Design Concepts of Nitroxyl Radicals

Literature Seminar
2018/3/10
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1. Introduction

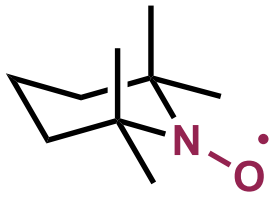
1. Introduction

Nitroxyl radicals (nitroxides, aminoxyl radicals)

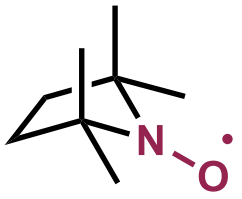
Fremy's salt

The first nitroxyl radical (1845)

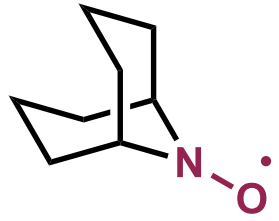
Representatives



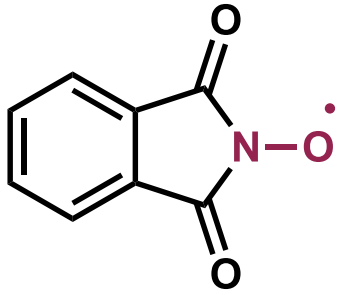
TEMPO



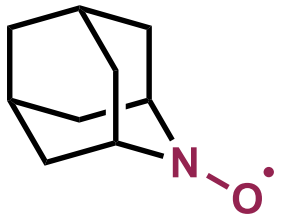
PROXYL



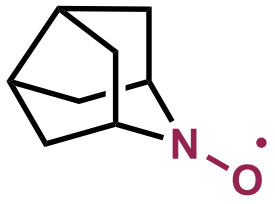
ABNO



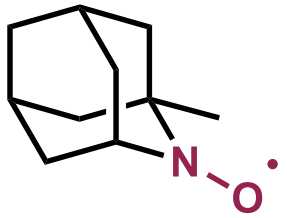
PINO



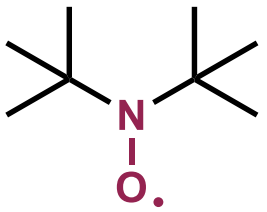
AZADO



Nor-AZADO

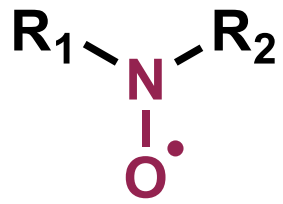


1-Me-AZADO



DTBN

Use of Nitroxyl Radicals



nitroxyl radicals

Chemical use

- Oxidation catalyst
- Nitroxide mediated radical polymerization (NMP)
- Radical coupling
- Mechanism analysis

Biological use

- Spin probe
- Superoxide dismutase mimics
- Antioxidant

Material use

- Dye-sensitized solar cells
- Organic radical battery

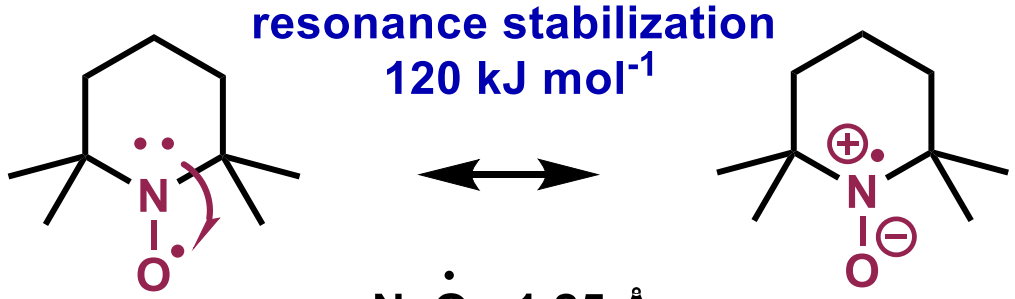
Tuning design for each purpose can improve the efficacy.

Property of Nitroxyl Radicals

- TEMPO is stabilized both thermodynamically and kinetically.

Thermodynamic stabilization

-> Delocalization of unpaired electron



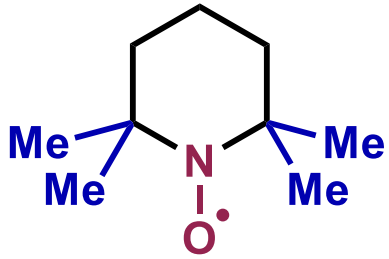
bond length

N–O : 1.25 Å
N–O : 1.20 Å (single bond)
N=O : 1.44 Å (double bond)

- N-O bond contains three electrons.
- Bond order of N-O is 1.5.

Kinetic stabilization

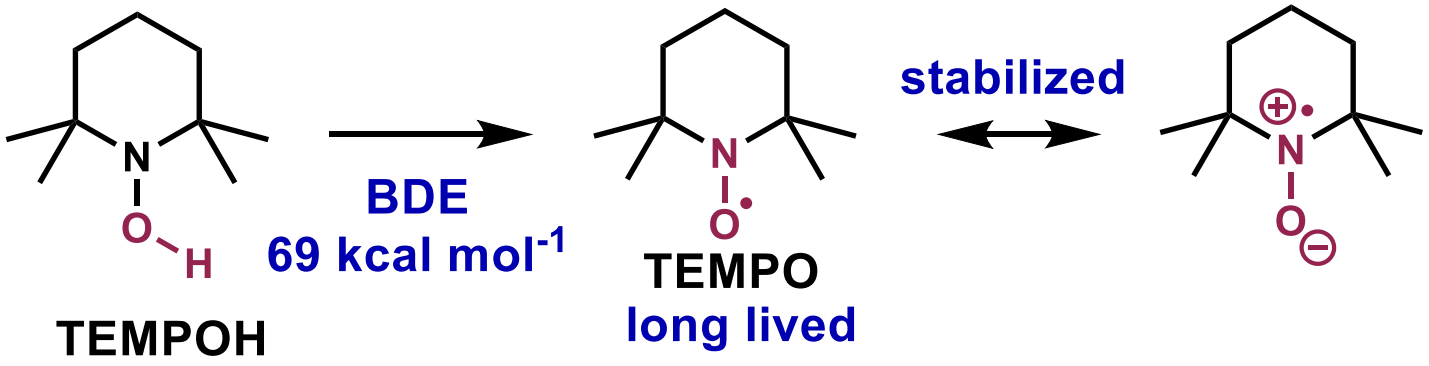
-> 4 α-methyl groups



- Four Me shield the radical.

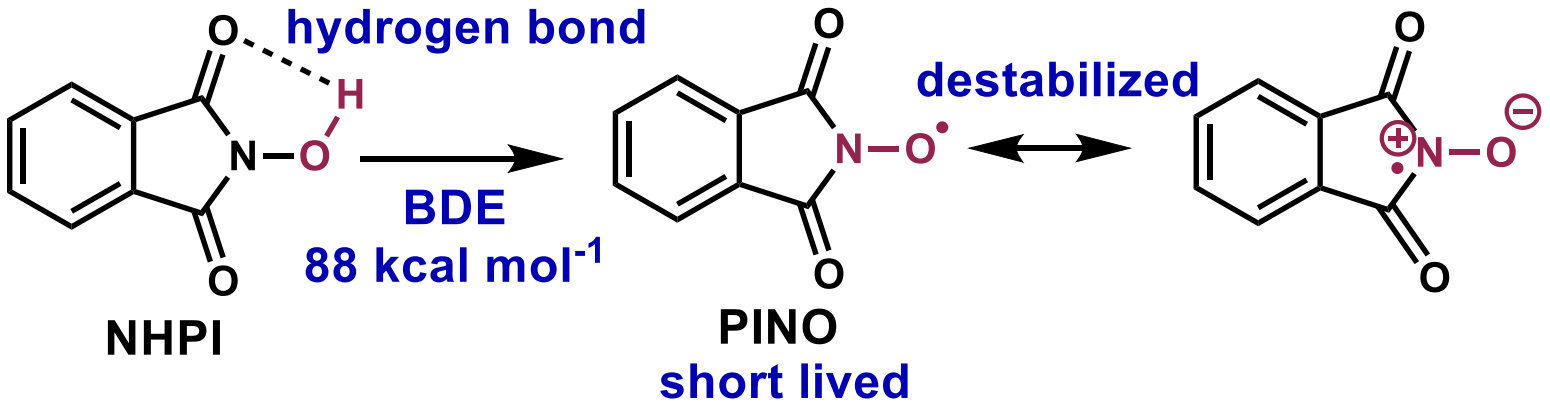
Wertz, S.; Studer, A. *Green Chem.* **2013**, *15* (11), 3116.

Property of Nitroxyl Radicals



TEMPO

- Thermodynamic driving force for direct H-abstraction is low.



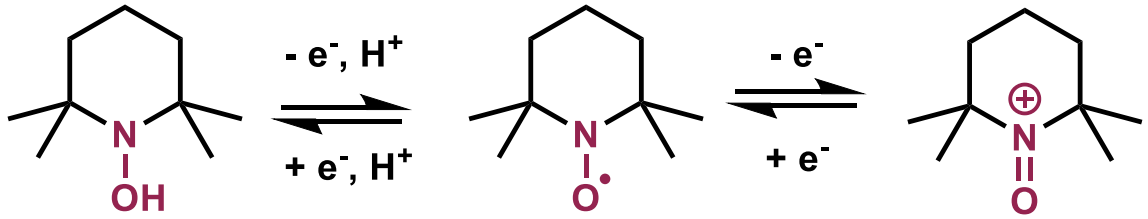
PINO

- Stronger H-abstraction reagent, but unstable. (generated in situ)
- Used in transition-metal mediated C-H functionalization with Co, Mn.

Wertz, S.; Studer, A. *Green Chem.* **2013**, *15* (11), 3116.

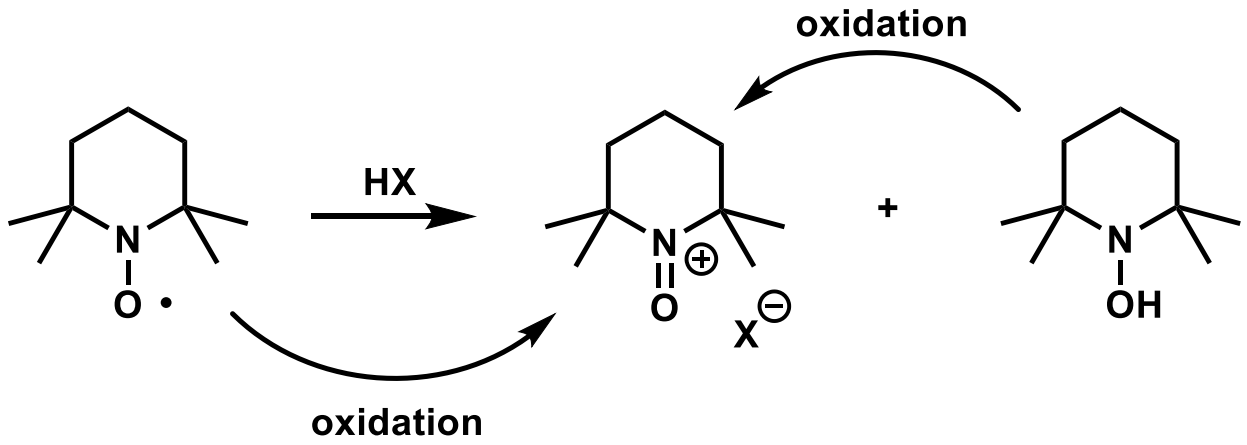
Oxidation State of Nitroxyl Radicals

Oxidation states of nitroxyl radical



- Oxoammonium ion acts as an active species in oxidation.
- Oxoammonium salt can be isolated with proper counteranion. (e.g. BF_4^-)

Generation of oxoammonium salt

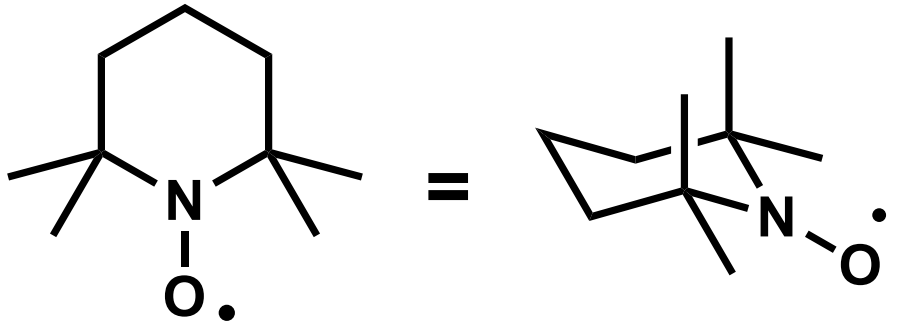


- Acid cause disproportionation.
- Nitroxyl radical and hydroxylamine are oxidized into oxoammonium salt.

2. TEMPOs and AZADOs

2-1. TEMPOs

TEMPO (2,2,6,6-tetramethylpiperidyl-1-oxyl)

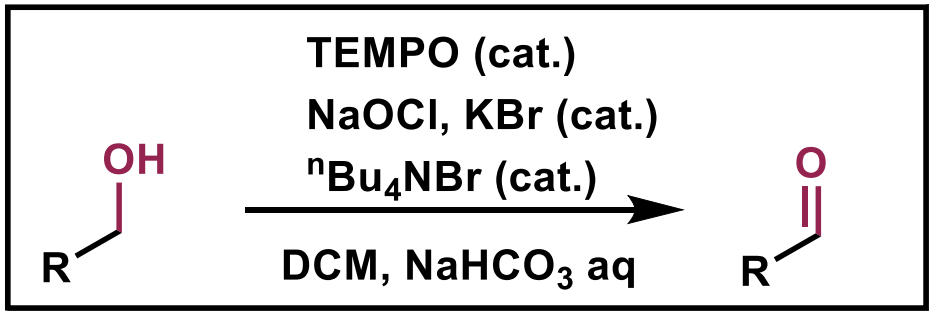


TEMPO

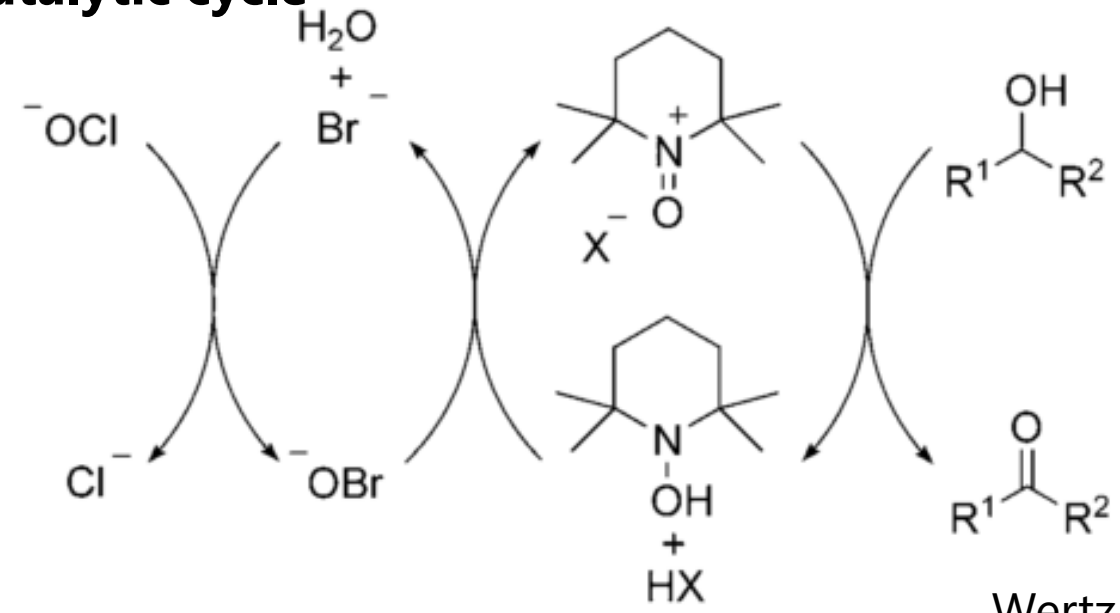
- Alcohol oxidation catalyst.
- 1° alcohol > 2° alcohol.
- Terminal oxidant: NaOCl, $PhI(OAc)_2$, oxone, I_2, O_2, etc..

Alcohol Oxidation by TEMPO

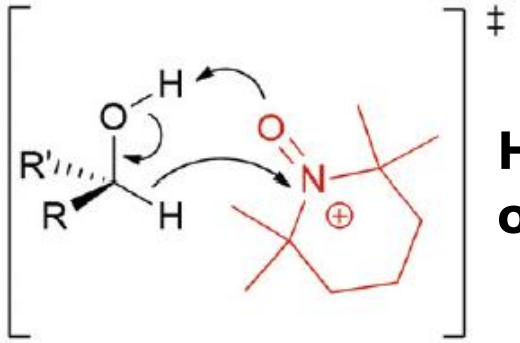
Oxoammonium as active species



Catalytic cycle

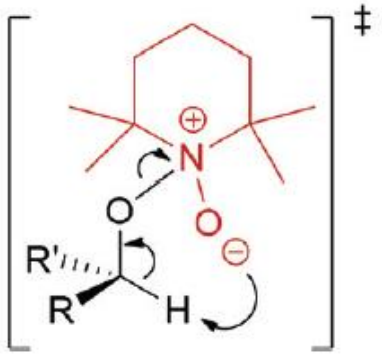


pH < 4



Hydride-transfer to oxoammonium cation

pH > 5



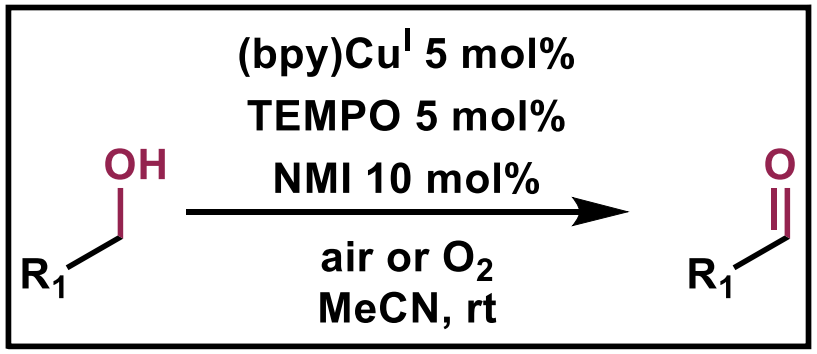
Cope-type elimination from alcohol adduct

Wertz, S.; Studer, A. *Green Chem.* **2013**, *15* (11), 3116.

Tebben, L.; Studer, A. *Angew. Chem. Int. Ed.* **2011**, *50* (22), 5034.

Alcohol Oxidation by TEMPO

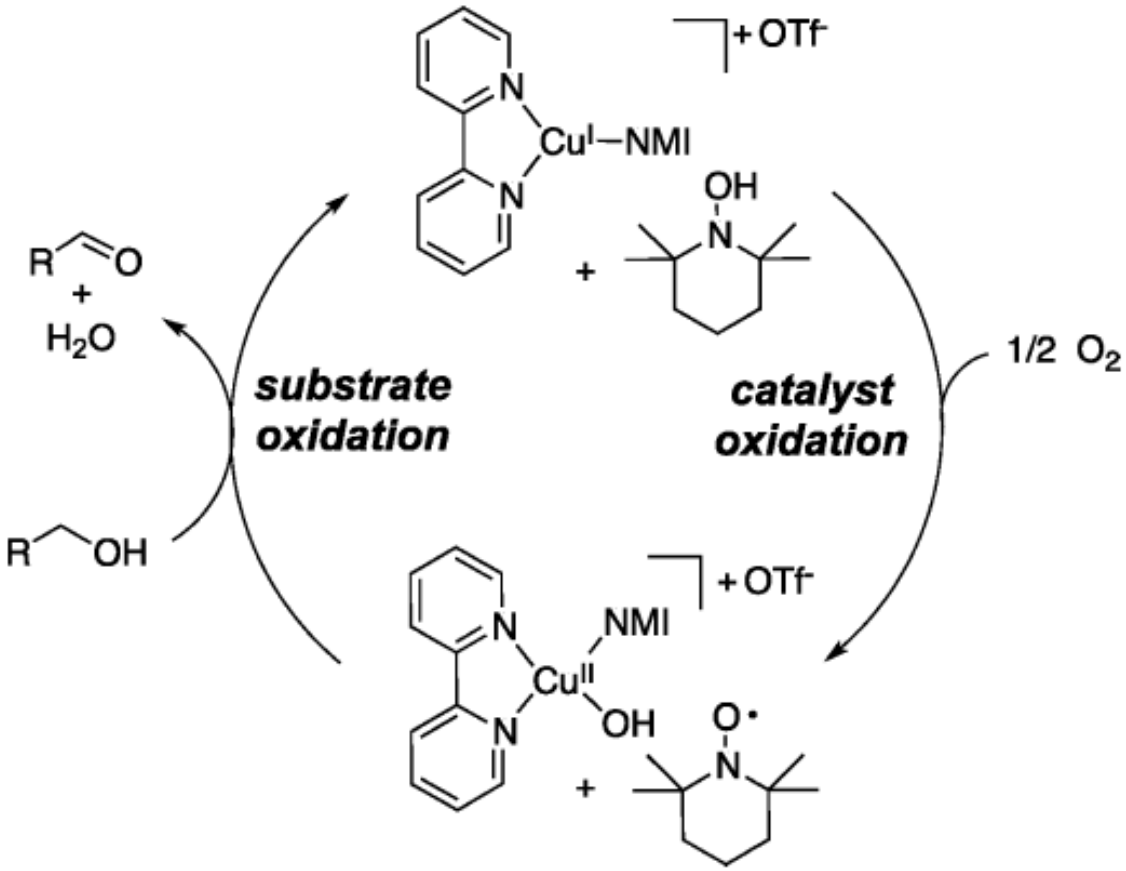
Aerobic oxidation with Cu



NMI: *N*-methylimidazole

- Cu(II) isn't sufficiently strong oxidant for the oxidation of TEMPO to TEMPO$^+$.
- Oxoammonium cation isn't generated.

Simplified catalytic cycle

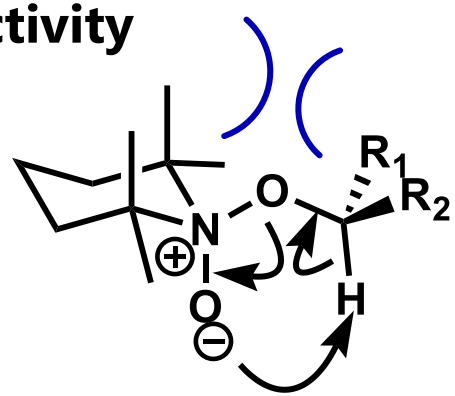


Stahl, S. S. *et al. J. Am. Chem. Soc.* **2013**, *135* (6), 2357.

2-2. AZADOs

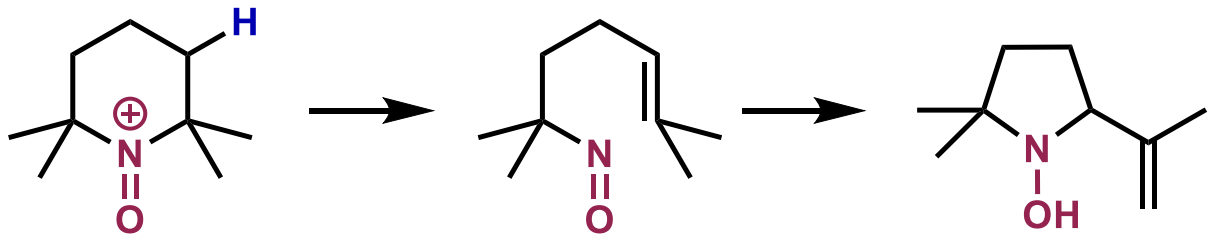
Problems with TEMPO

reactivity



Alcohol oxidation intermediate

stability

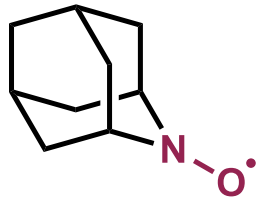


TEMPO$^+$

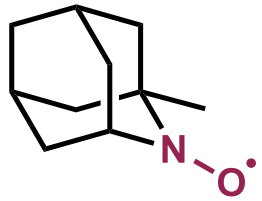
steric repulsion between Me and R1, R2
-> 1° alcohol > 2° alcohol

Development of AZADOs

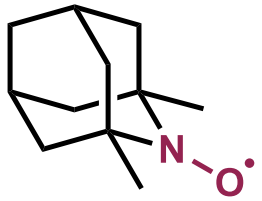
AZADO: 2-azaadamantane *N*-oxyl



AZADO



1-Me-AZADO

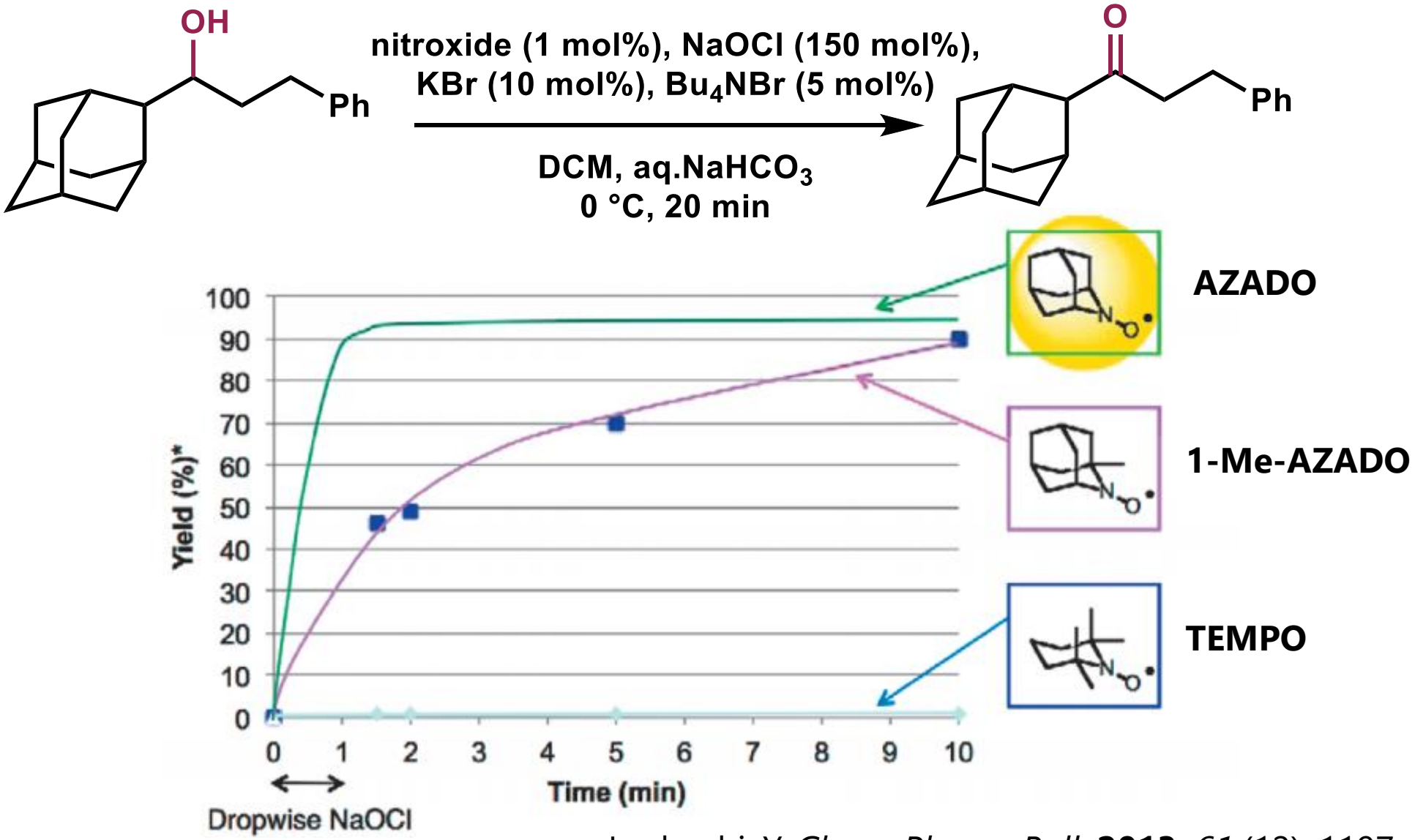


1,3-diMe-AZADO

Steric hindrance

Iwabuchi, Y. *Chem. Pharm. Bull.* **2013**, *61* (12), 1197.

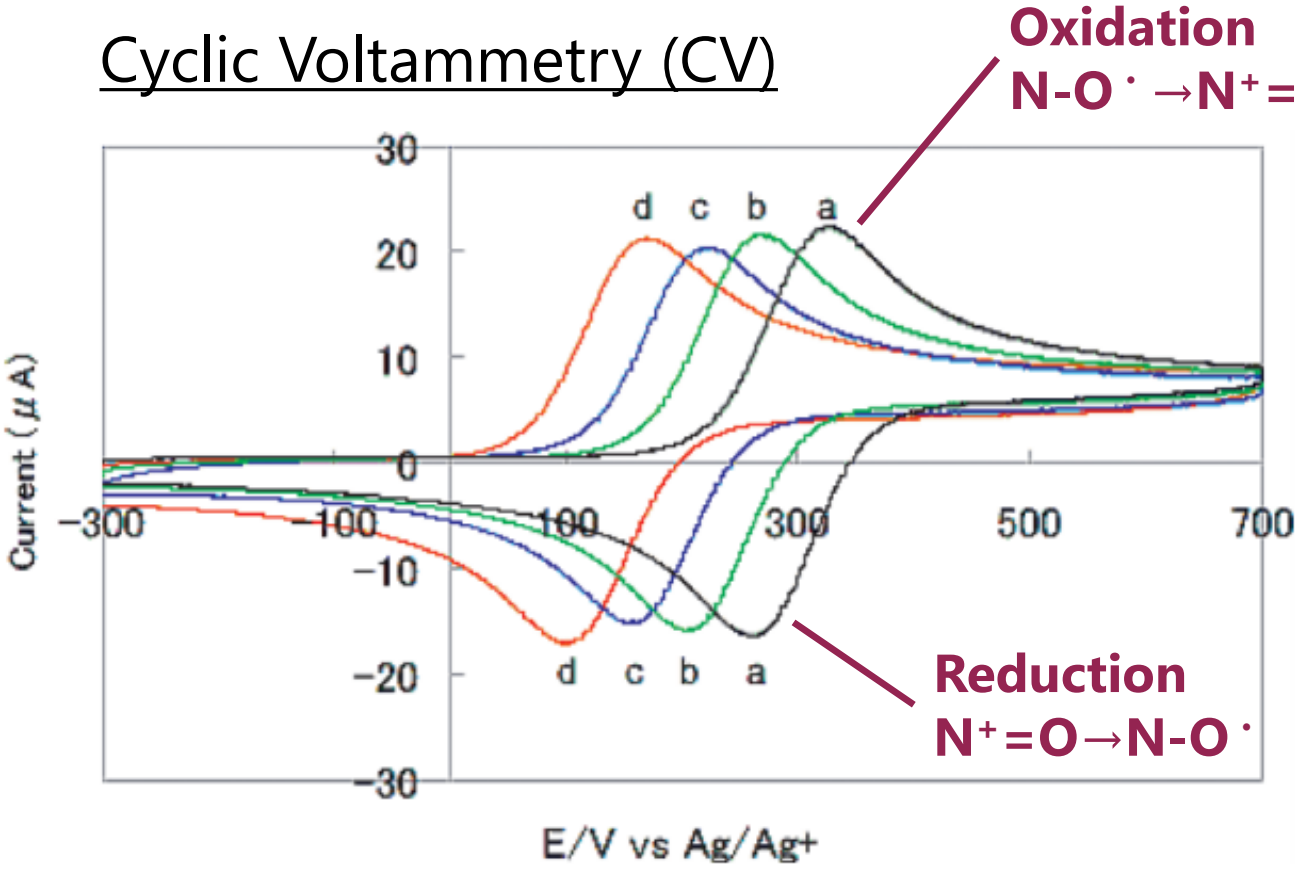
Catalytic Activity



Iwabuchi, Y. *Chem. Pharm. Bull.* **2013**, *61* (12), 1197.

Redox Property

Cyclic Voltammetry (CV)



- Stable for >100 measurement cycles.

Redox Potential (E^0 vs Ag/Ag^+)

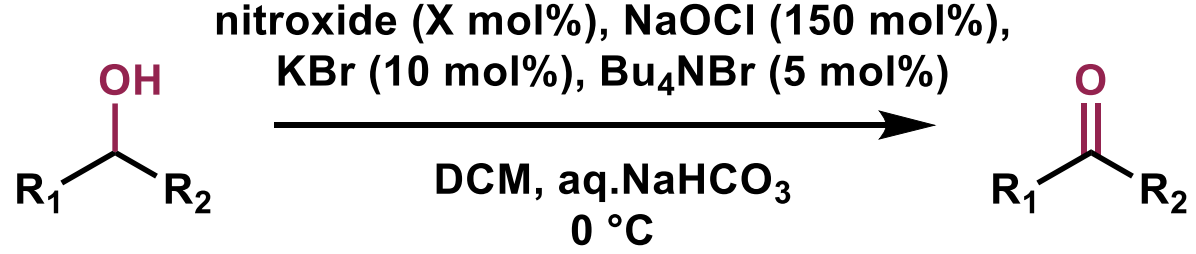
nitroxide	E^0	
a: TEMPO	294	**Readily Reduced**
b: AZADO	236	
c: 1-Me-AZADO	186	
d: 1,3-diMe-AZADO	136	**Readily Oxidized**

Catalytic activity: **a: TEMPO ~ d: 1,3-diMe-AZADO << c: 1-Me-AZADO < b: AZADO**

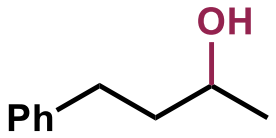
➡ High catalytic activity is mainly due to kinetic factors.

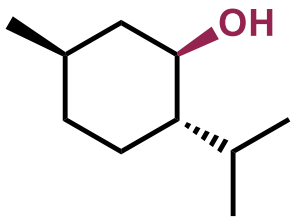
Iwabuchi, Y. *Chem. Pharm. Bull.* **2013**, *61* (12), 1197.

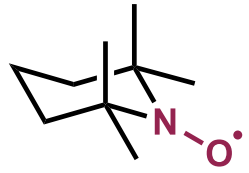
Development of ABNO and Nor-AZADO



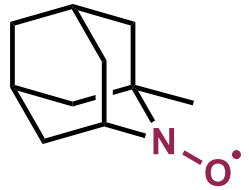
nitroxide X mol%	TEMPO	1-Me-AZADO	AZADO	ABNO	Nor-AZADO
1	97%	99%	99%	100%	99%
0.01	28%	97%	99%	94%	99%
0.005	n.d.	76%	96%	91%	96%
0.003	n.d.	67%	74%	24%	92%
1	5%	95%	99%	94%	99%
0.01	n.d.	61%	98%	95%	98%
0.005	n.d.	41%	96%	92%	96%
0.003	n.d.	25%	87%	8%	92%



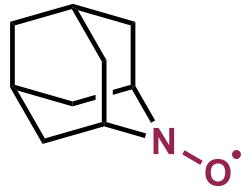




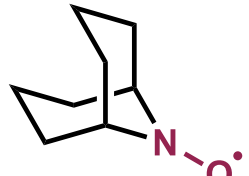
TEMPO



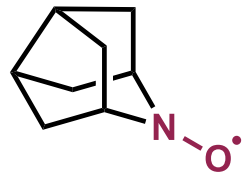
1-Me-AZADO



AZADO



ABNO



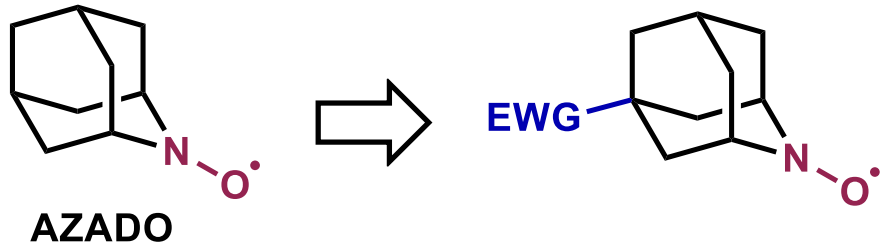
Nor-AZADO

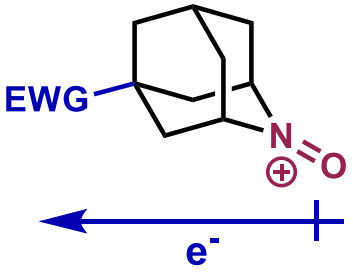
- Nor-AZADO showed higher catalytic activity than AZADO.

Iwabuchi, Y. *Chem. Pharm. Bull.* **2013**, *61* (12), 1197.

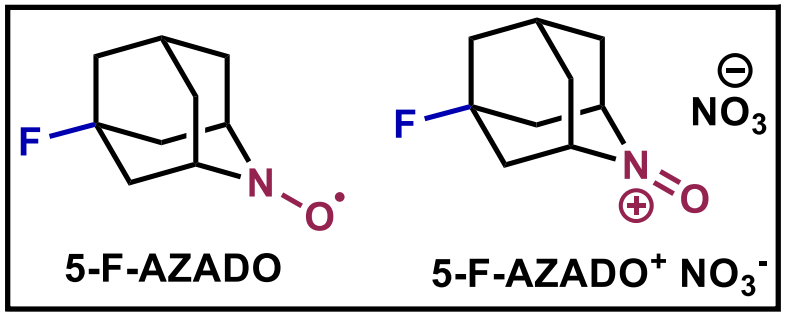
5-F-AZADO

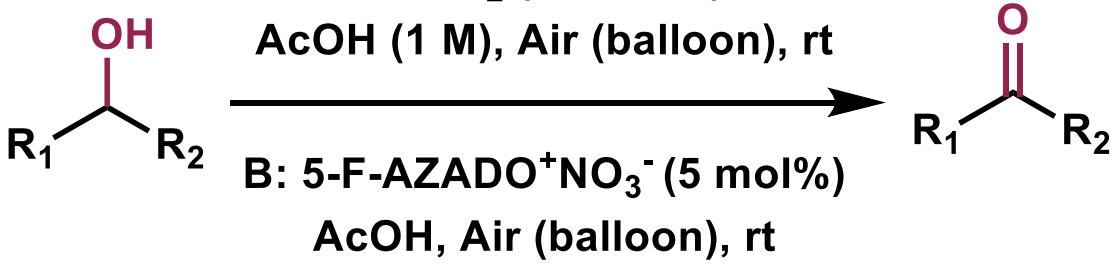
Introduction of electron-withdrawing group





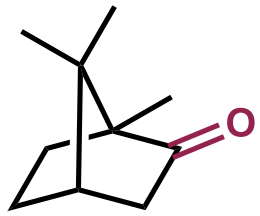
e⁻ poor oxoammonium salt



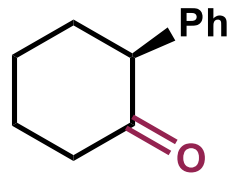


- NOx works as reoxidant.

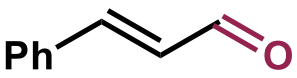
wider scope of substrate



A: 85%, 9 h
B: 84%, 2 h



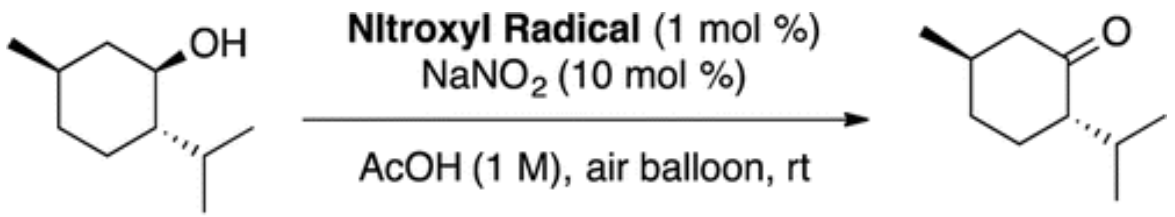
A: 98%, 3.5 h
B: 98%, 2 h

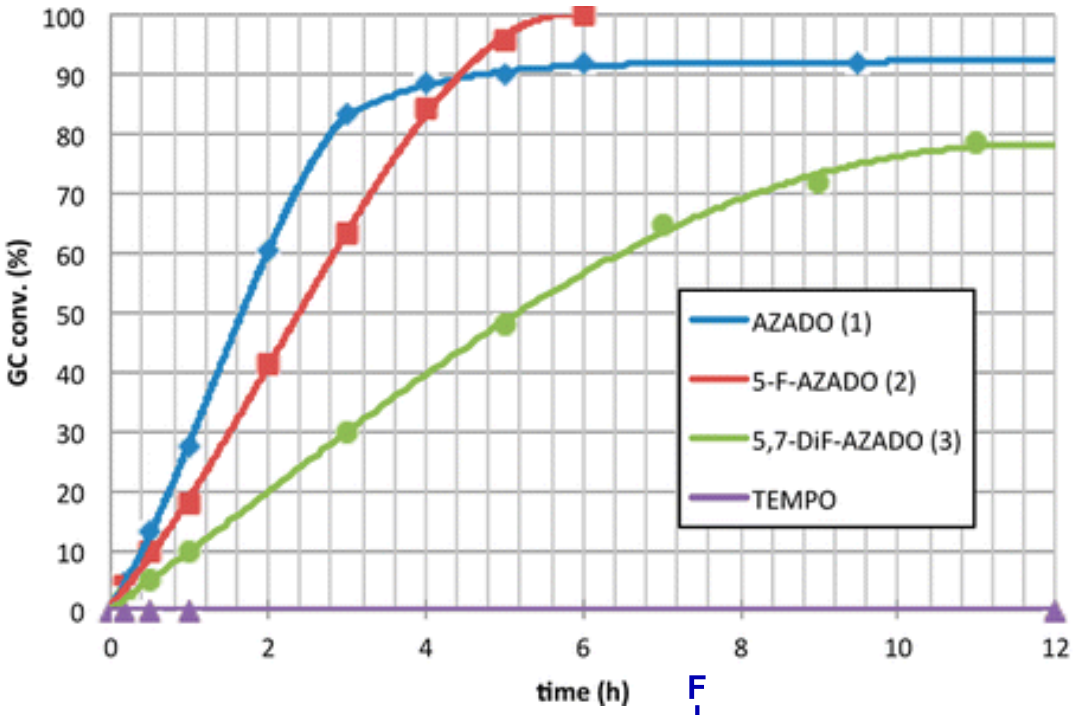


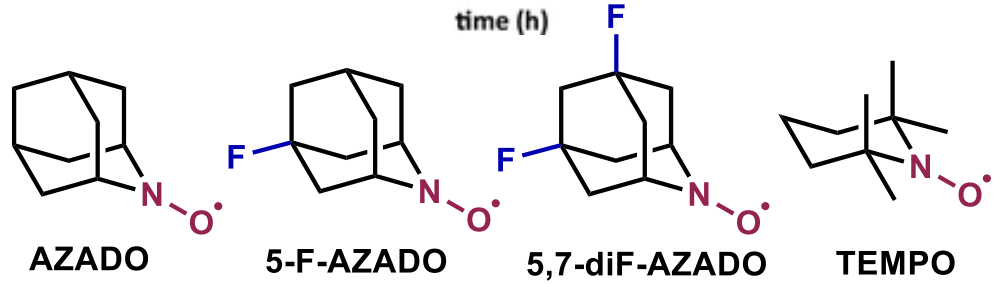
A: 93%, 3 h
B: 95%, 2 h

Iwabuchi, Y. *et al. J. Am. Chem. Soc.* **2011**, *133* (17), 6497.

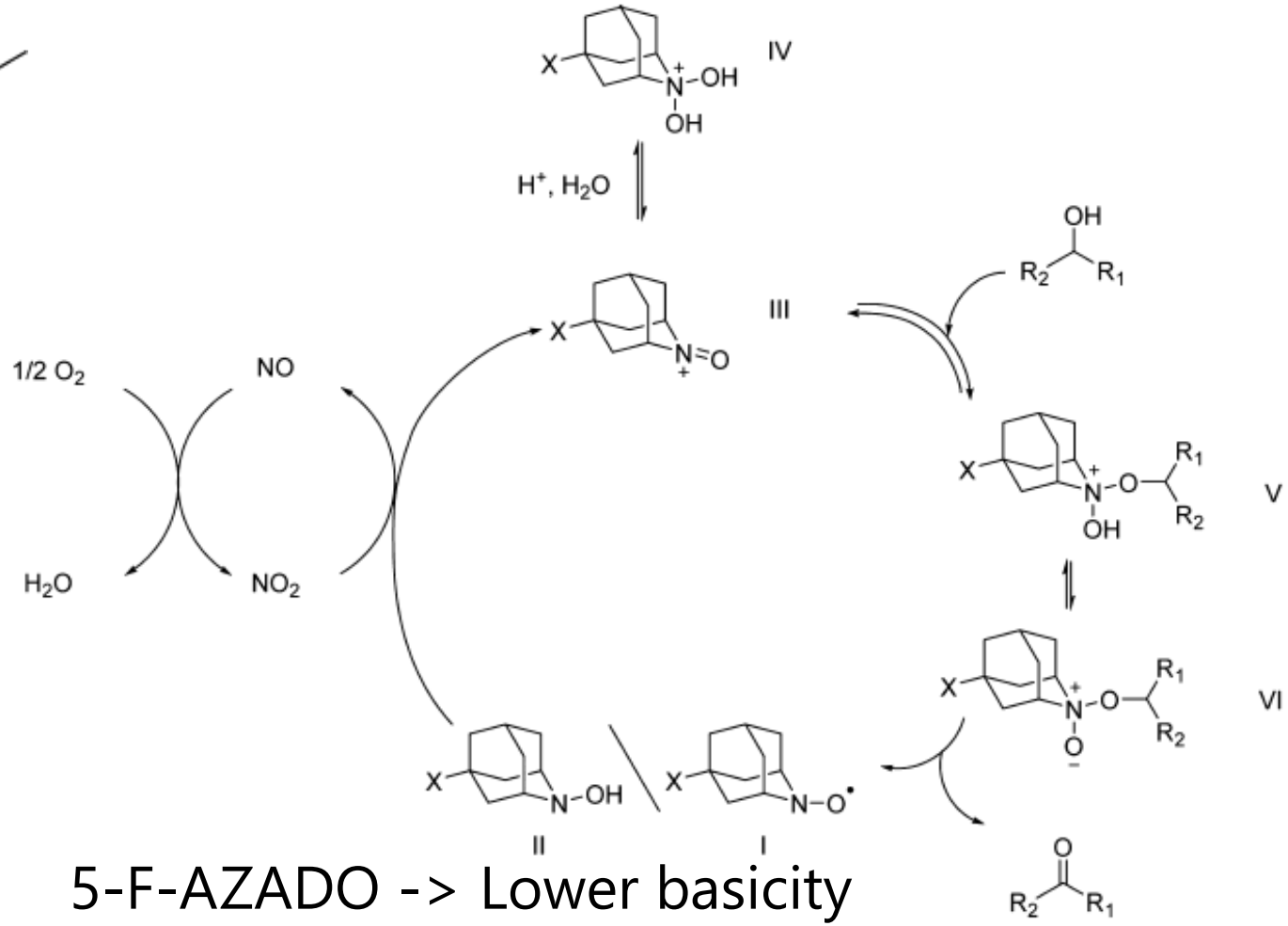
Mechanism Analysis with 5-F-AZADO







Proposed mechanism

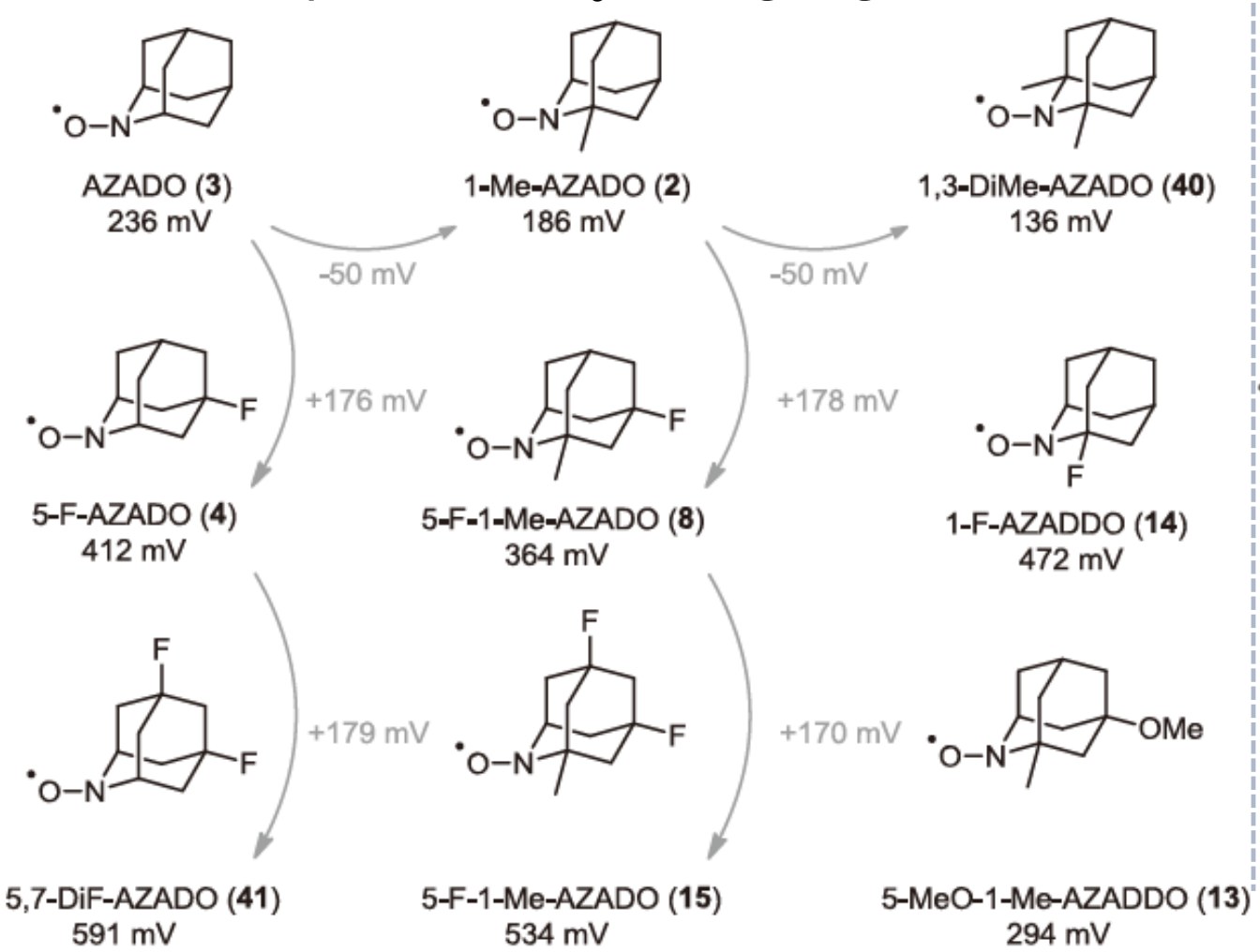


5-F-AZADO -> Lower basicity prevents the formation of IV and V.

Iwabuchi, Y. *et al.* *J. Org. Chem.* **2014**, *79*, 10256.

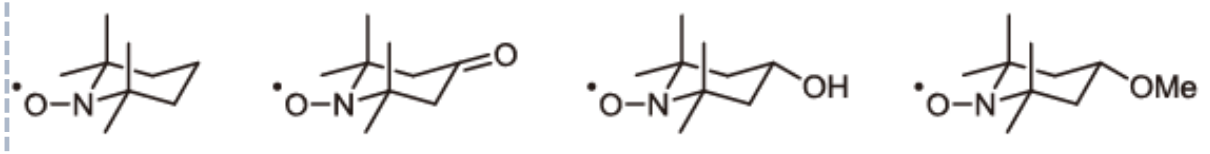
General Trend of Redox Property

Redox potential E_0 (vs Ag/Ag^+)



ABNOs

TEMPOs



EWG

-> destabilization of $N^+=O$

-> higher redox potential

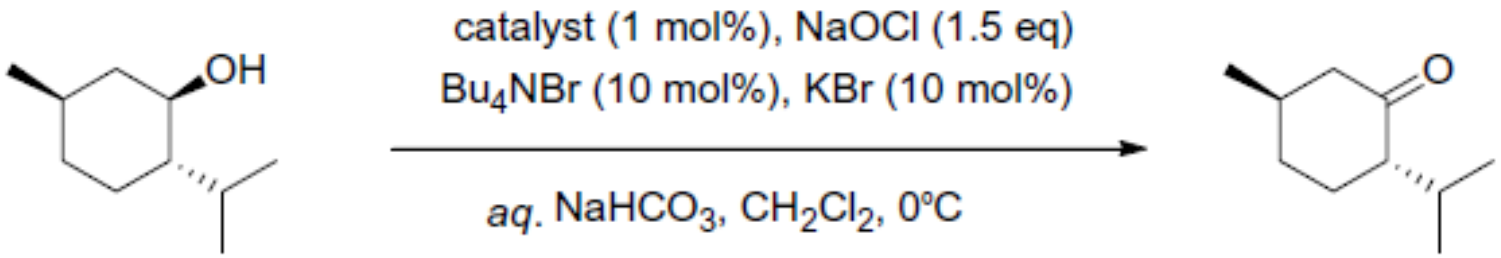
EDG

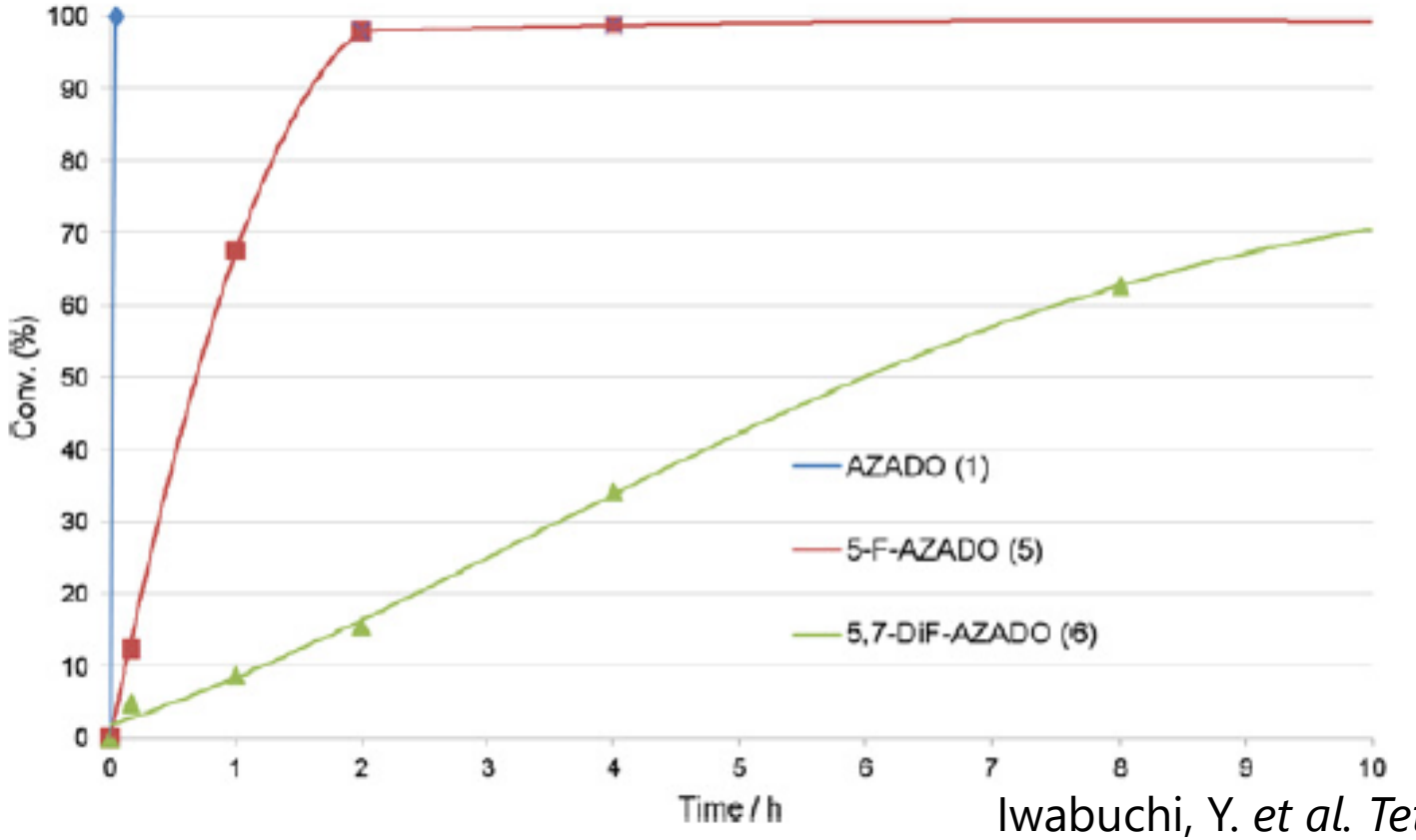
-> stabilization of $N^+=O$

-> lower redox potential

Iwabuchi, Y. *et al. Tetrahedron Lett.* **2012**, *53* (16), 2070.

Catalytic Activity vs Redox Potential





Redox potential
AZADO 236 mV
5-F-AZADO 412mV
5,7-diF-AZADO 591 mV

Readily Oxidized

- The lower the redox potential, the higher the catalytic activity.

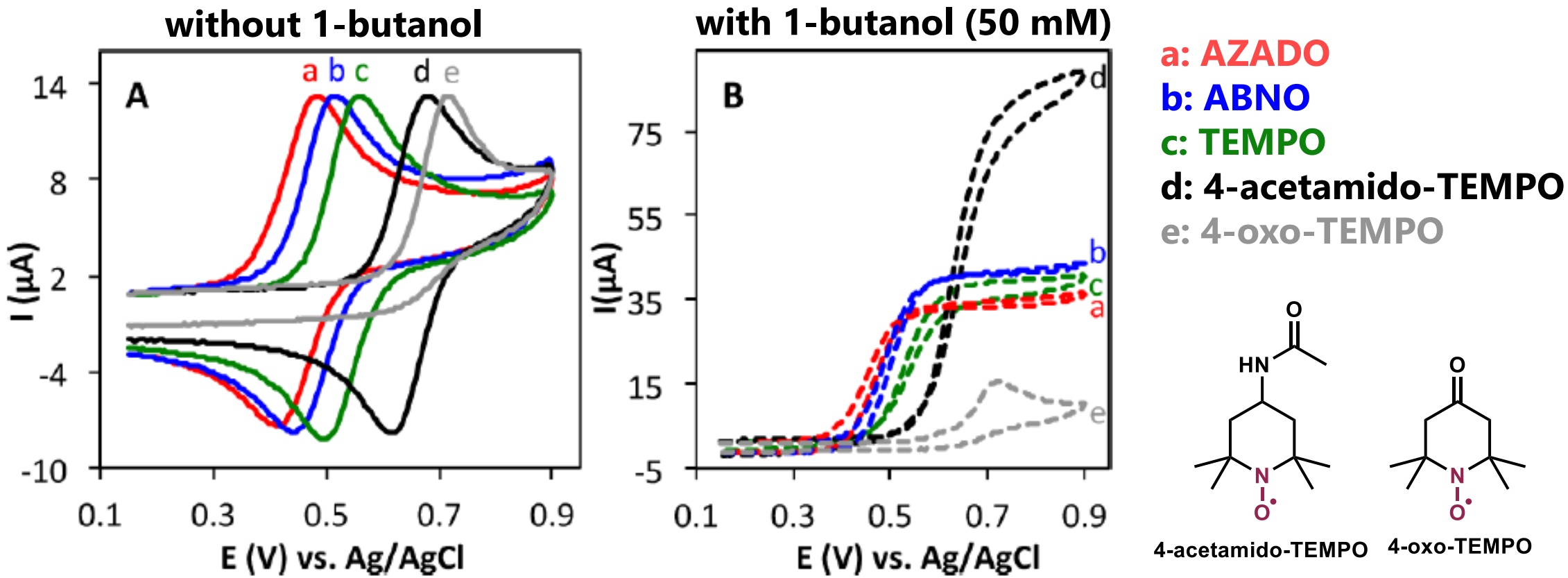
(Probably because reoxidation into oxoammonium species is favorable.)

- Redox potential is an important factor.

Iwabuchi, Y. *et al. Tetrahedron Lett.* **2012**, *53* (16), 2070.

2-3. Steric Effect vs Driving Force

Cyclic voltammogram

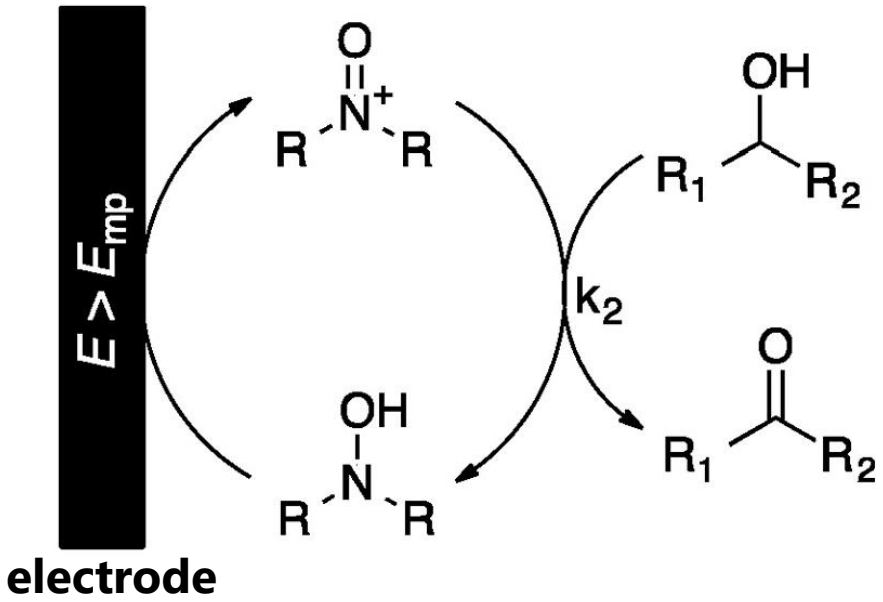


Increment of oxidation current and disappearance of reduction current
-> electrocatalysis

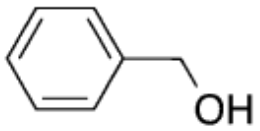
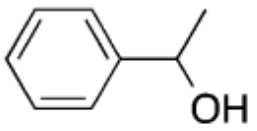
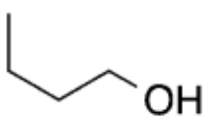
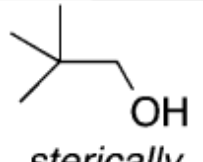
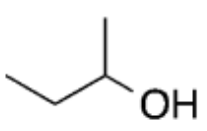
Stahl, S. S. *et al.* *J. Am. Chem. Soc.* **2015**, *137* (46), 14751.

Oxidation Under Electrochemical Conditions

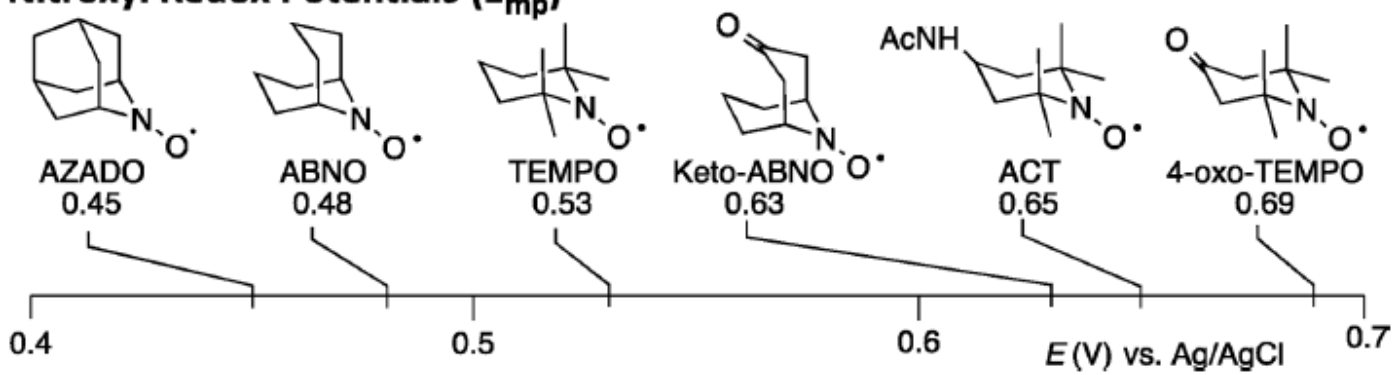
Electrochemical oxidation



TOFs of alcohol oxidation

	 1° benzylic	 2° benzylic	 1° aliphatic	 sterically hindered 1° aliphatic	 2° aliphatic
ABNO	1088	238	588	337	87
AZADO	1128	358	488	298	78
TEMPO	853	118	568	198	18
ACT	1228	378	708	388	73

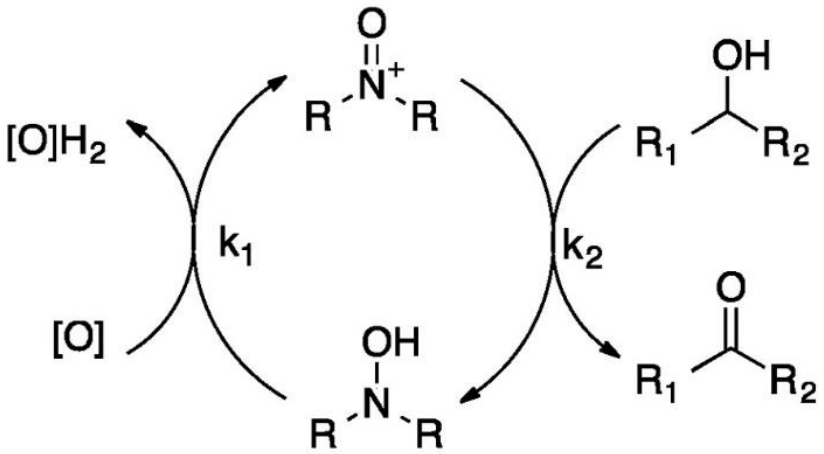
Nitroxyl Redox Potentials (E_{mp})



Stahl, S. S. *et al. J. Am. Chem. Soc.* **2015**, *137* (46), 14751.

Oxidation Under Chemical Conditions

Chemical oxidation

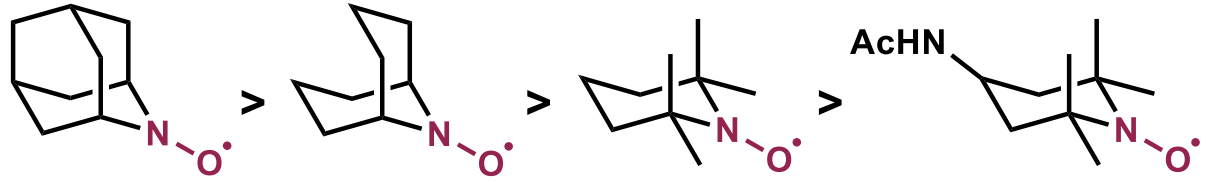


[O]
NaOCl
Br_2
$PhI(OAc)_2$
cat. NO_x, O_2

Stahl, S. S. *et al.* *J. Am. Chem. Soc.* **2015**, *137* (46), 14751.

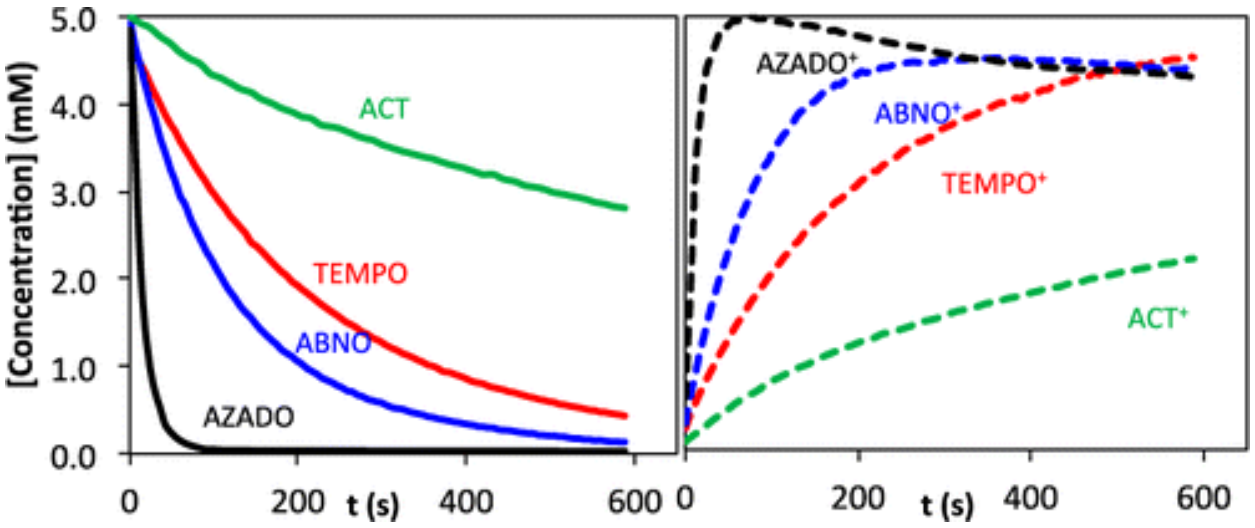
1-Butanol oxidation with NaClO

relative rate



	AZADO	ABNO	TEMPO	ACT (4-acetamido-TEMPO)
k_{obs} (s^{-1})	0.0232	0.0112	0.0051	0.003

Concentration in the presence of NaClO

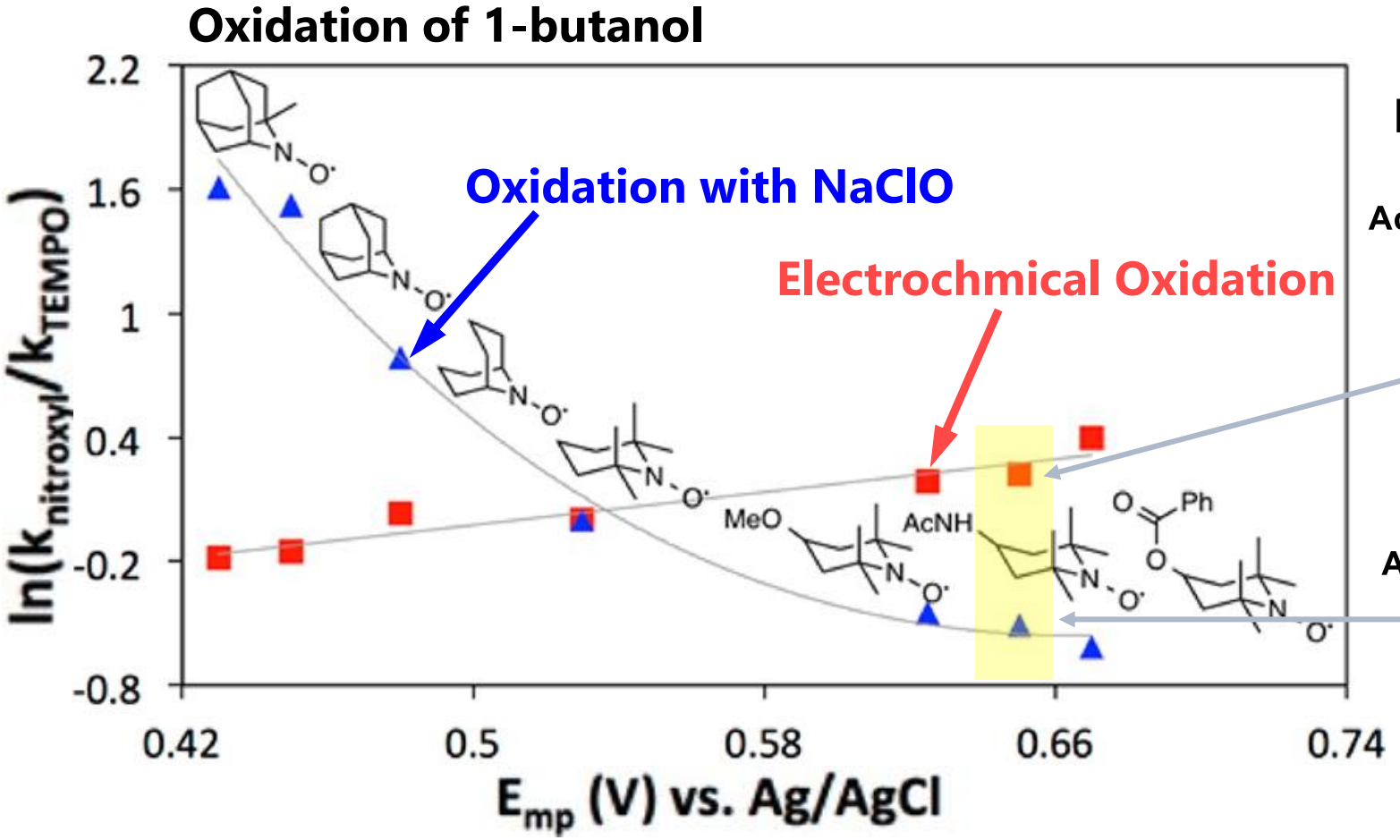


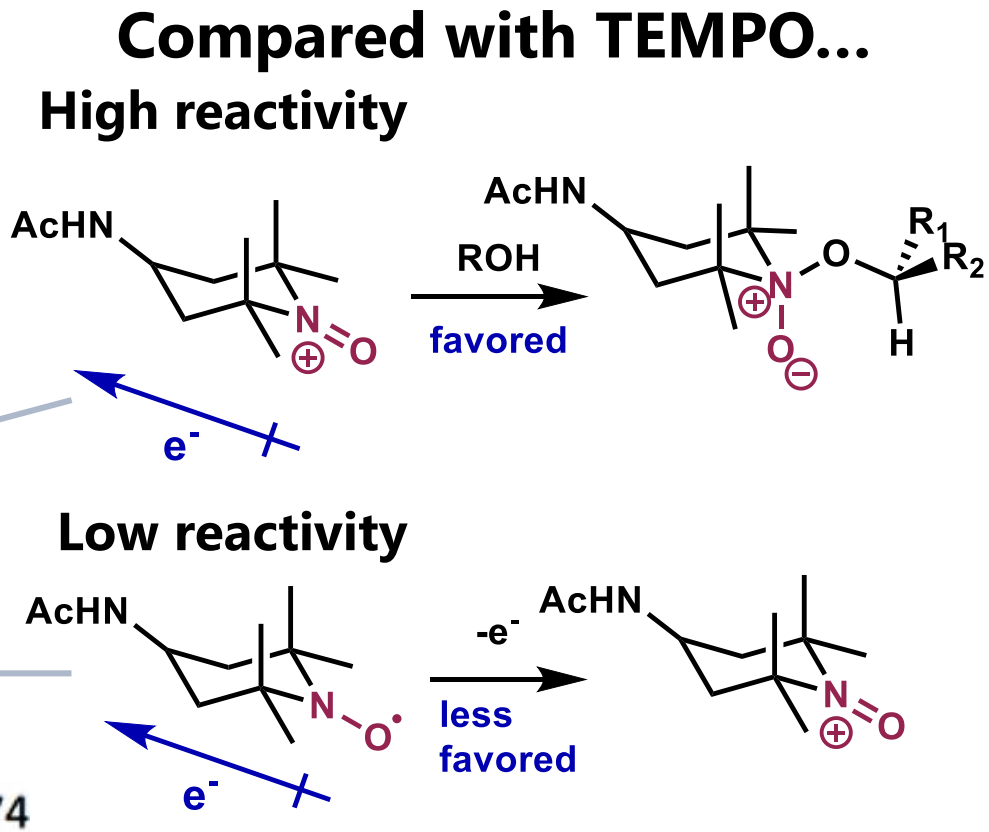
Left : nitroxyl radical
Right : oxoammonium

Poor catalytic activity of 4-acetamido-TEMPO
Formation of N-O˙ ->N^+=O (reoxidation) is slow.

Intrinsic Catalytic Activity of 4-Acetamido-TEMPO

Chemical conditions vs electrochemical conditions

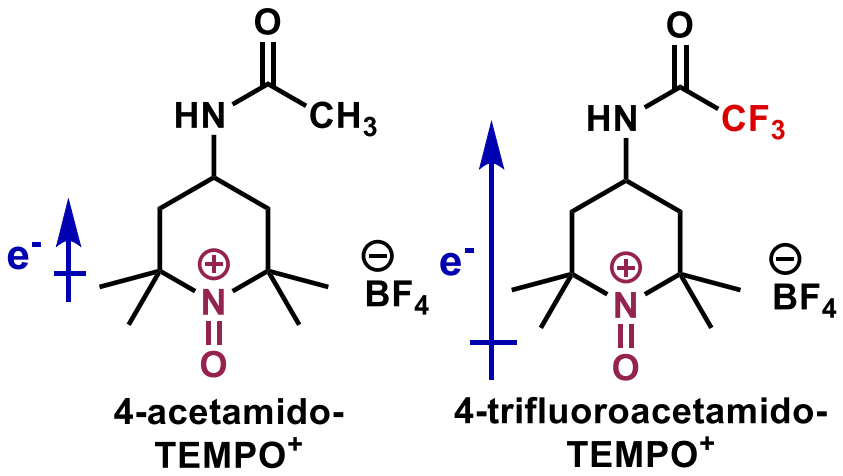


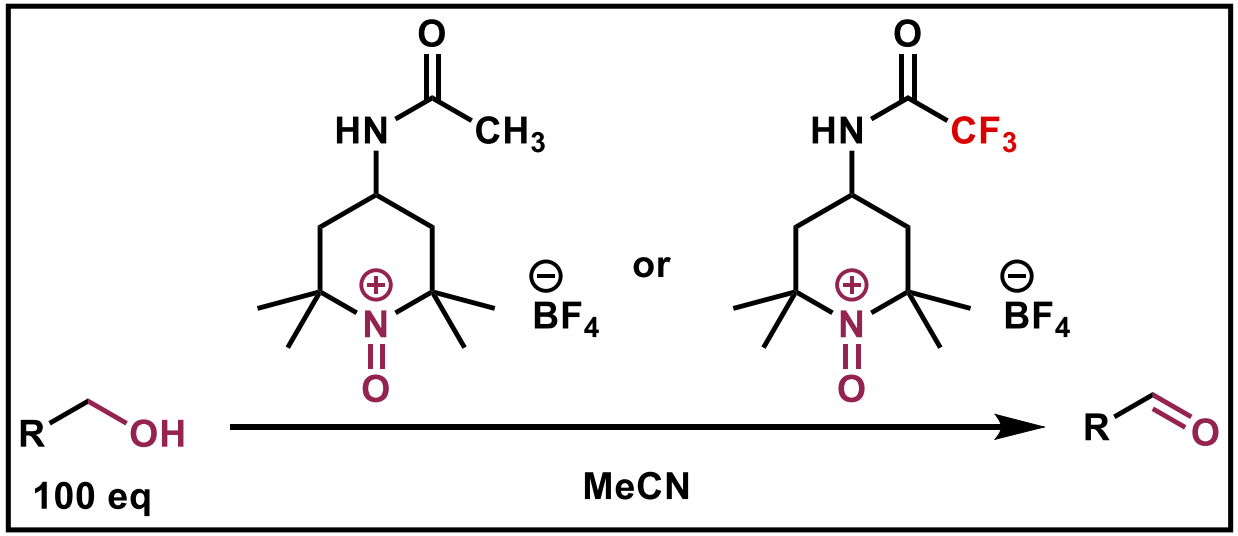


- Intrinsic reactivity can overcome the steric effect.

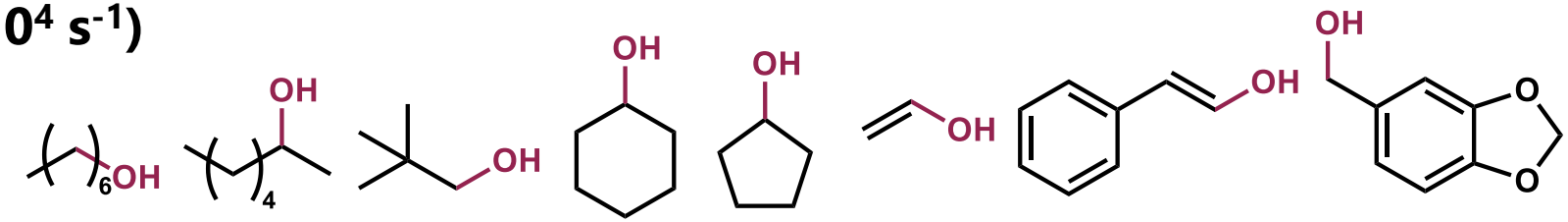
Stahl, S. S. *et al.* *J. Am. Chem. Soc.* **2015**, *137* (46), 14751.

Use of Stoichiometric Amount of Oxoammonium





Rate of oxidation (k * 10^4 s^{-1})



4-acetamido-TEMPO+	1.73	9.14	0.385	18.9	19.1	28.2	145	365
4-trifluoroacetamido-TEMPO+	3.71	16.7	0.965	33.3	33.3	58.0	2666	980

- 1.7-3.2 times faster than 4-acetamido-TEMPO.

Bailey, W. F. *et al. J. Org. Chem.* **2017**, *82* (21), 11440.

Short Summary

- AZADOs were designed to achieve higher reactivity.
- Steric property and electric property are important for them.

3. Design Concepts of Nitroxyl Radicals

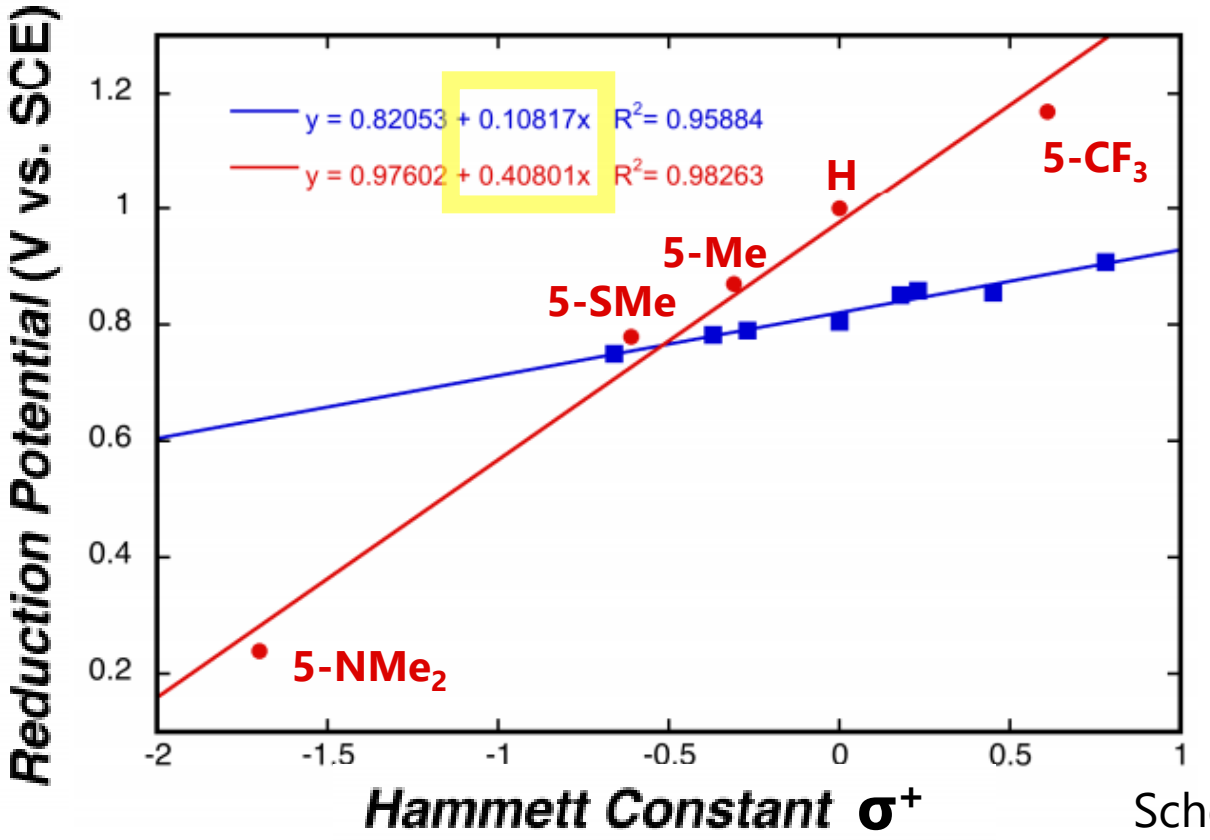
3-1. Effect of Direct Conjugation on Redox Property

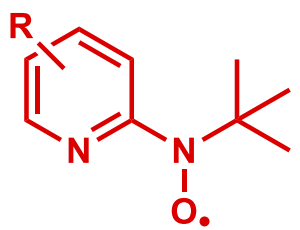
Piperidine, isoindoline, azaphenalene derivatives

- SOMO is localized on N-O bond.
- Substituent effects: σ-inductive effects.

2-Pyridyl nitroxyl radicals

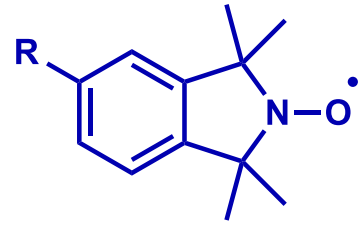
Direct conjugation of N-O with Py.





R = 4-NMe_2, 5-NMe_2, 3-OMe, 5-SMe, 5-Me, H, 5-CF_3

2-Pyridylhydroxylamine



R = H, CO_2H, OH, OMe, Br, I, NO_2, NH_2

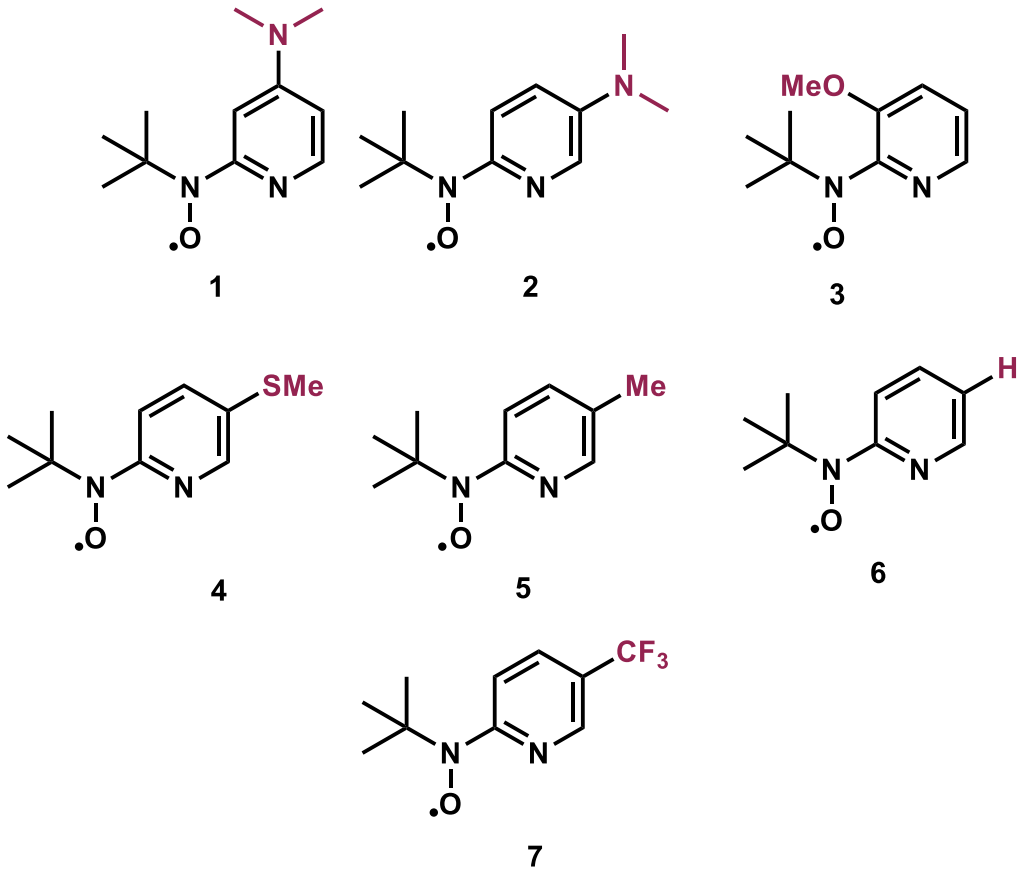
isoindoline

- Over 4 times sensitive to substituent effect than isoindoline.

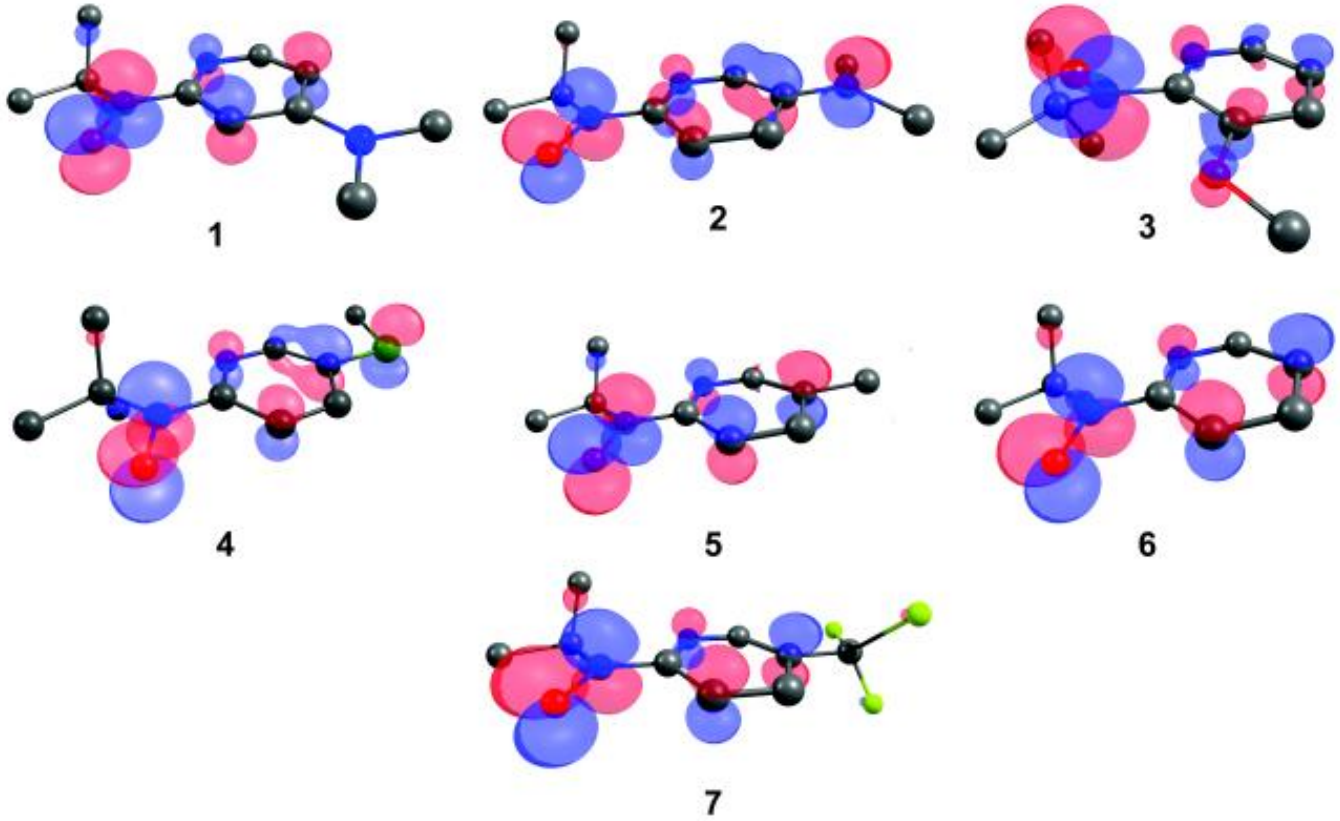
->easy to tune the reactivity and stability.

Schelter, E. J. *et al. J. Org. Chem.* **2013**, *78* (12), 6344.

SOMOs of 2-Pyridyl nitroxides



SOMO (calculated)

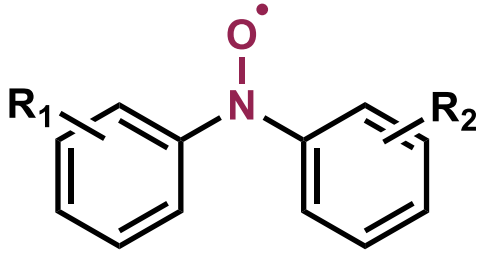


SOMO delocalizes at 1-, 3-, 5- position.
-> Substituent at 1-, 3- and 5- position can affect the energy of SOMO and enables redox property tuning.

Schelter, E. J. *et al. J. Org. Chem.* **2013**, *78* (12), 6344.

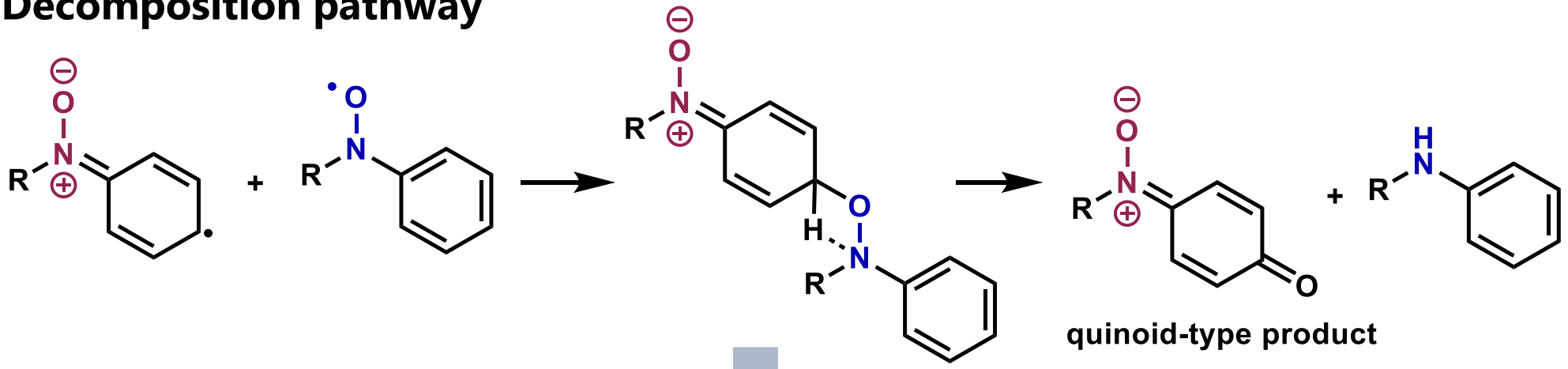
3-2. Twisted Diaryl-Nitroxyl Radical

Diaryl-Nitroxyl radical



- Normally unstable due to spin delocalization on Ar.

Decomposition pathway

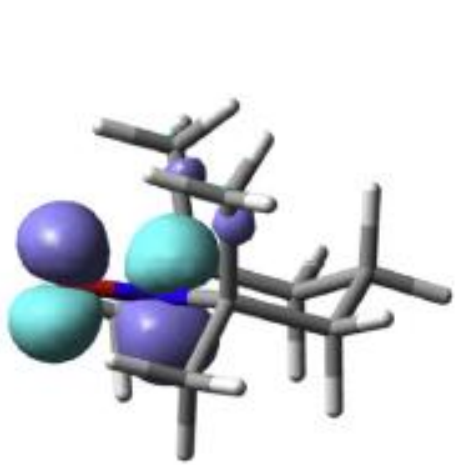


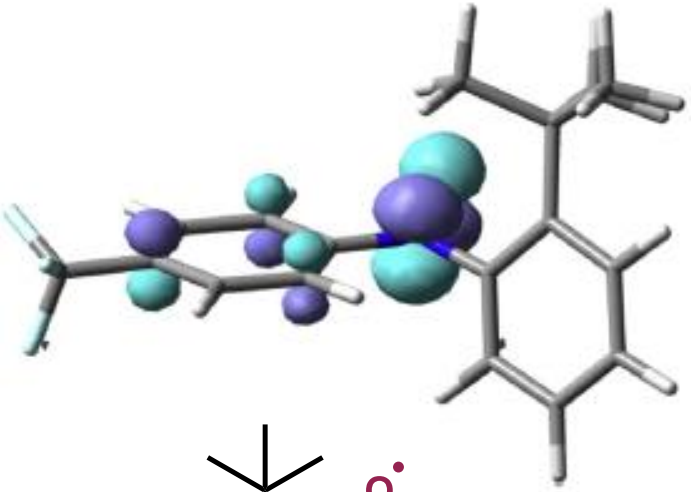
- Substituent at *p*-position can prevent this pathway.

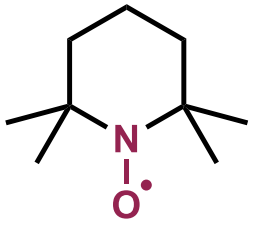
Magdesieva, T. V. *et al. Eur. J. Org. Chem.* **2017**, *2017* (32), 4726.

Magdesieva, T. V. *et al. Electrochim. Acta* **2018**, *260*, 459.

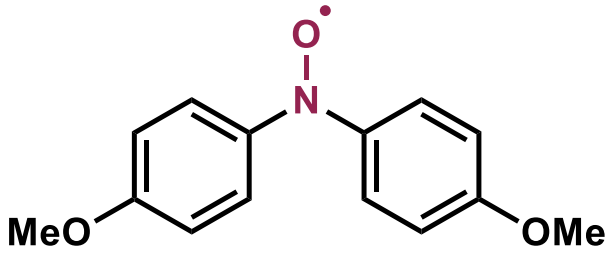
Calculated Structure and SOMO

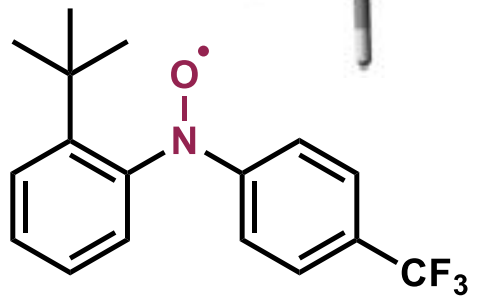






TEMPO





twisted diaryl-nitroxyl radical

- One ring with *o*-substituent is out of conjugation due to its bulkiness.

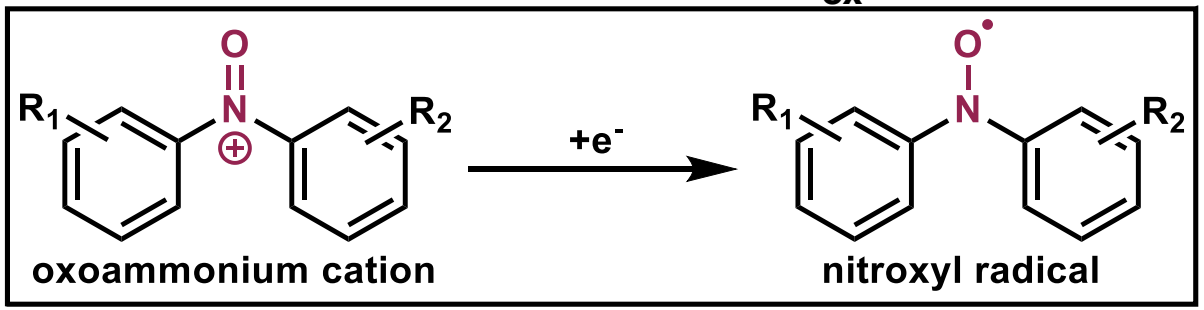
-> Spin delocalization over the ring is prevented.

Magdesieva, T. V. *et al. Electrochim. Acta* **2018**, *260*, 459.

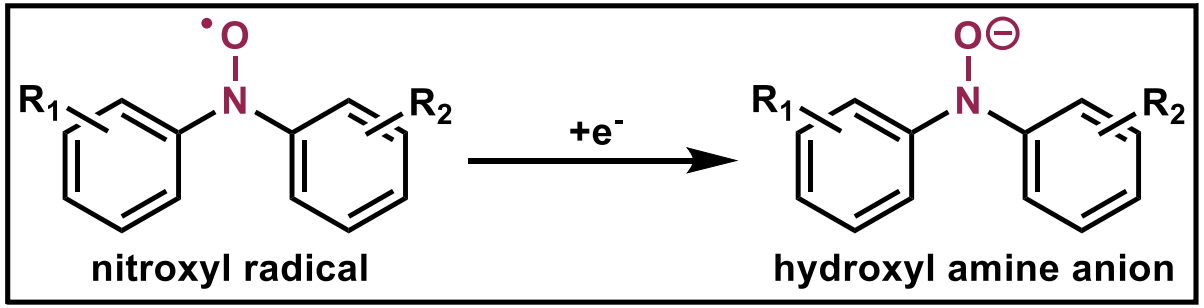
Redox Property

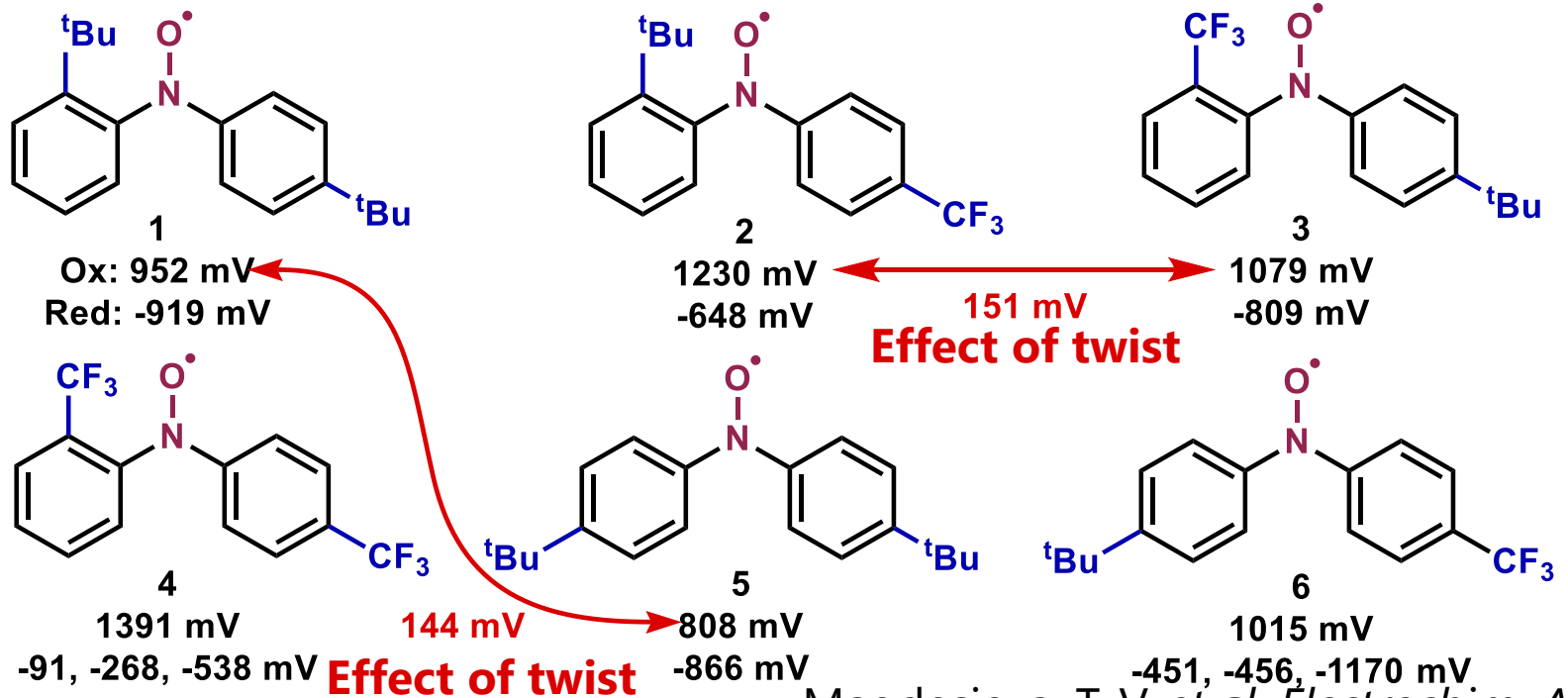
Redox potential E^0 (vs Ag/Ag^+)

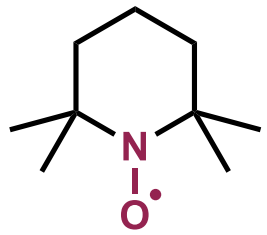
Oxidation (N-O˙ <-> N^+=O) : E^0_{ox}



Reduction (N-O˙ <-> N-O^-) : E^0_{red}





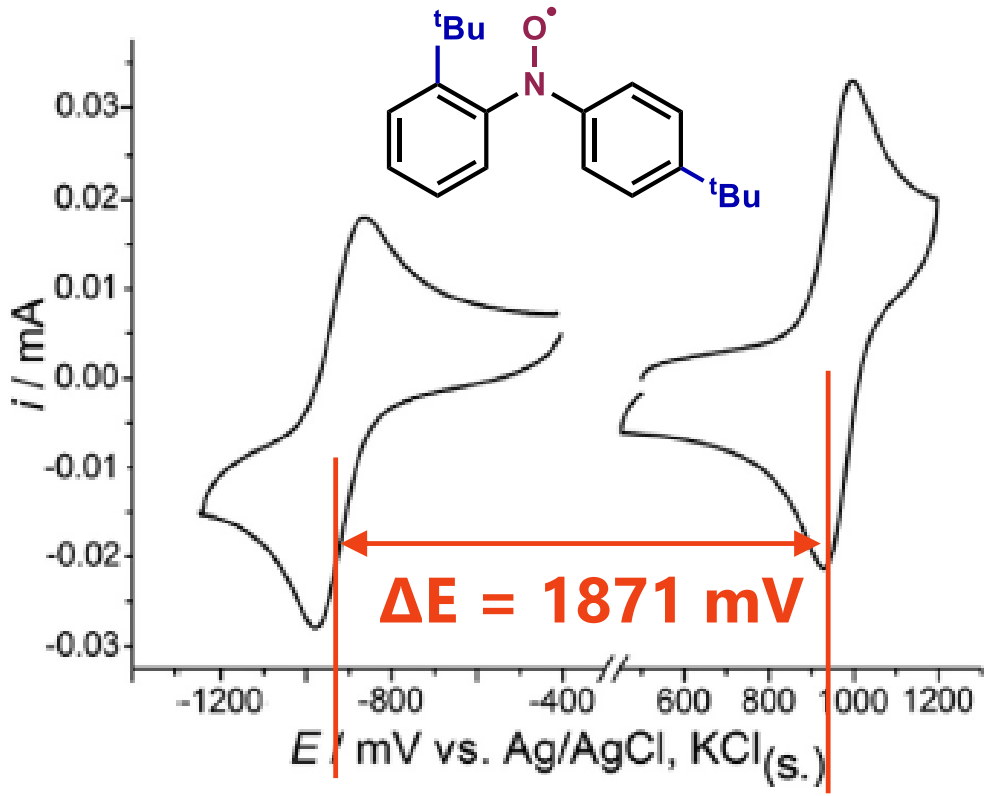


TEMPO
Ox: 700 mV

Magdesieva, T. V. *et al. Electrochim. Acta* **2018**, *260*, 459.

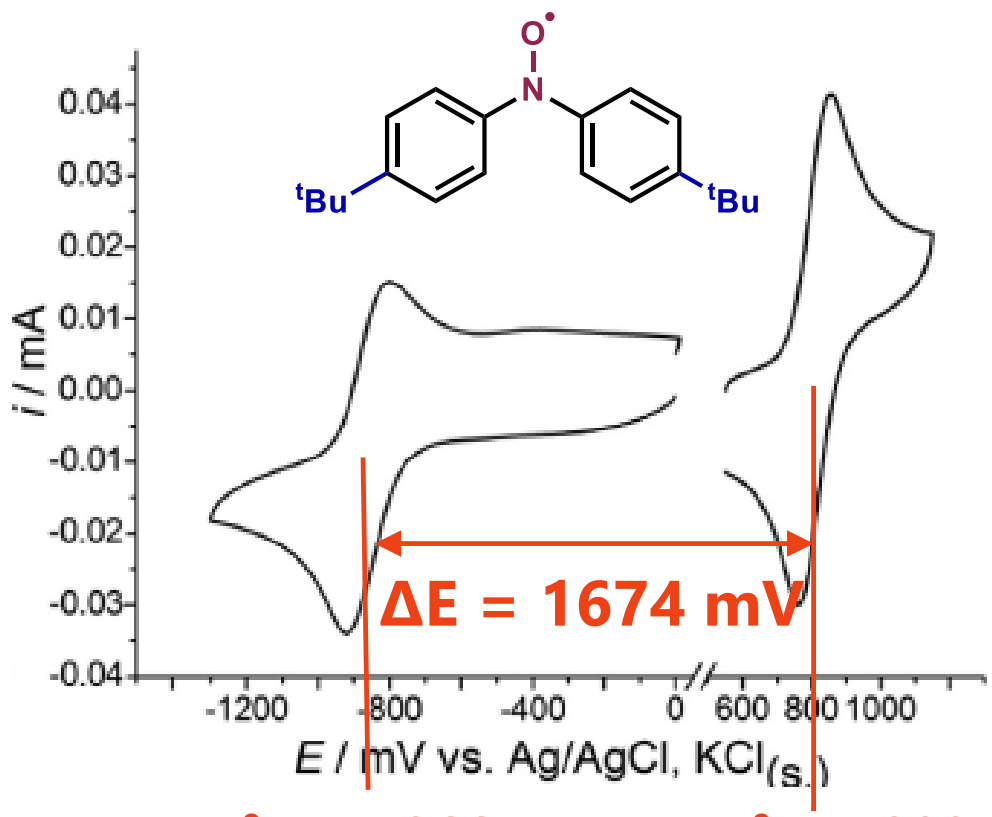
Interesting Property

1: twisted



E^0_{red} = -919 mV E^0_{ox} = 952 mV

5: non-twisted



E^0_{red} = -866 mV E^0_{ox} = 808 mV

- **$\Delta E = E^0_{ox} - E^0_{red}$** increases when twist exists.

<-> Inductive substituent normally shifts **E^0_{ox}** and **E^0_{red}** to the same direction.

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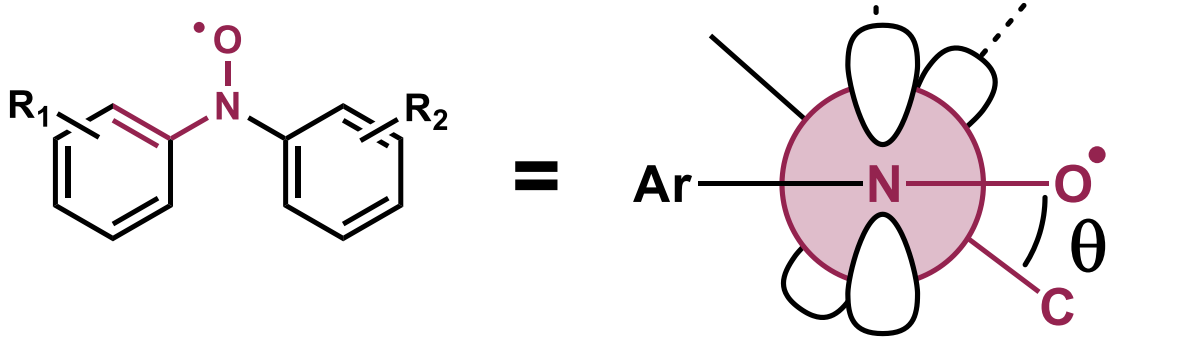
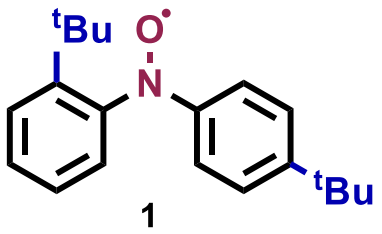
Torsion Angle

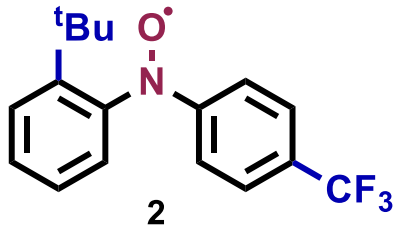
O-N-C-C torsion angle (**θ**) : θ is larger. -> conjugation is less.



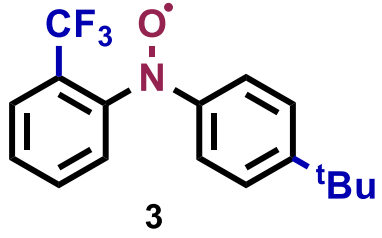
	θ (°)		
	N–O•	⊕N=O	N–O⊖
1	67.4	45.4	44.6
2	69.8	38.5	51.8
3	52.2	49.8	24.6
4	59.9	41.7	30.2
5			
6			



1



2



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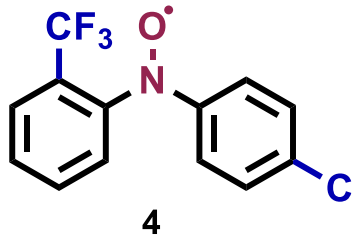

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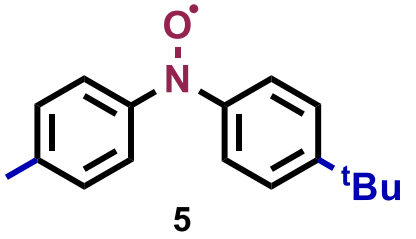
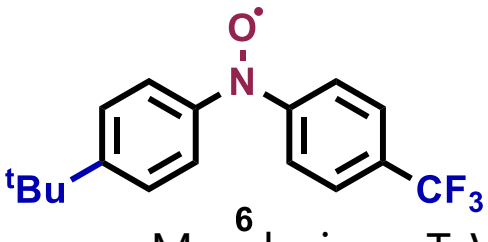


5



6

Torsion angle θ depends on

- Position of substituents
- Electronic property of substituents

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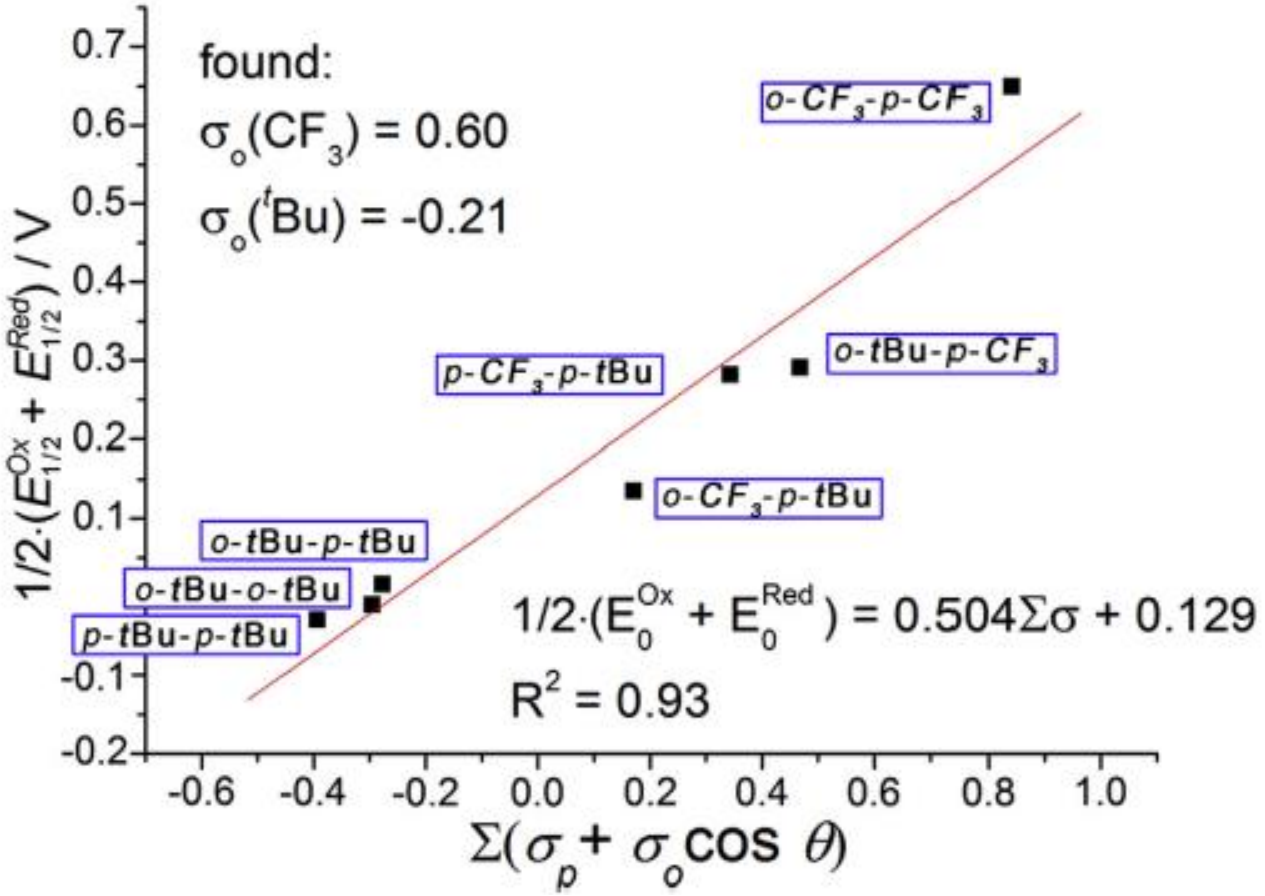
Relationship Between θ and Redox Potential

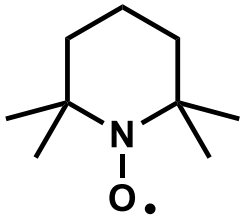


- Plotted $E^0_{ox}+E^0_{red}$ vs $\Sigma(\sigma_p+\sigma_o\cos\theta)$
- Such σ_o was determined that makes R^2 minimum.

Magdesieva, T. V. *et al. Electrochim. Acta* **2018**, *260*, 459.

3-3. α-Hydrogen Nitroxyl Radicals

Nitroxyl radicals with tertiary alkyl group

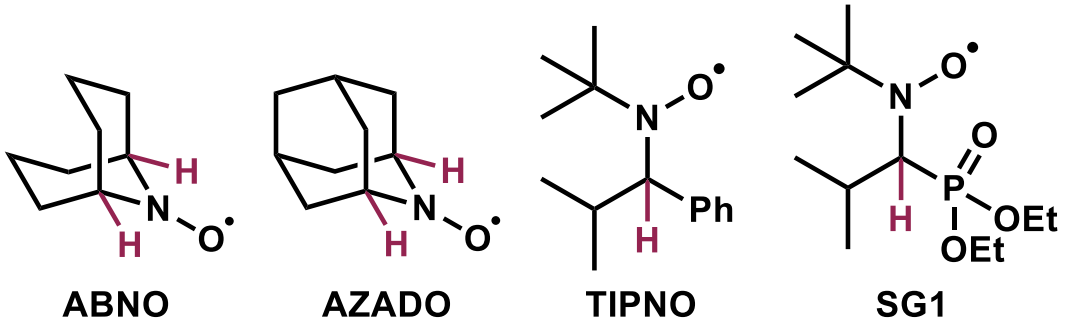


TEMPO derivatives

- Stable but highly encumbered.

Replacing Me with H for higher reactivity

Conventional α-hydrogen nitroxyl radicals



ABNO AZADO TIPNO SG1

Oxidation catalyst

Polimerization catalyst

stable α-hydrogen nirroxyl radicals

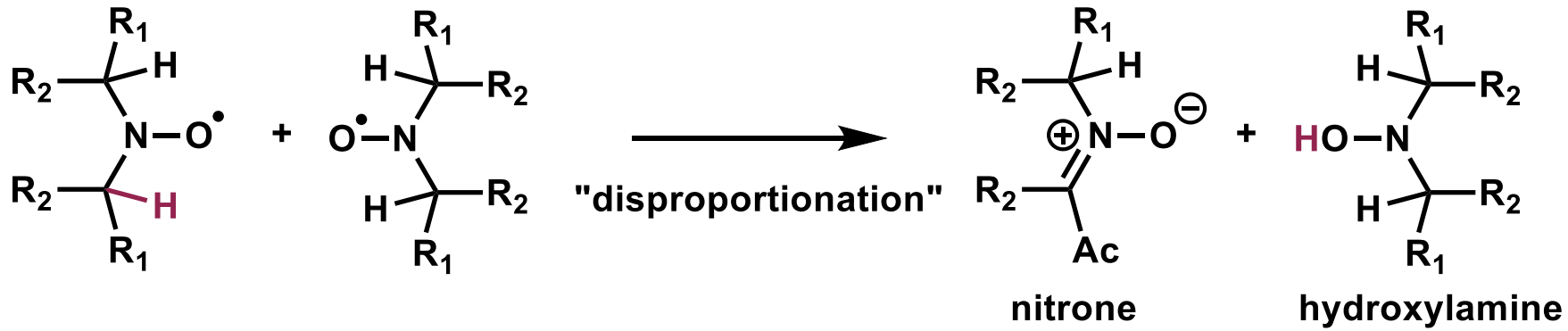
- Only acyclic and bicyclic system had been reported.
- The examples aren't abundant.

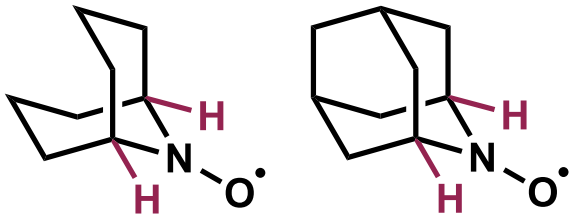
New design concept

Amar, M. *et al. Nat. Commun.* **2015**, *6*, 1.

Disproportionation of α-Hydrogen Nitroxyl Radicals

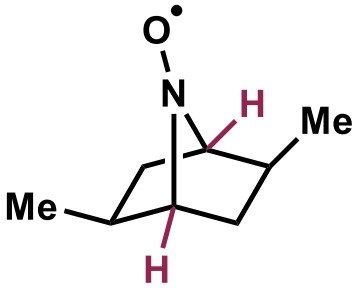
Disproportionation of α-hydrogen nitroxyl radicals





- Bridgehead H inhibit the formation of nitrone. (Bredt's rule)

But...

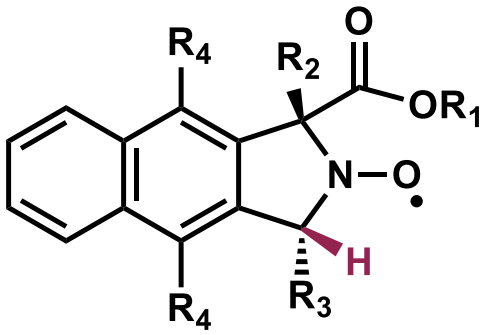


- bridgehead H strategy isn't necessarily effective.

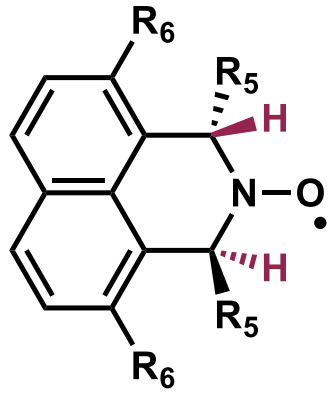
Amar, M. *et al. Nat. Commun.* **2015**, *6*, 1.

Design Concept of α-Hydrogen Nitroxyl Radicals

New α-hydrogen nitroxyl radicals

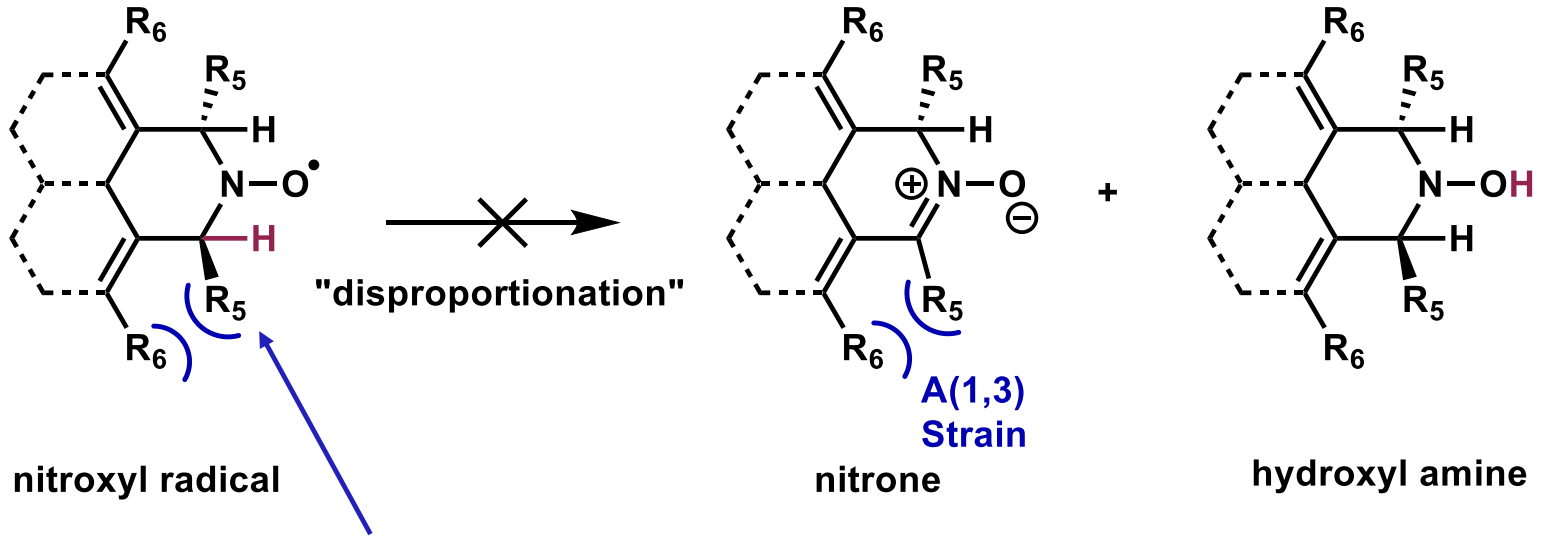


isoindoline nitroxide (IINO)



2,3-dihydro-isoazaphenalene nitroxide (IAPNO)

Design concept



1: pushing out the substituent

- R_6 push R_5 away from the plane.

-> H abstraction by another molecule is inhibited.

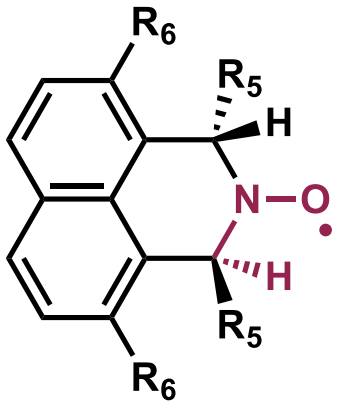
2: 1,3-allylic strain

- Nitrone formation is disfavored due to A(1,3) strain.

Amar, M. *et al. Nat. Commun.* **2015**, *6*, 1.

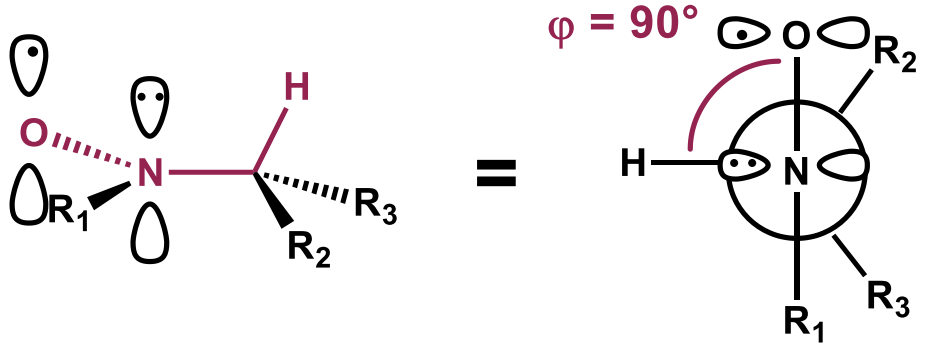
Design Concept of α-Hydrogen Nitroxyl Radicals

3: H-C-N-O angle (Φ)



IAPNO

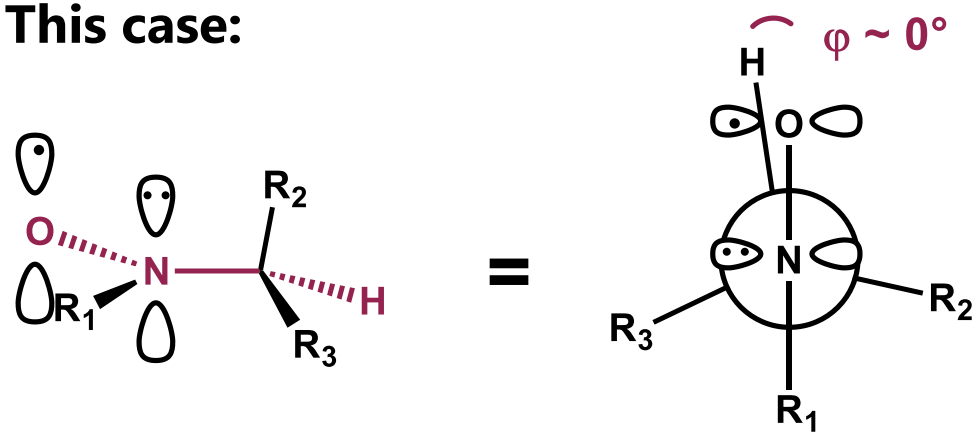
Ideal angle for C-H abstraction:



- C-H bond overlaps SOMO.

-> H abstraction is favored.

This case:



- C-H bond is orthogonal to SOMO.

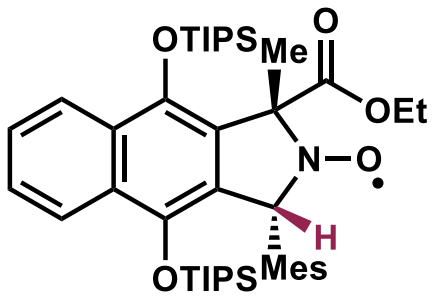
-> H abstraction is disfavored.

Based on these concepts, improved stability of was expected.

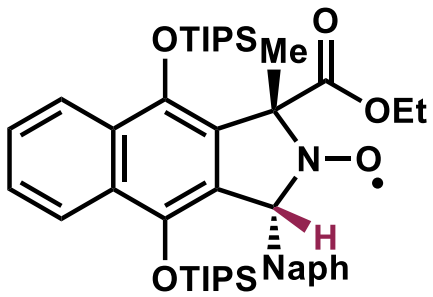
Amar, M. *et al. Nat. Commun.* **2015**, *6*, 1.

Results

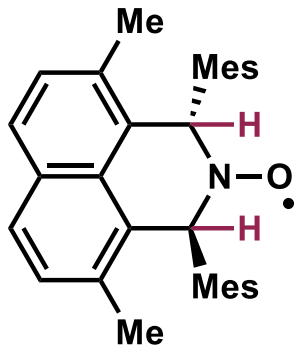
Synthesized molecules



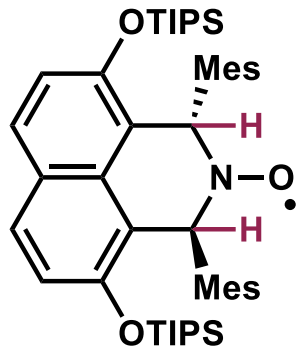
25a



25b



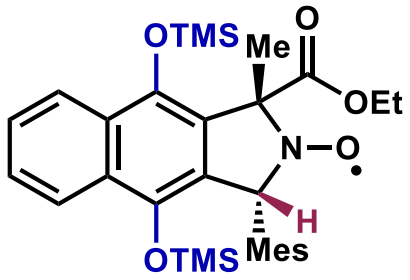
32



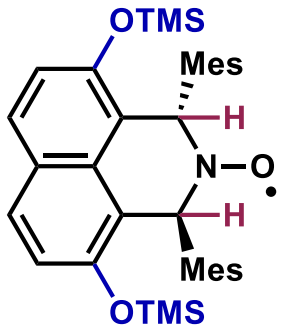
35

Stable for months.

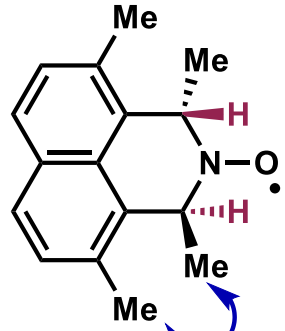
DFT calculation



36 (TIPS -> TMS in 25a)



37 (TIPS -> TMS in 35)



38 less steric repulsion

calculated reaction free energies ($\Delta G_{298,\,sol}$, kcal mol^{-1})

Radical	Disproportionation	SET to give 11/12	Radical pair precomplex	$\Delta G^{\ddagger}_{298}$ (H abstraction)
36	−20.8	76.6	27.2	38.4
32	−25.4	72.3	13.0	44.5
38	−12.5	69.6	−17.2†	6.6
35	−24.3	73.3	—‡	—‡
37	−25.0	71.4	—‡	—‡

- Disproportionation is thermodynamically favored.

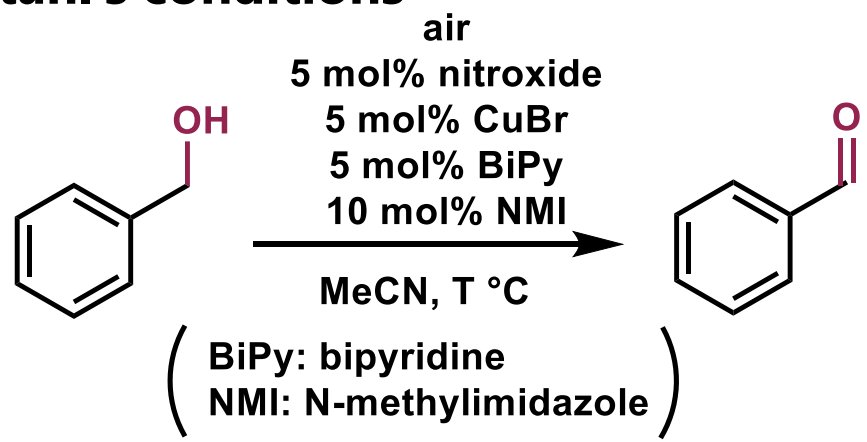
-> Stability of the nitroxyl radicals is due to kinetic factors.

Amar, M. *et al. Nat. Commun.* **2015**, *6*, 1.

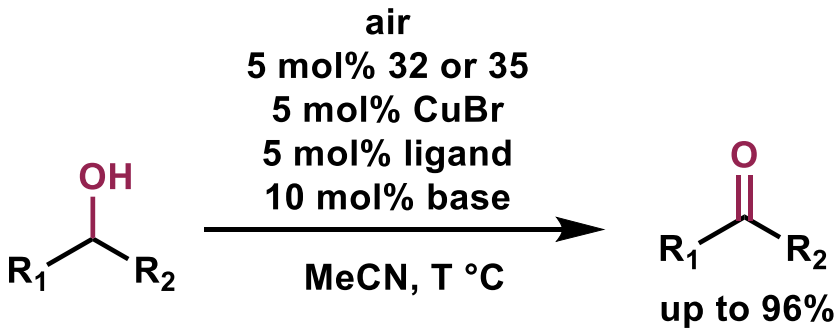
Potential as Catalyst

Aerobic alcohol oxidation

Stahl's conditions



Further investigation



Nitroxide	Reaction time (h)	*T* (°C)	Yield (%)
3 (TEMPO)	3	25	95
25a	6	55	82
25b	1.5	25	92
32	2	25	96
35	1	25	96

- In some Nitroxides, catalytic activity is better than TEMPO.

Amar, M. *et al. Nat. Commun.* **2015**, *6*, 1–9.

alcohol	ligand	base	T (°C)
1° benzyl, allyl, propargyl	**BiPy**	**NMI**	**rt**
2° benzyl	**BiPy**	**NMI**	**55**
1° alkyl	**4,4-(^{t}Bu)$_2$BiPy**	**DMAP**	**55**

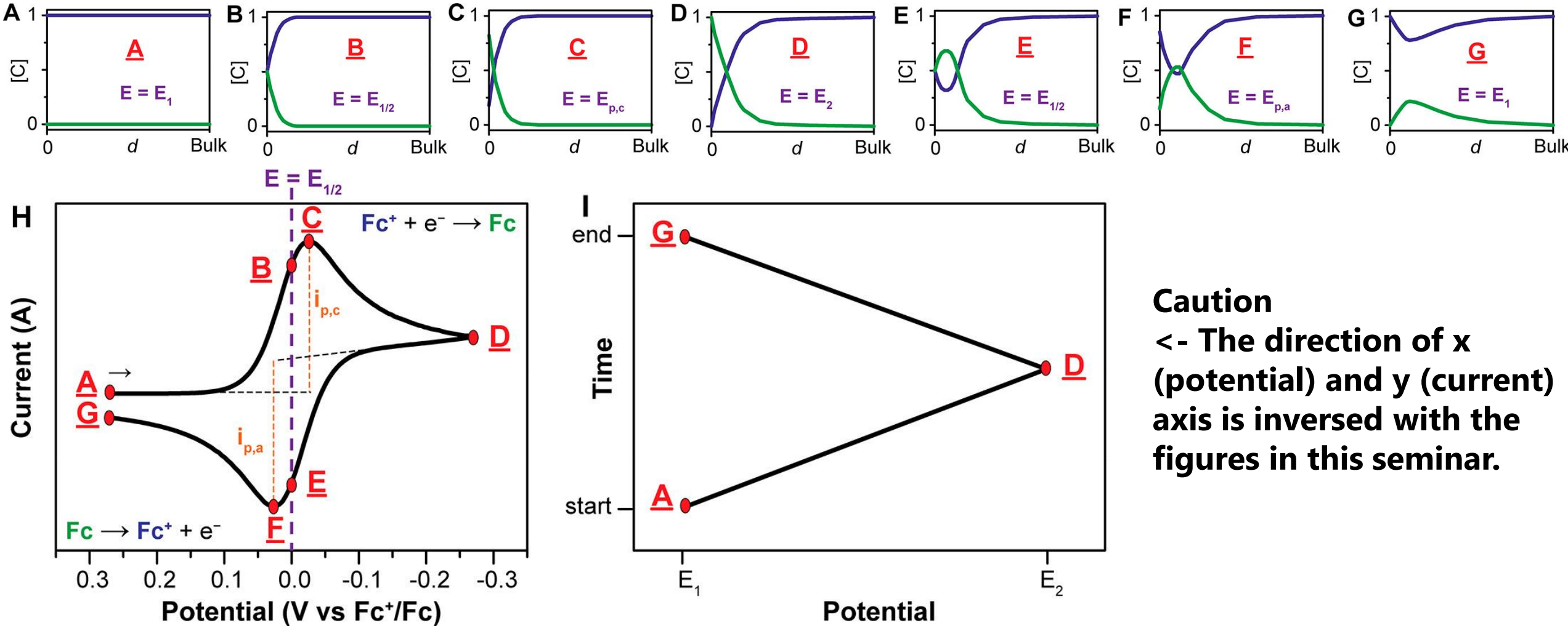
- Nitroxide 35 shows 2~3 times higher catalytic activity than TEMPO.

Szpilman, A. M. *et al. ChemCatChem* **2015**, *7* (7), 1129.

4. Summary

- Reactivity and stability of nitroxyl radical can be tuned by the parameters here and maybe by other parameters.
- The examples of the use of fine-tuned nitroxyl radicals aren’t many, so the best design of nitroxyl radicals for the purpose could improve the efficiency.

Appendix: Cyclic Voltammetry



Caution
<- The direction of x (potential) and y (current) axis is inversed with the figures in this seminar.

Dempsey, J. L. *et al. J. Chem. Educ.* **2018**, *95* (2), 197.