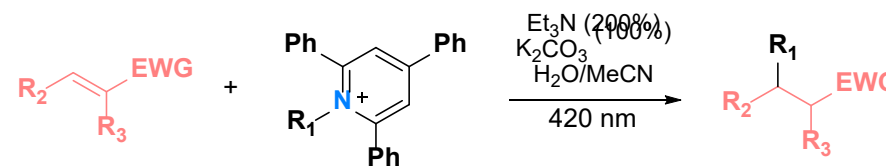


Excitation Promoted Pyridinium C-N Homolysis?

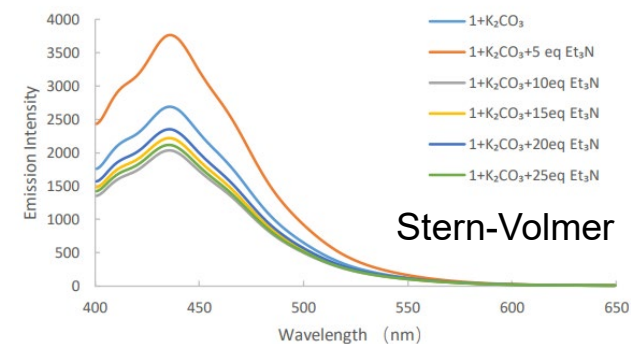
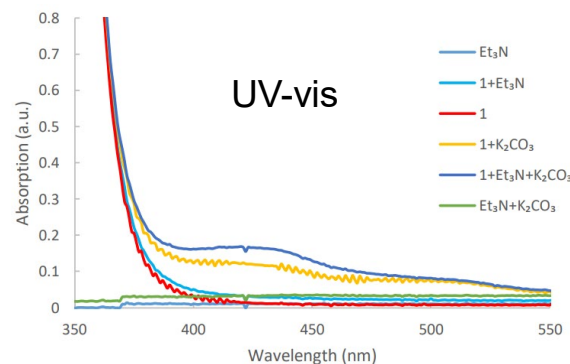
□ Base intensified absorption



□ Control experiments



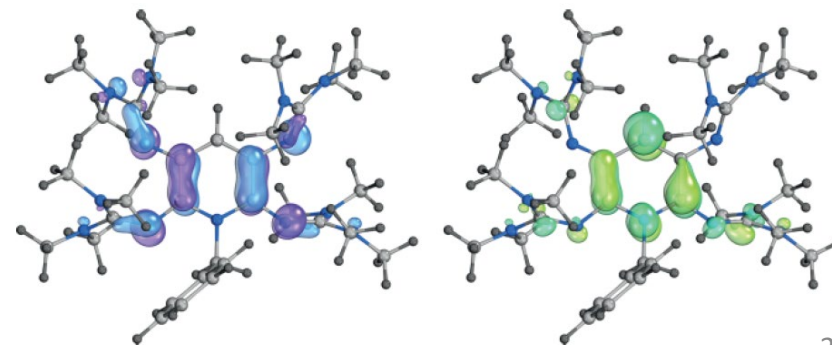
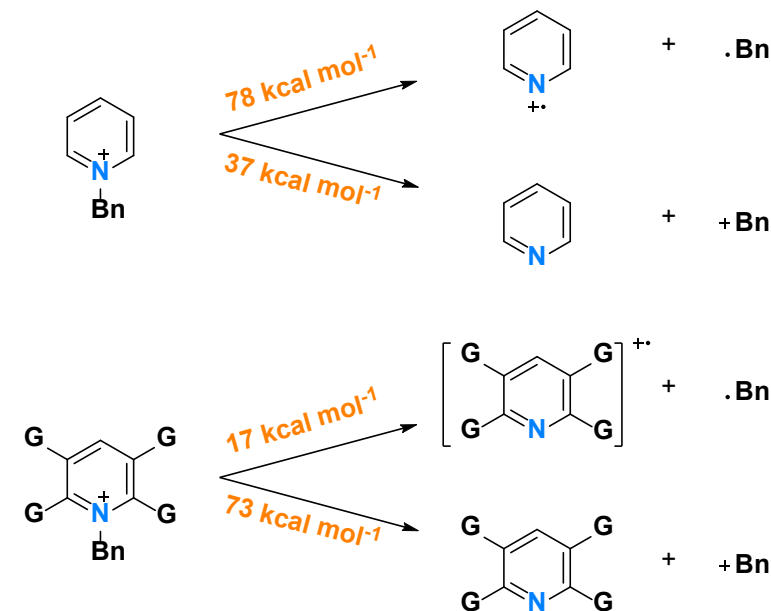
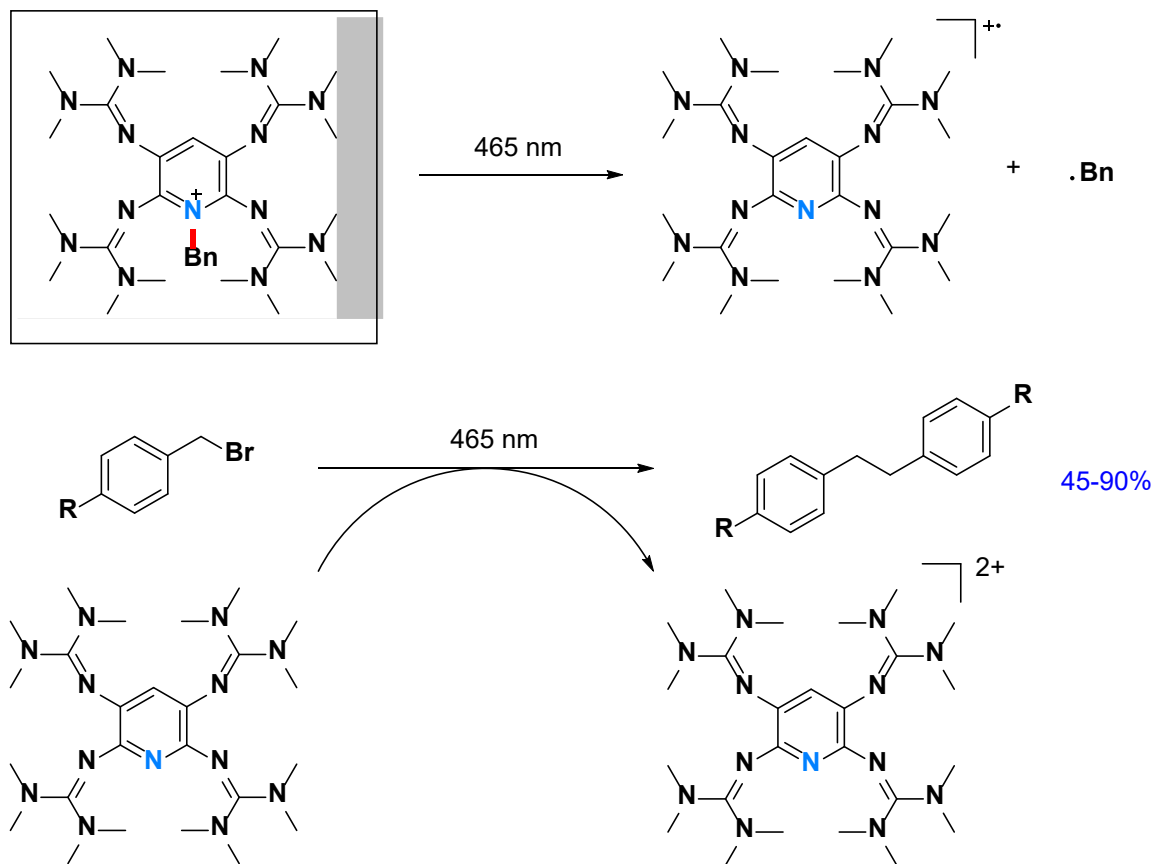
Changes from condition	Yield
no change from condition A	97%
no K ₂ CO ₃ under condition A	50%
KF instead of K ₂ CO ₃ under condition A	63%
without Et ₃ N	trace
no light	N.D.
no light, 60 °C	N.D.



■ Probably not an excitation-homolysis mechanism

Excitation Promoted Pyridinium C-N Homolysis

□ 2,3,5,6-tetrakis(tetramethylguanidino)pyridinium salts



H. Himmel *et al.* *Chem. Eur. J.* **2014**, *20*, 5288.

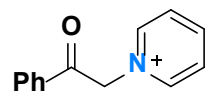
H. Himmel *et al.* *Eur. J. Org. Chem.* **2016**, 5045.

Outline

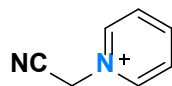
- Introduction
- Katritzky salt
 - History of development
 - Methodologies
 - Structure-property relationships
- **Pyridinium ylide**
 - Ground and excited state properties
- Summary

Pyridinium Ylides

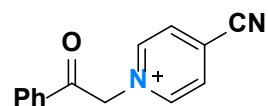
□ Synthesis and properties



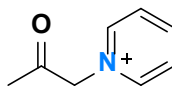
9.7



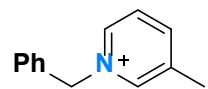
16.5



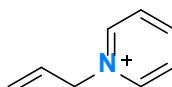
7.0



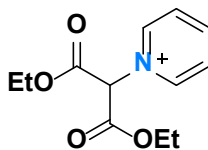
11.8



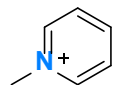
20.5



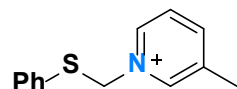
18.7



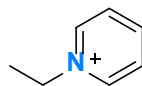
5.6



26.0

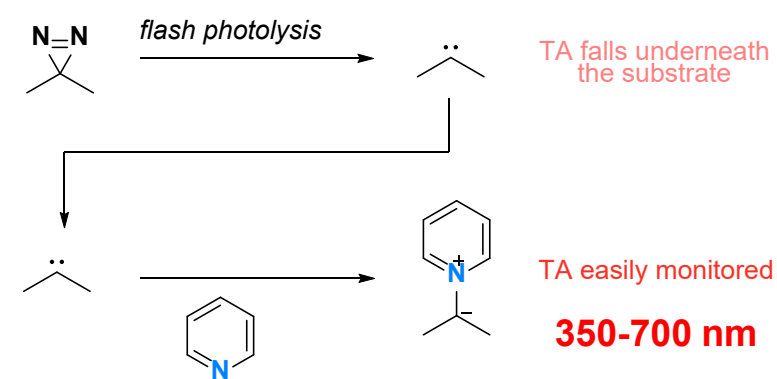
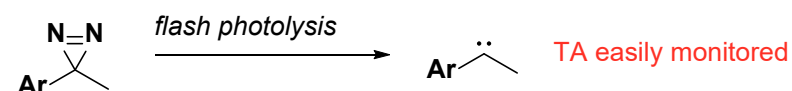


17.7

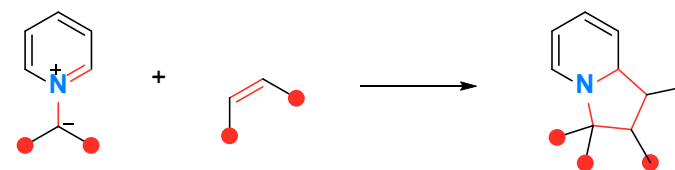


25.5

■ Probe of carbene dynamics

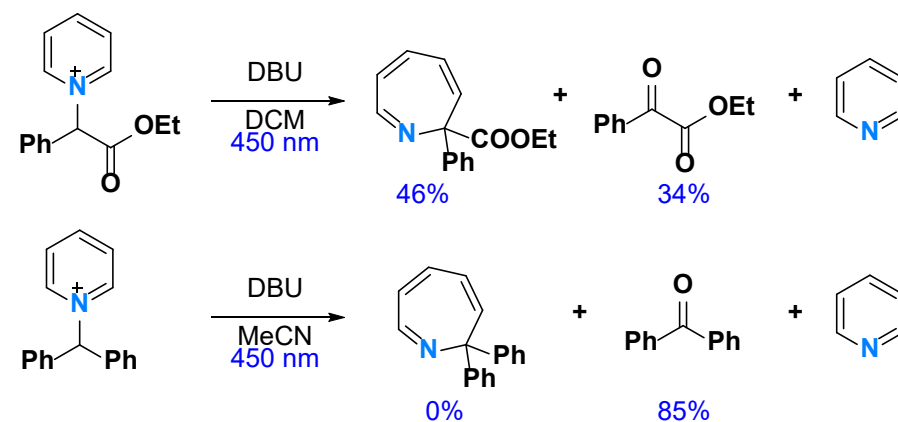
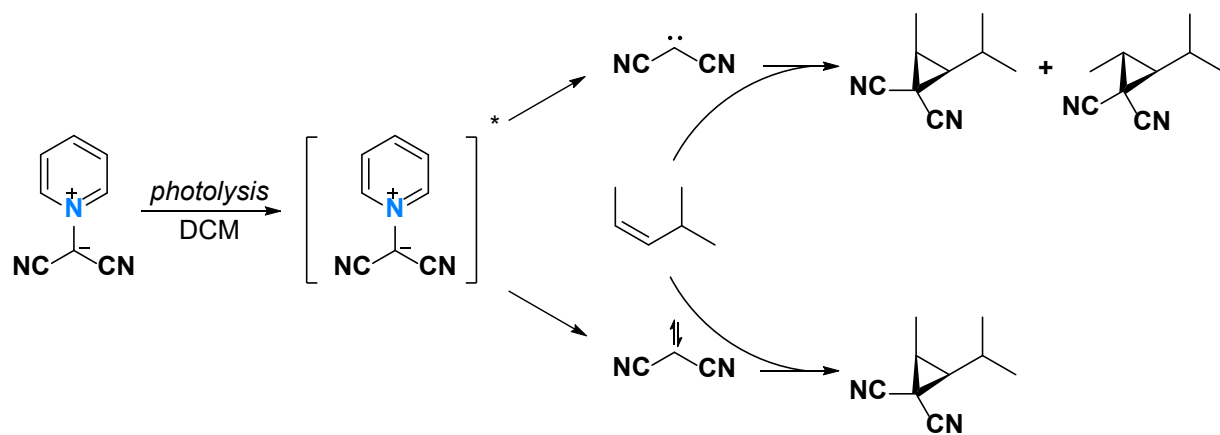
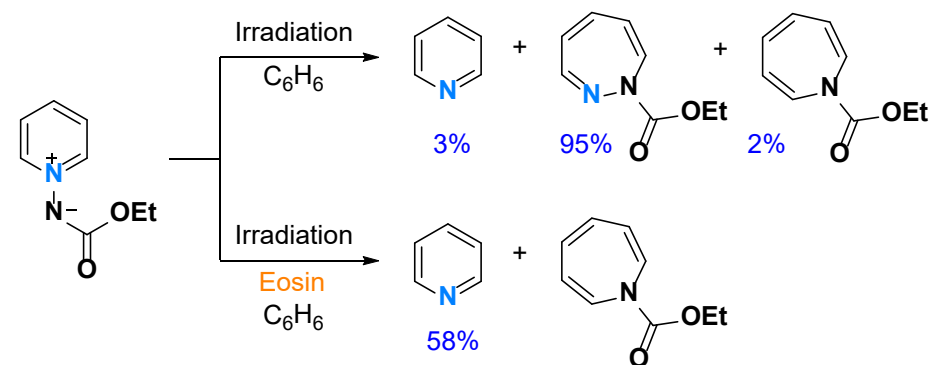
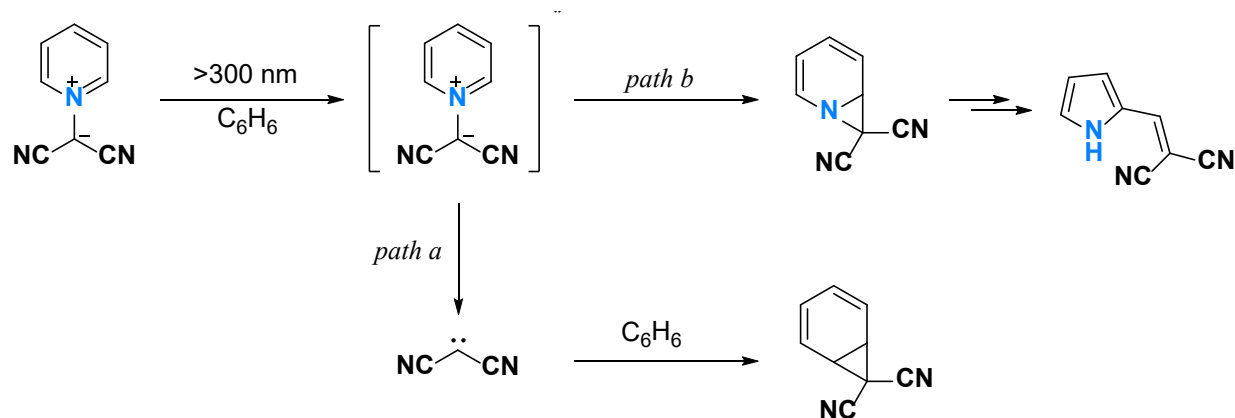


■ Most reactions involves [3+2]



Photochemistry of Pyridinium Ylides

□ Ring expansion and carbene formation

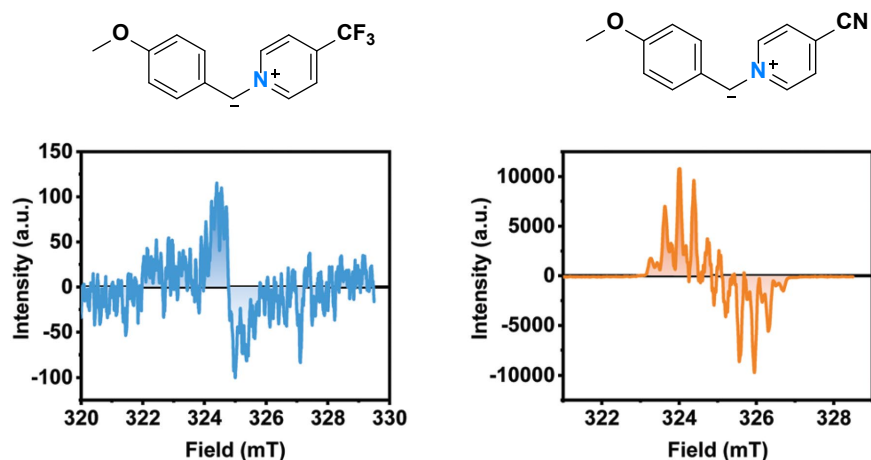


J. Streith *Pure & Appl. Chem.*, **1977**, *49*, 30.

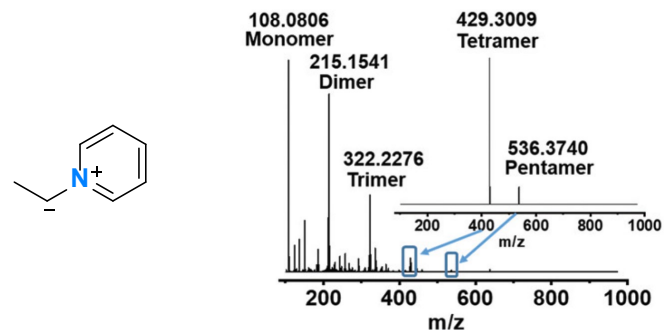
A. B. Beeler *et al. Org. Lett.* **2021**, *23*, 525.

Are Pyridinium Ylides Diradicals?

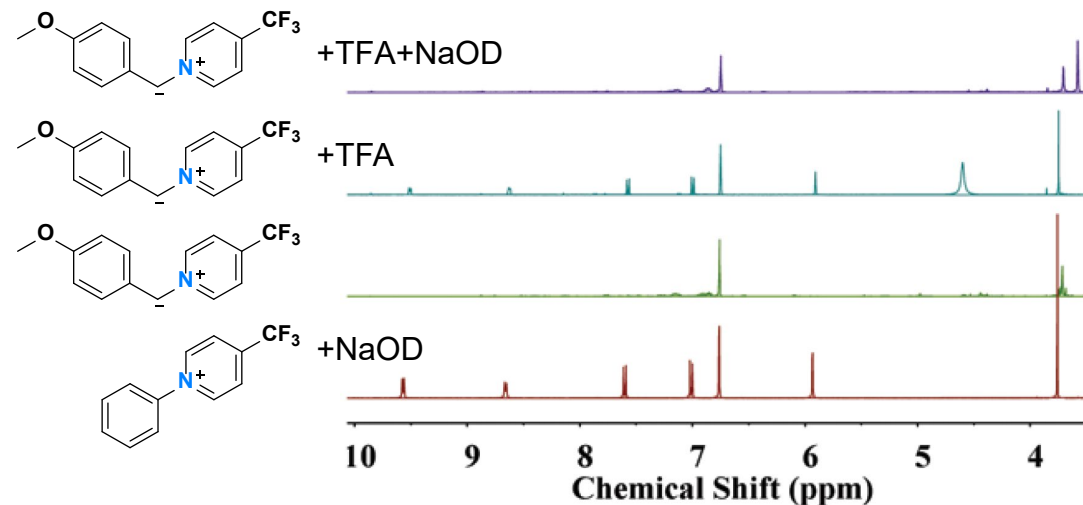
- EPR studies on pyridinium ylides
- pK_a -dependent EPR signal intensity in solution



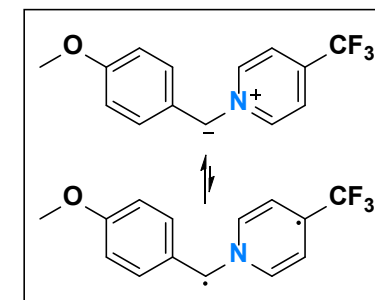
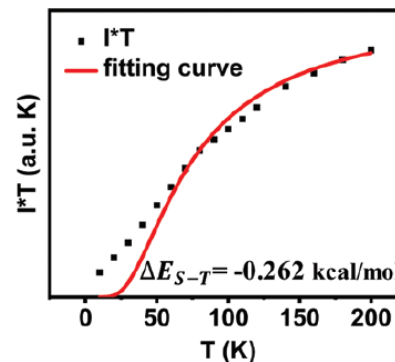
- MS signals of oligomers detected



- Reversible radical-like signal in ^1H NMR

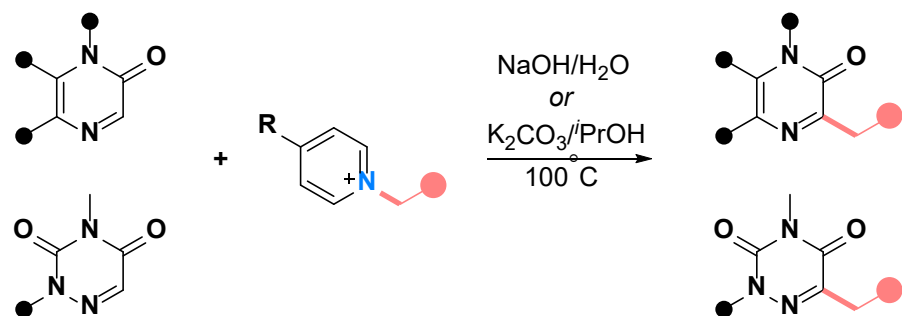


- Thermally activated triplet (0.26 kcal mol $^{-1}$ above GS)

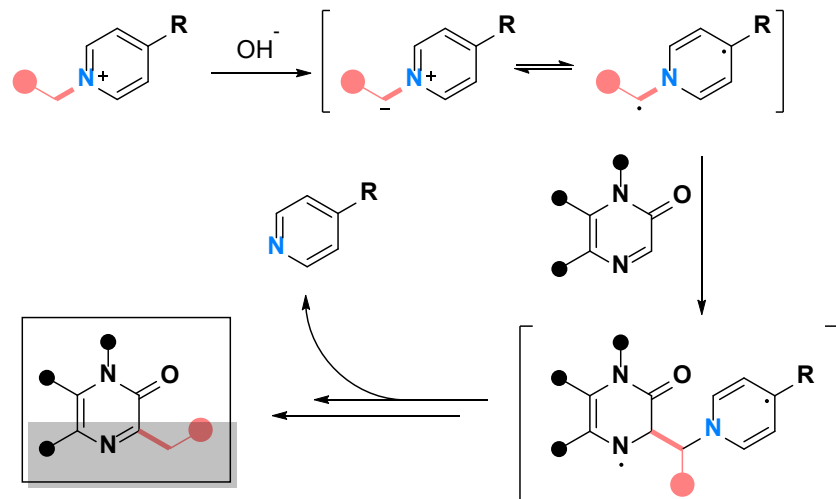


Are Pyridinium Ylides Diradicals?

□ Reaction of pyridinium ylides



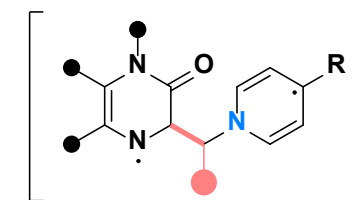
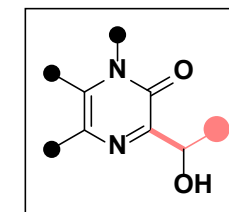
■ Proposed mechanism



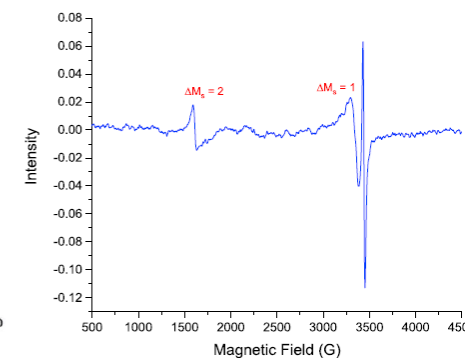
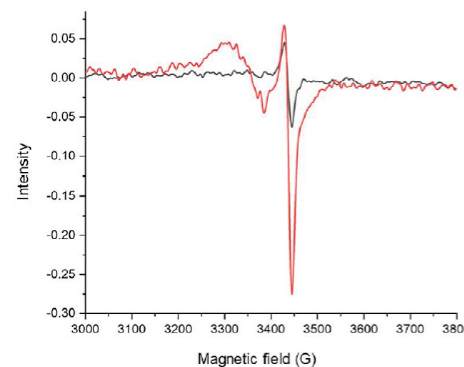
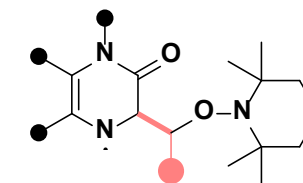
■ Mechanistic studies

1a + pyridinium salt	standard conditions	alkylated products	
	TEMPO	(w)	(w/o)
2a	9 equiv	(24%)	3a (96%)
2b	10 equiv	(8%)	3a (97%)
6n	9 equiv	(0%)	7m (75%)
6l	10 equiv	(16%)	7k (91%)
2a	BHT 10 equiv	(62%)	3a (96%)

TEMPO/BHT-adducts (not detected)



-py ↓ +TEMPO



Summary

- ❑ Katritzky salts are **easily synthesized** from heating mixture of primary/secondary amines and corresponding pyrylium salts.
- ❑ The **SET chemistry** of Katritzky salts is well established, while N-C homolysis at the **excited state** remains elusive.
- ❑ The factors controlling **reduction potential** and **fragmentation rate** of substituted pyridinium salts are somewhat orthogonal, thereby allowing modifications for promising properties.
- ❑ Pyridinium ylides, easily generated in very **mild conditions**, might be a thermally activated triplet diradical. In special cases, photo-release of carbene is possible.

Summary

