# *N-Oxy Radical Chemistry*

## *- Toward Application for Efficient Catalysis -*

**Literature Seminar**
**Shogo HASHIZUME (D1)**
**'12. 7. 2. (Mon.)**

# Today's Contents

**1. Fundamentals of *N*-Oxy Radical Species**

**2. Aminoxyl Radical-Mediated Reactions**

**3. Imidoxyl Radical-Mediated Reactions**

**4. Iminoxyl Radical-Mediated Reactions**

**5. Perspectives**
  *– For exploration of novel & efficient N-oxy radical catalysis*

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2. Aminoxyl Radical-Mediated Reactions

3. Imidoxyl Radical-Mediated Reactions

4. Iminoxyl Radical-Mediated Reactions

5. Perspectives
   – *For exploration of novel & efficient N-oxy radical catalysis*
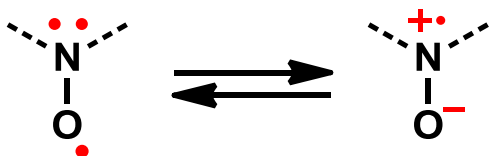
# Why N-OHs Generate Radicals ??

**Radical = *Subvalent* compounds**
*one less bond than principle of general valency*

➡️ *Radical states is generally reactive and difficult to generate*

**But, some radicals are stable to isolate or generatable although transient.**

**Due to…**
**- *Delocalization* of unpaired electron by conjugation**
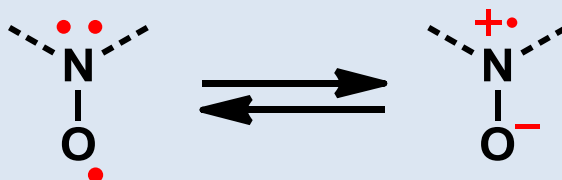**- *Steric shielding* of unpaired electron**

**Stability of *N*-oxy radical owes much to delocalization of the unpaired electron over *N-O* bond.**
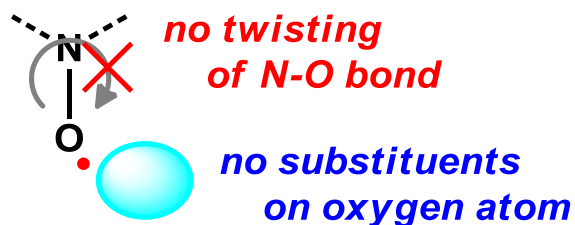
# What Makes *N*-Oxy Radical Stable ??

## Factors to stabilize the radical state:
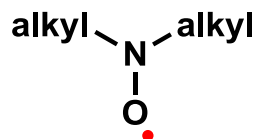
### 1. Enough conjugation with N's lone pair



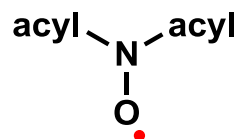**- *Conformational advantage for conjugation***



**no twisting of N-O bond**

**no substituents on oxygen atom**

*Conjugation is not reduced by steric freedom*

**- *Varied stabilities depending on N's electron density***



alkyl–N–alkyl
|
O•

**aminoxyl radical**
**(*e.g.* TEMPO)**

**stable, isolable**

acyl–N–acyl
|
O•

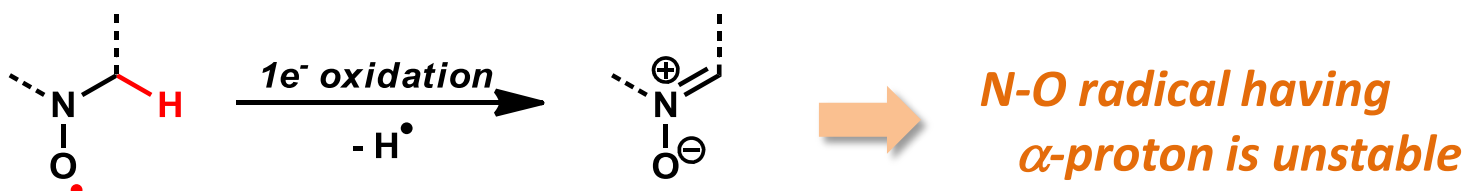**imidoxyl radical**
**(*e.g.* PINO)**

**unstable, not isolable**

# What Makes *N*-Oxy Radical Stable ??
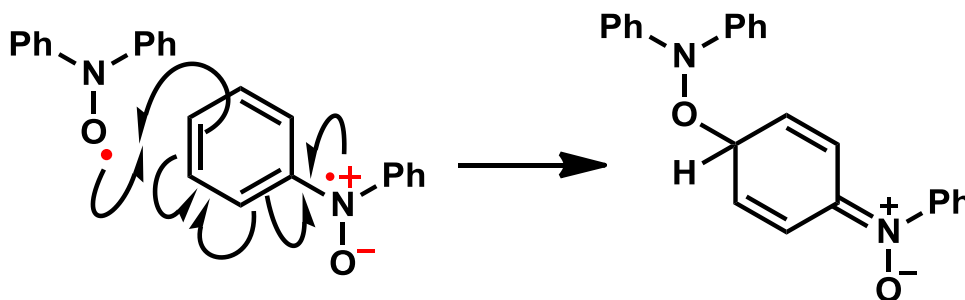
**Factors to stabilize the radical state:**

**2. Structure *NOT* to cause self-decomposition**



**non-radical products**

*- More one-electron oxidation to afford nitrone*



*1e⁻ oxidation*

*- H•*

*N-O radical having α-proton is unstable*

*- Radicalic dimerization*

# Considering Bond-Dissociation-Energy (BDE)

**Bond-Dissociation-Energy (BDE)**
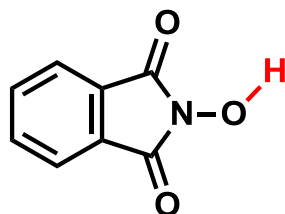
**= Enthalpy change  when a bond is cleaved by <u>homolysis</u>**

$$\text{R—H} \quad \xrightarrow{\Delta H} \quad \text{R}\cdot \; + \; \cdot\text{H}$$

**Useful representation of generation & stability of radical**

*<u>BDEs of some compounds</u>*

Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255; and reviews on *N*-oxy radical
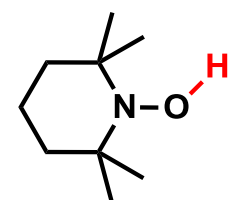
**TEMPOH**
*ca.*70 kcal/mol

**NHPI**
*ca.*88 kcal/mol
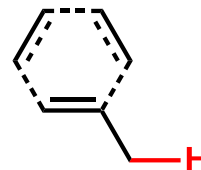
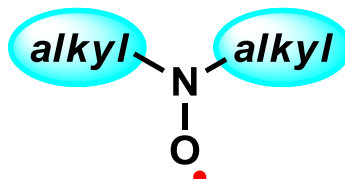*allylic or benzylic C-H*
*ca.*90 kcal/mol

alkane—H

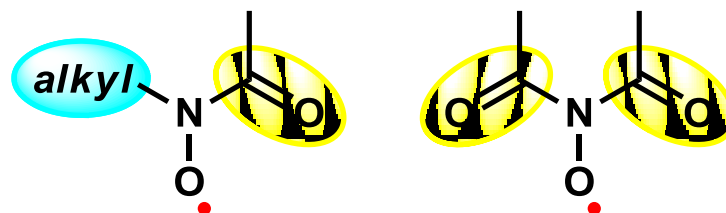*ca.*95-105 kcal/mol

*stable isolable*  ⟵⟶  *unstable not isolable*

# Classification of *N*-Oxy Radicals
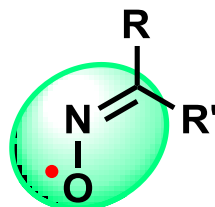
**1. Aminoxyl Radical**
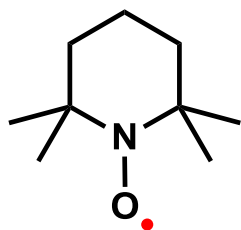
**2. Imidoxyl/Amidoxyl Radical**
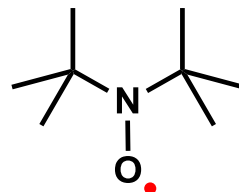
**3. Iminoxyl Radical**

# Aminoxyl Radicals

*Bulky/sterically restricted aminoxyl radicals are generally stable & isolable.*
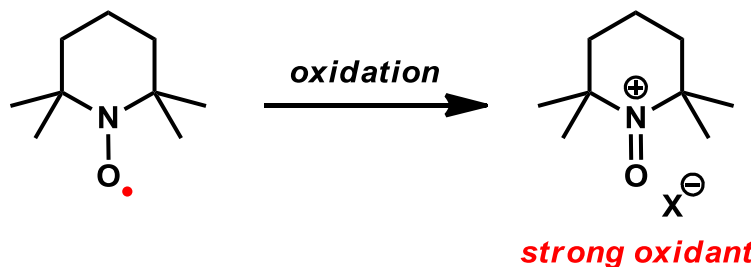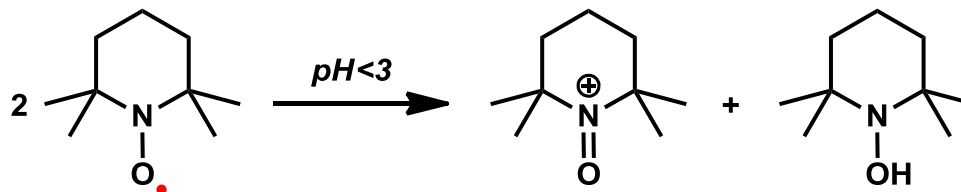
**TEMPO**
Lebedev, Nazarnovskii (1960)

**Di-*tert*-butylnitroxyl**
Hoffmann, Hnderson (1960)

*One more oxidation of TEMPO affords oxoammonium cation.*

oxidation

*strong oxidant*

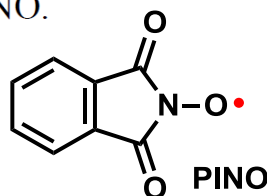*Disproportionation occurs under acidic conditions.*

pH<3

9

# Imidoxyl/Amidoxyl Radicals

**PINO radical**: *Not isolated but detected in situ generation*



**Figure 2.** EPR spectrum of PINO.

3.0 G

$\alpha_N$ = 4.36 G : smaller than other N-O

g = 2.0073 : larger than other N-O

*These values indicate*
*strong decrease of spin density on nitrogen*
*small increase of spin density on oxygen*

PINO

**EWG on N increases BDE =** *unstable radical state* **due to decrease of conjugation**

Table 2. BDE Values of O−H Bonds for *N*-Hydroxy Derivatives

| *N*-hydroxy derivative | BDE (kcal/mol) |
| --- | --- |
| 1 | 69.6 |
| 2 | 70.6 |
| 3 | 71.4 |
| 4 | 69.7 |
| 5 | 78.5 |
| 6 | 79.2 |
| 7 | 80.2 |
| NHPI | 88.1 |

6: R$_1$=Me, R$_2$=Ph

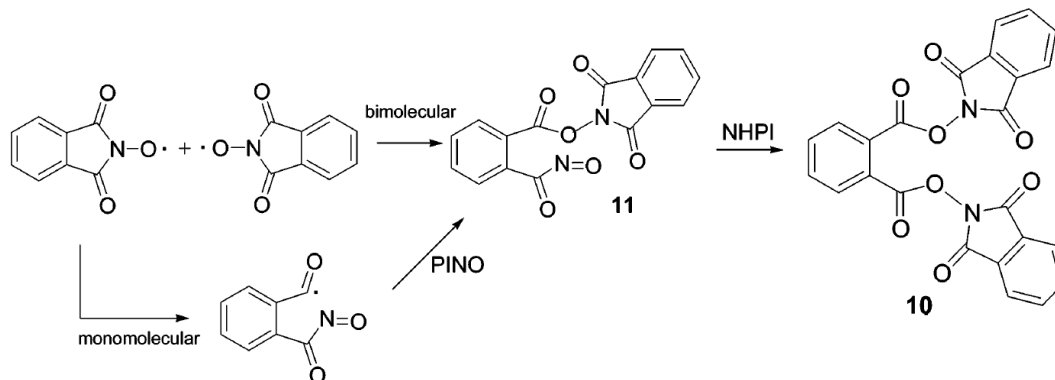7: R$_1$=CMe$_3$, R$_2$=3,5-(NO$_2$)$_2$C$_6$H$_3$
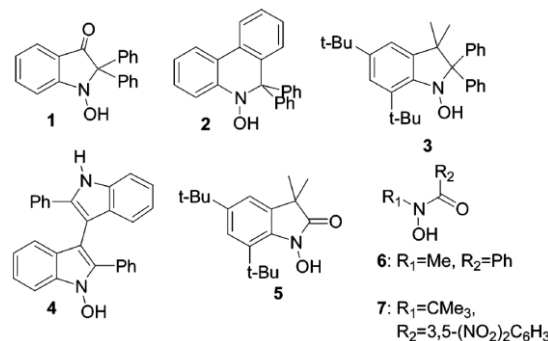
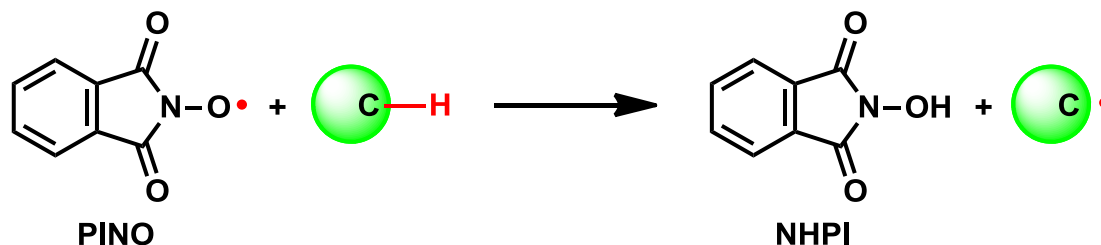Recupero, F. *et al. Chem. Rev.* **2007**, *107*, 3800.

# Imidoxyl/Amidoxyl Radicals

**PINO radical cause <u>self-decomposition</u>**

*due to its non-persistency (especially high temp.)*



**PINO often cause H-abstraction because of <u>its unstability</u>.**

# Iminoxyl Radicals

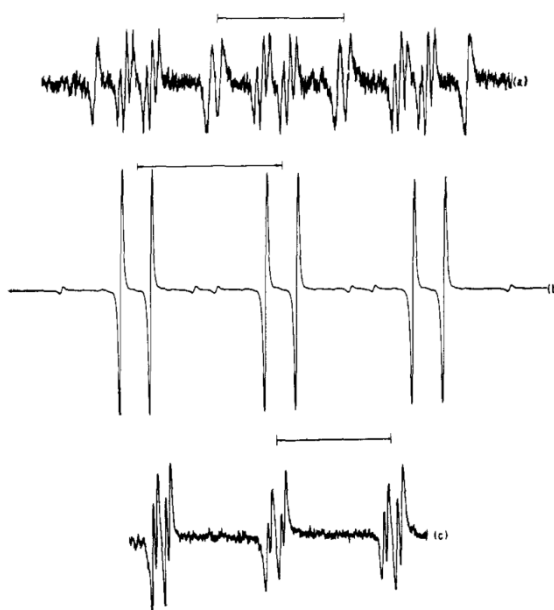## - First identified iminoxyl radicals
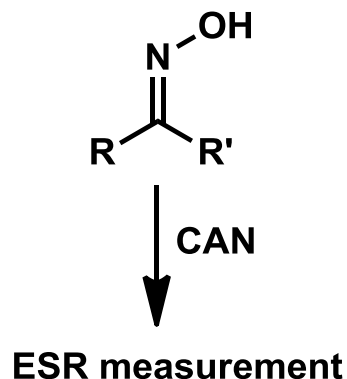
Fig. 1.—First derivative e.s.r. spectra of iminoxy radicals derived from (a) *syn*-benzaldoxime, (b) phenylglyoxaldoxime, and (c) *p*-nitrosophenol. The scale is 29.2 for a, 29.3 for b, and 33.0 gauss for c.

**ESR measurement**

**CAN**
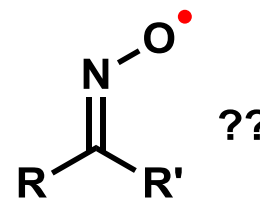
*Suggesting generation*
*of oxime radical*

- *Large nitrogen coupling constant*
   *The unpaired e⁻ on N is not in pure 2p_z orbital.*
   *(=Having σ-radical characteristics?)*

- *cis/trans isomers detected (Fig.1a)*
   *Isomerization by conjudation occurs*

# Iminoxyl Radicals

## - Isolated stable iminoxyl radicals

Ingold, K. U. *et al.*
*JACS* **1971**, *93*, 5278.
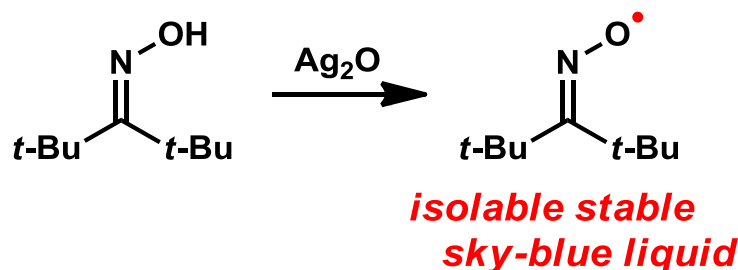


**First example of**
**isolated iminoxyl radical**

## - Carorimetric studies on iminoxyl radicals

Mahoney, L. R.; Ingold, K. U. *et al.*
*JACS* **1973**, *95*, 8610.



*80.0 kcal/mol*        *80.9 kcal/mol*        *84.3 kcal/mol*

*Isolablity of stable oxime radical is due to its low BDE.*

# What Stabilizes Iminoxyl Radicals ??

Bordwell, F. G.; Zhang, S.-H. *et al. JACS* **1995**, *117*, 4858.
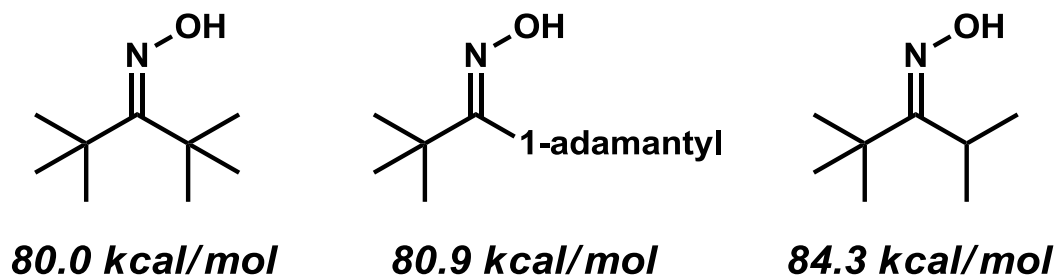
**Table 1.** Equilibrium Acidities in DMSO and BDEs for the O–H Bonds in Oximes

| no. | oxime | $pK_{HA}$ | $E_{ox}(A^-)^b$ (eV) | $BDE^c$ (kcal) |
|---|---|---|---|---|
| 1. | $Me_2C=NOH^a$ | 26.0 | −0.569 | 95.8 |
| 2. | $Et_2C=NOH^a$ | 25.2 | −0.673 | 92.3 |
| 3. | $t\text{-}Bu(Me)C=NOH$ | 24.4 | −0.675 | 91.1 |
| 4. | $4\text{-}t\text{-}Bu\text{-}c\text{-}C_5H_9C=NOH$ | 23.7 | −0.651 | 90.7 |
| 5. | $c\text{-}C_5H_{10}C=NOH^a$ | 24.2 | −0.700 | 90.3 |
| 6. | camphor | 24.8 | $−0.829^R$ | 88.1 |
| 7. | norcamphor | 24.4 | −0.827 | 87.6 |
| 8. | $i\text{-}Pr_2C=NOH$ | 24.2 | $−0.812^R$ | 87.7 |
| 9. | $t\text{-}Bu_2C=NOH$ | 24.4 | $−0.977^R$ | 84.2 |
| 10. | $t\text{-}Bu(1\text{-}Ad)C=NOH$ | 24.3 | $−1.078^R$ | 81.7 |

$^a$ $pK_{HA}$ and $E_{ox}(A^-)$ values taken from ref 3. $^b$ Oxidation potentials measured under the conditions previously described[6] and referenced to the ferrocene/ferrocenium couple. Values marked with a superscript R are reversible. $^c$ Calculated by using eq 1 with the empirical constant $C = 73.3$ kcal/mol.[5] The absolute values are probably no better than ±3 kcal/mol, but the relative values are believed to be accurate to better than 1 kcal/mol.

*Decreasing BDE parallels*
*increasing **the steric hinderance**.*

*Bulkier alkyl group increase*
*relief of steric strain by loss of H-atom*

Scheme 1
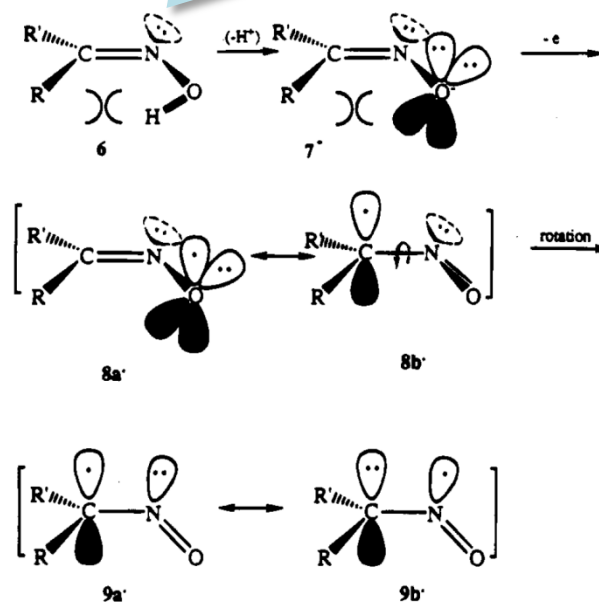
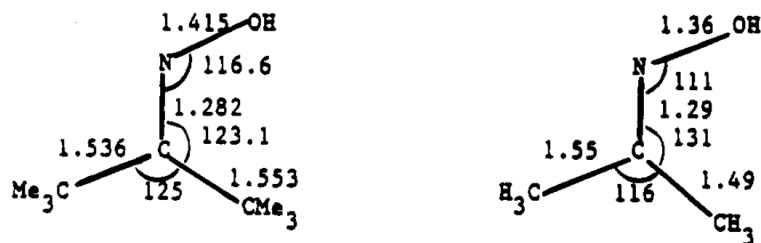## *The steric hinderance effects*

**Figure 2.** Structure of di-*tert*-butyl ketoxime and dimethyl ketoxime with bond lengths (Å) and bond angles (deg).

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1. Fundamentals of *N*-Oxy Radical Species

**2. Aminoxyl Radical-Mediated Reactions**

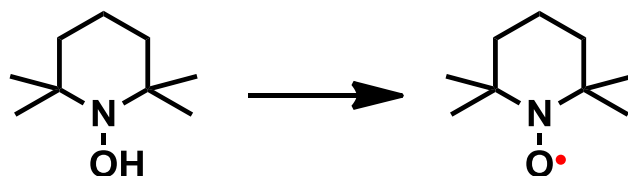3. Imidoxyl Radical-Mediated Reactions

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5. Perspectives
   – *For exploration of novel & efficient N-oxy radical catalysis*

# Aminoxyl Radical-Mediated Reactions

**TEMPO : most popular aminoxyl radical**



*Stability of the radical state* = **easy to be oxidized**

➡ **Useful mediator for redox reaction ??**

*Main topic =* **Alcohol oxidation**

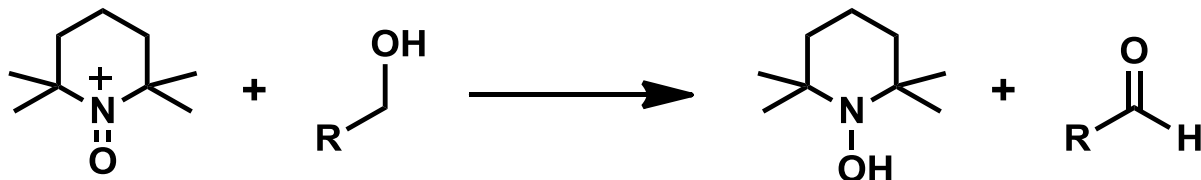**2-1. Copper-TEMPO catalysis**
**2-2. Ruthenium-TEMPO catalysis**
**2-3. Metal-free catalysis**
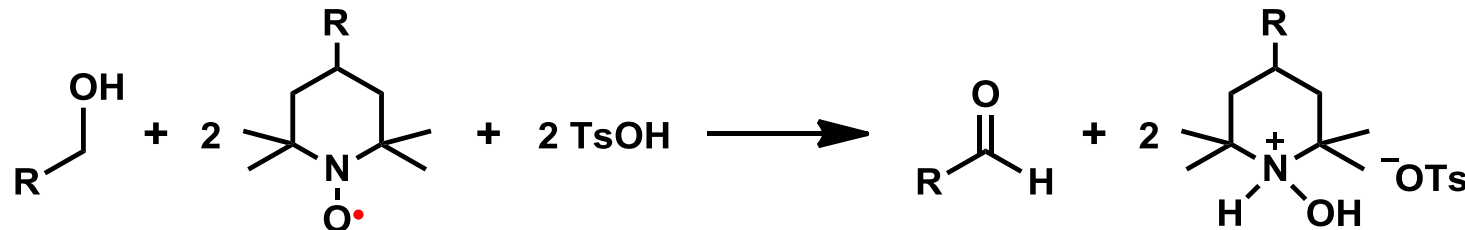
# Early Works on TEMPO-Mediated Oxidation

## - With stoichiometric oxoammonium cation

## - With stoichiometric TEMPO

*Oxidation proceed by in situ disproportionation of TEMPO*
*(TEMPO is known to disproportionate at acidic pH.)*

# Mechanism of TEMPO-Mediated Oxidation ??

Semmelhack *et al.* TL **1986**, *27*, 1119.

## *Considerable mechanism*

## *Hammet study*

Relative reaction rates:

1.0          2.2          2.1

*Only slight positive charge
at benzylic carbon in RDS*     **Path b unfavorable**

## *Cyclopropyl carbinol*

standard
condition

**No ring-opening**     *Path a
unfavorable*

## *Via intermediate 4*

MgBr

Ph

*m*CPBA
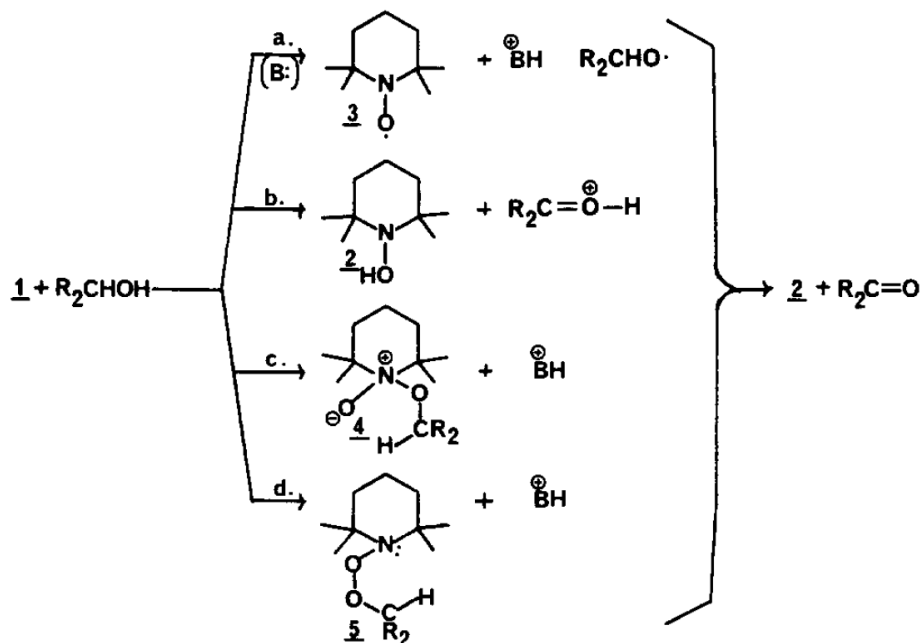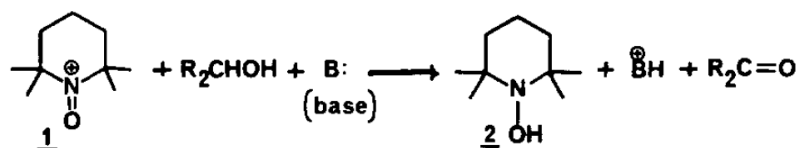
*Path c
favorable??*

**Which is actual mechanism ??**

# Mechanism of TEMPO-Mediated Oxidation ??

Semmelhack *et al. TL* **1986**, *27*, 1119.

### *Considerable mechanism*



**Possible pathway**
(Although cannot rule out *d*)

### *Hammet study*

**Relative reaction rates:**



| **1.0** | **2.2** | **2.1** |

*Only slight positive charge
at benzylic carbon in RDS*  → **Path b unfavorable**

### *Cyclopropyl carbinol*



**No ring-opening** → *Path a
unfavorable*

### *Via intermediate 4*



*m*CPBA → **Path c
favorable??**

19
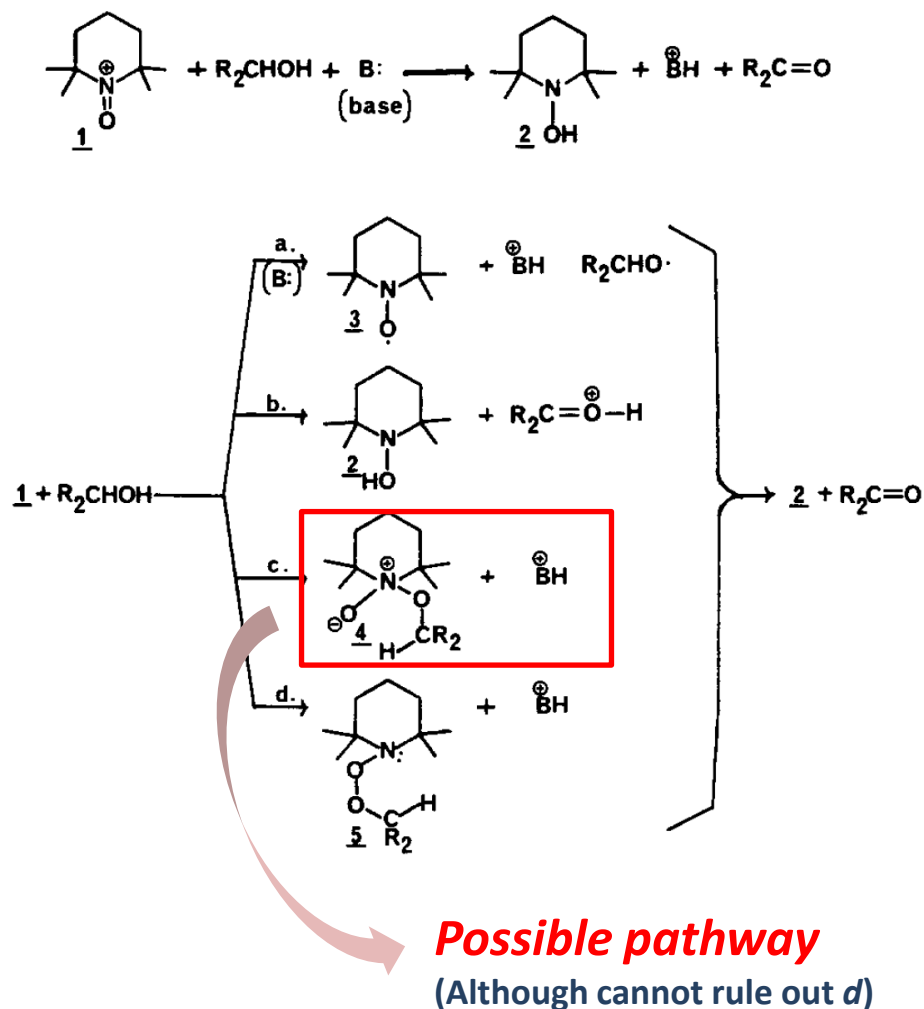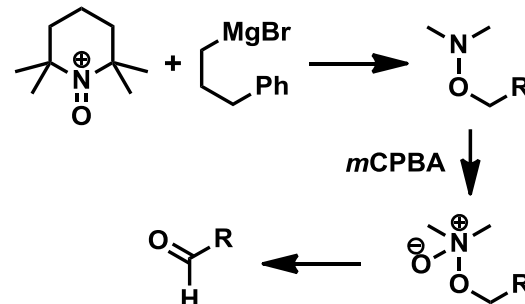
# Copper-TEMPO Catalysis with $O_2$

## - Cu(II)-phen.-*t*Bu$_2$nitroxide catalysis

$$CH_3OH + O_2 \xrightarrow[\substack{Cu(NO_3)_2 \\ phenanthroline \\ tBu\diagdown \\ N-O \cdot \\ tBu \diagup \\ 30\ °C}]{} H_2CO$$

### *Mechanism proposed by them*

$$CH_3OH + LCu^{II} + R_2NO \cdot \xrightarrow{slow} H_2CO + LCu^{I} + R_2NOH + H^+$$

$$R_2NOH + LCu^{II} \longrightarrow R_2NO \cdot + LCu^{I} + H^+$$
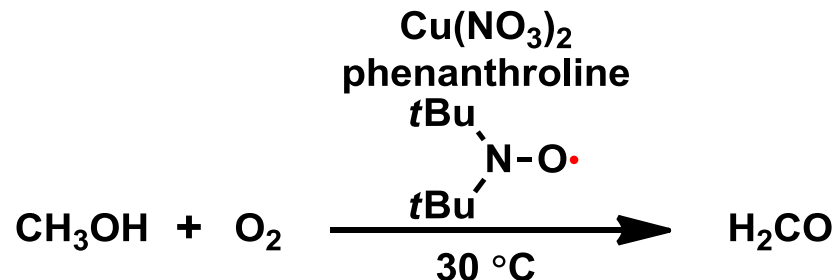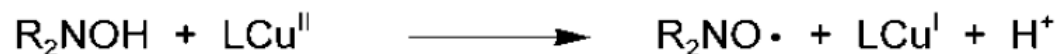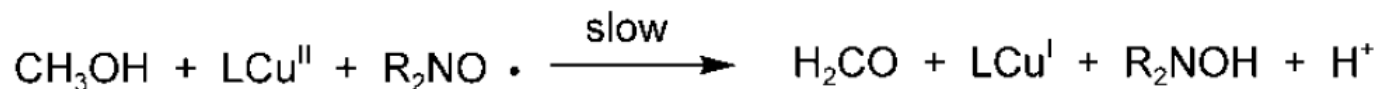
*Oxidation proceeds by cooperation of Cu(II) and N-O radical ??*

# Copper-TEMPO Catalysis with O$_2$

## - Cu(I)-TEMPO catalysis

Semmelhack, M. F. *et al.*
*JACS* **1984**, *106*, 3374.



benzylic
or
allylic

*Mechanism proposed by them*



**Table I.** Conversion of Alcohols to Aldehydes with Oxygen[a]

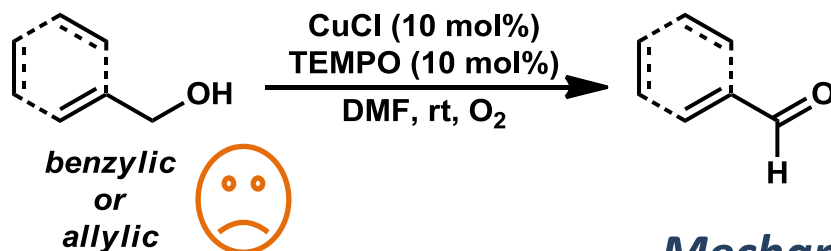| entry | alcohol | aldehyde | time, h | yield[b] |
|---|---|---|---|---|
| 1 | p-MeOC$_6$H$_4$CH$_2$OH | p-MeOC$_6$H$_4$CHO | 1.0 | 96% |
| 2 | p-MeOC$_6$H$_4$CH$_2$OH | p-MeOC$_6$H$_4$CHO | 24.0[c,e] | 97% |
| 3 | p-MeOC$_6$H$_4$CH$_2$OH | p-MeOC$_6$H$_4$CHO | 1.0[e,f] | 92% |
| 4 | p-MeOC$_6$H$_4$CH$_2$OH | p-MeOC$_6$H$_4$CHO | 2.0[f,g] | 91% |
| 5 | p-MeOC$_6$H$_4$CH$_2$OH | p-MeOC$_6$H$_4$CHO | 6.0[h] | 80% |
| 6 | p-MeOC$_6$H$_4$CH$_2$OH | p-MeOC$_6$H$_4$CHO | 7.0[i] | 25%[j] |
| 7 | C$_6$H$_5$CH$_2$OH | C$_6$H$_5$CHO | 4.0[k] | 94%[d] |
| 8 | p-NO$_2$C$_6$H$_5$CH$_2$OH | p-NO$_2$C$_6$H$_4$CHO | 7.0 | 85% |
| 9 | piperonyl alcohol | piperonal | 16.0[l,m] | 85% |
| 10 | (E)-hex-2-en-1-ol | (E)-2-hexenal | 1.75 | 100%[d] |
| 11 | geraniol | geranial | 1.75 | 92% |
| 12 | cinammyl alcohol | cinammaldehyde | 2.75 | 93% |
| 13 | myrtenol | myrtenal | 2.0 | 92% |
| 14 | 2-cyclohexenol | 2-cyclohexenone | 18.5[n] | 0% |

[a] Unless otherwise noted, according to the standard procedure: 10 mmol of alcohol, 1.0 mmol of CuCl, 1.0 mmol of **1**, 0.4 M in DMF (25 mL), at 25 °C. [b] Unless otherwise noted, the yields are based on distilled or chromatographed material. [c] Using 1 mol % of CuCl and of **1**. [d] Determined by GLPC analysis of the crude product. [e] At 1.0 M in DMF. [f] Using 100 mmol of alcohol, 10 mmol of CuCl, and 10 mmol of **1**. [g] At 6.67 M in alcohol in DMF. [h] At −20 °C. [i] At −60 °C. [j] 75% unreacted alcohol detected by NMR analysis on the crude product. [k] 5 mol % CuCl and **1**. [l] 2 mol % CuCl and **1**. [m] Using 25 mmol alcohol. [n] 100 mol % of CuCl and **1**.
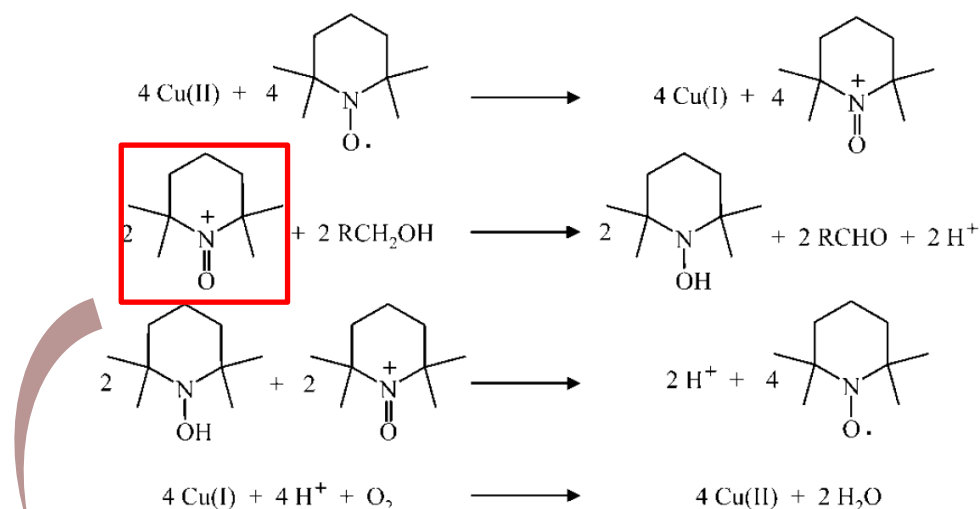
**Figure 20.** Semmelhack mechanism for CuCl/TEMPO-catalyzed oxidation of alcohols.

*Actual oxidant ??*

# What's The Correct Mechanism??

## - Mechanistic study

Sheldon, R. A. *et al. Org. Biomol. Chem.* **2003**, *1*, 3232.

### - Cu(I) is oxidized by TEMPO



Fig. 4 UV spectra of 2 mM solutions of Cu(I)(OAc)–TEMPO (■), Cu(II)(OAc)₂ (▲), TEMPO (x) and Cu(I)OAc (◆) in acetonitrile under an inert atmosphere.

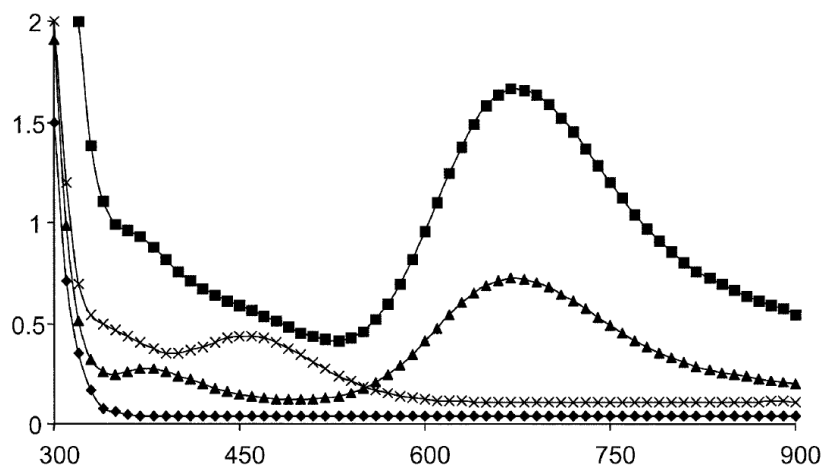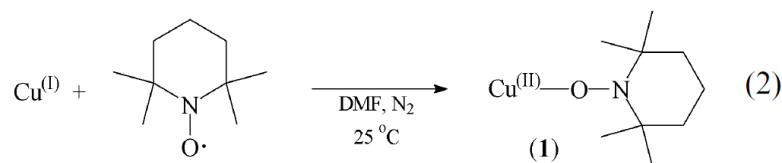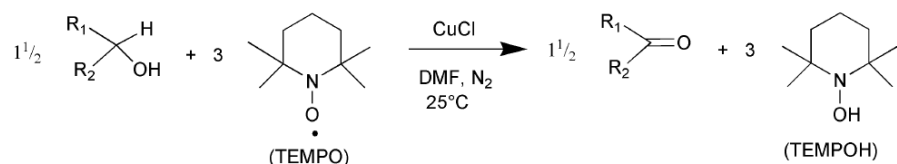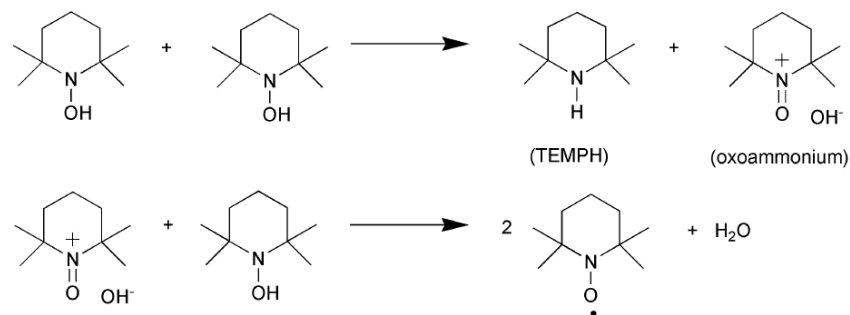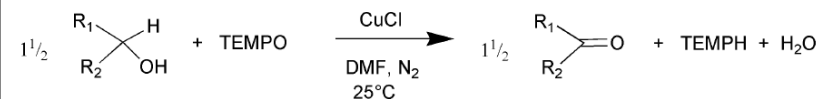### - Cu(I)-catalyzed reaction using stoichiometric TEMPO



Fig. 5 CuCl-catalysed oxidation of alcohol under nitrogen using TEMPO as terminal oxidant.

# What's The Correct Mechanism??

## - Mechanistic study
Sheldon, R. A. *et al. Org. Biomol. Chem.* **2003**, *1*, 3232.

### - KIE and Hammet correlation study

**Table 2** Kinetic isotope effects and Hammett $\rho$-values for the oxidation of benzyl alcohols

| System | Kinetic isotope effect $(k_H/k_D)^b$ | Hammett $\rho$-value | Reference |
|---|---|---|---|
| CuCl–TEMPO–O$_2$ | 5.42 | −0.16 | |
| Oxoammonium chloride | 1.7–2.3 | −0.3 | 27 |
| RuCl$_2$(PPh$_3$)$_3$–TEMPO–O$_2$ | 5.12 | −0.58 | 17 |
| CuCl–TEMPO–N$_2{}^a$ | 5.77 | — | |
| [Cu(II)BSP]–O$_2$ | 5.3 | −0.14 | 7 |
| Galactose oxidase | 5.02 | −0.09 | 28 |

$^a$ TEMPO is used as stoichiometric oxidant under an inert nitrogen atmosphere. $^b$ In all cases $\alpha$-deutero, $p$-methyl benzyl alcohol was used for the determination of KIE.

➡ *Similar to GO/GO-mimics rather than oxoammonium salt*
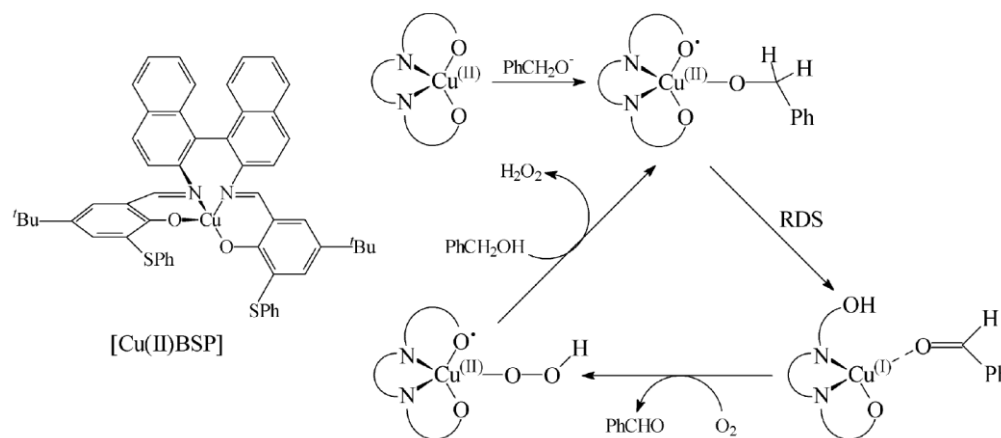


**Fig. 1** [Cu(II)BSP]-catalysed aerobic oxidation of benzyl alcohol (adapted from ref. 7).

# What's The Correct Mechanism??

## - Plausible mechanism

Sheldon, R. A. *et al. Org. Biomol. Chem.* **2003**, *1*, 3232.
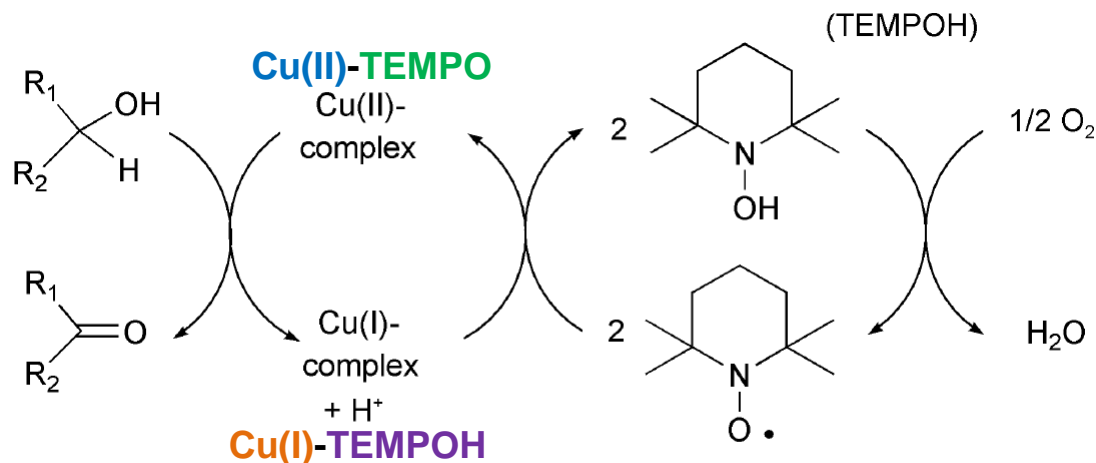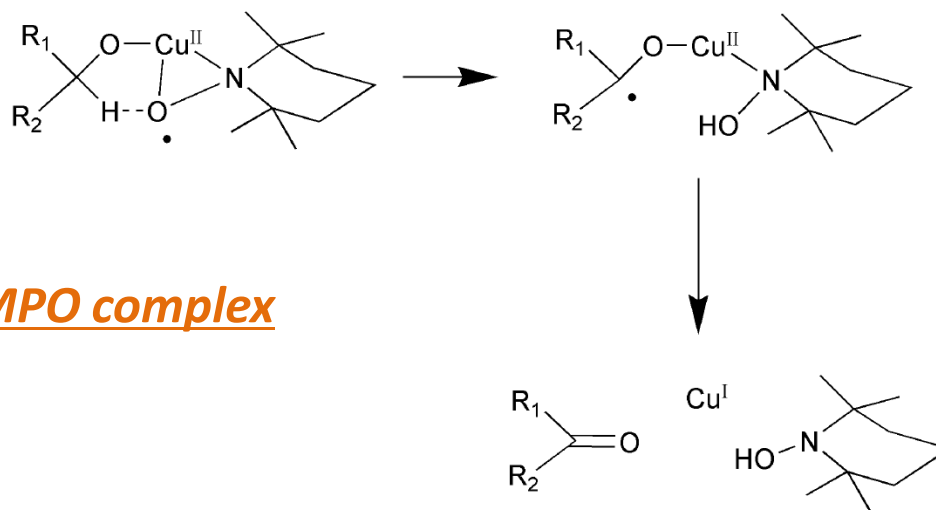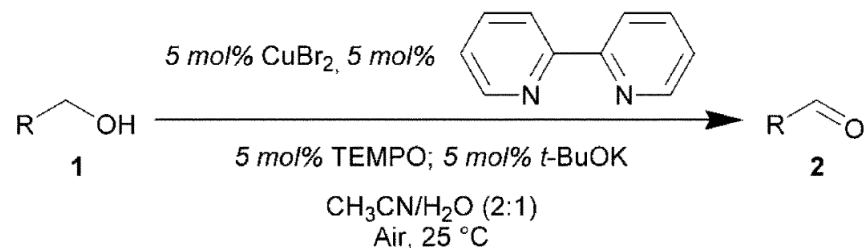


**Fig. 3** Copper-centred mechanism for the Cu–TEMPO catalysed aerobic oxidation of alcohols.



*Key step occurs via alkoxycopper(II)-TEMPO complex*

**Fig. 7** Intramolecular transfer of β-hydrogen, followed by oxidative elimination.

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# Selective Copper-TEMPO Oxidation

| Entry | Alcohol | Time/h | Conversion (%)[a] |
|-------|---------|--------|---------------|
| 1 | Benzyl alcohol | 2.5 | 100 |
| 2 | 1-Phenylethanol | 5 | No reaction |
| 3 | Crotyl alcohol | 5 | 91 |
| 4 | Geraniol | 5 | 100 |
| 5 | Octan-1-ol | 24 | 61 |
| 6 | Octan-1-ol | 24 | 95[b] |
| 7 | Octan-2-ol | 5 | No reaction |
| 8 | Benzyl alcohol + octan-2-ol | 1.5 | 67/0[c] |

[a] Selectivity always >99% based on GC. [b] Reaction performed at 40 °C with 7.5 mol% TEMPO. [c] 67% Benzaldehyde and no octan-2-one detected.

## *Remarkable selectivity for primary over secondary*
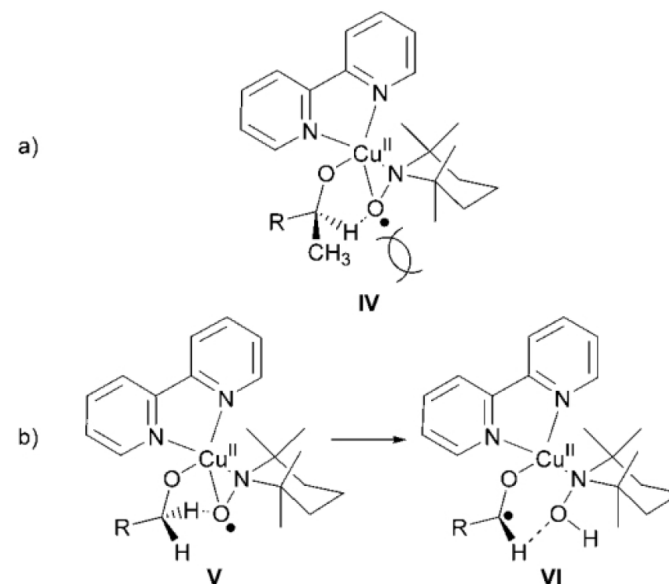
## *Rationalization of the selectivity*



**Fig. 3** Possible explanations for the lack of reactivity of secondary alcohols. a) Steric hindrance due to the methyl group of the secondary alcohol preventing the formation of species **IV**; b) stabilisation of the radical species **VI** by the second β-hydrogen of the primary alcohol.
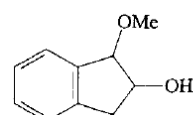
# Ruthenium-TEMPO Catalysis with O$_2$

RuCl$_2$(PPh$_3$)$_3$ (x mol%)
TEMPO (3x mol%)
PhCl, 100 °C, O$_2$

broad scope of alcohols
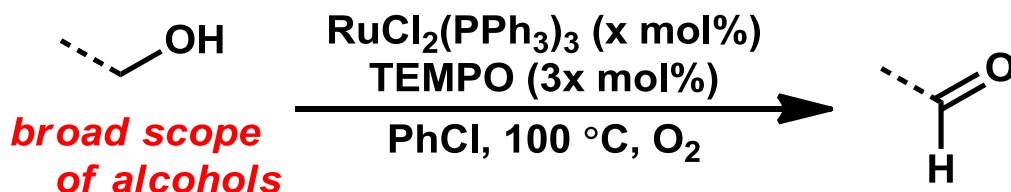
Sheldon, R. A. *et al.*
*JACS* **2001**, *123*, 6826.
*Plat. Metals Rev.* **2001**, *45*, 15.

**Table 2.** Ruthenium/TEMPO-Catalyzed Aerobic Oxidation of Several Alcohols[a]

| entry | substrate | product | S/C ratio | time (h) | convn (%)[b] |
|-------|-----------|---------|-----------|----------|--------------|
| 1 | octan-2-ol | octan-2-one | 100 | 7 | 98 (90) |
| 2[c] | octan-1-ol | octanal | 50 | 7 | 85 |
| 3 | benzyl alcohol | benzaldehyde | 200 | 2.5 | >99 (90) |
| 4 | *p*-nitrobenzyl alcohol | *p*-nitrobenzaldehyde | 200 | 6 | 97 |
| 5 | 1-phenylethanol | acetophenone | 100 | 4 | >99 (93) |
| 6 | cyclooctanol | cyclooctanone | 100 | 7 | 92 |
| 7 | adamantan-2-ol | adamantan-2-one | 100 | 6 | 98 |
| 8[c] | geraniol | geranial | 67 | 7 | 91 |
| 9[c] | 3-methyl-2-buten-1-ol | 3-methyl-2-butenal | 67 | 7 | 96 |
| 10[c] | octan-2-ol/octan-1-ol | octan-2-one/octanal | 50 | 7 | 10/80 |
| 11 | benzyl alcohol/1-phenylethanol | benzaldehyde/acetophenone | 200 | 3 | 90/5 |

[a] Reaction conditions: 15 mmol of substrate, RuCl$_2$(PPh$_3$)$_3$/TEMPO ratio of 1:3, 30 mL of chlorobenzene, 10 mL min$^{-1}$ O$_2$/N$_2$ (8/92; v/v), *p* = 10 bar, *T* = 100 °C. [b] Conversions based on GC results (selectivity >99% in all cases) using *n*-hexadecane as internal standard; numbers in parentheses are isolated yields. [c] O$_2$ atmosphere (see Experimental Section).
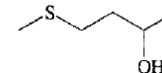
*Although these substrates are unreactive (deactivating catalyst by chelating??)*
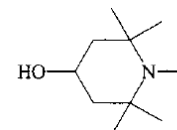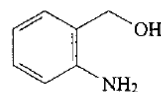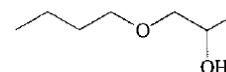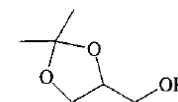
1-methoxyindan-2-ol    1,2,2,6,6-pentamethylpiperidin-4-ol    4-(methylthio)butan-2-ol

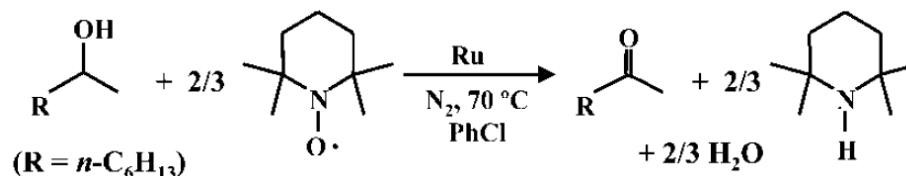2-aminobenzyl alcohol    butylproxitol    solketal

**Figure 2.** Unreactive alcohols.

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# Mechanism of Ruthenium-TEMPO Catalysis

## - Mechanistic study

Sheldon, R. A. *et al. JACS* **2001**, *123*, 6826.

*Reaction proceeds even in inert atmosphere with stoichiometric TEMPO*



$(R = n\text{-}C_6H_{13})$

*KIEs are same in the absence/presence of $O_2$*

**Table 4.** Kinetic Isotope Effect for the Ru/TEMPO-Catalyzed Aerobic Oxidation of *p*-Methyl-α-deuteriobenzyl Alcohol at Different Temperatures[a]

| entry | temp (°C) | time (h) for 100% convn | kinetic isotope effect $(k_H/k_D)$[b] |
|-------|-----------|-------------------------|---------------------------------------|
| 1 | 25 | 67 | 5.1 |
| 2 | 43 | 40 | 5.0 |
| 3 | 63 | 6 | 4.1 |
| 4 | 83 | 3 | 4.0 |
| 5 | 100 | 2 | 3.9 |
| 6 | 118 | 1.5 | 3.4 |

[a] Reaction conditions: 5 mmol of *p*-methyl-α-deuteriobenzyl alcohol, 0.05 mmol of RuCl$_2$(PPh$_3$)$_3$, 0.25 mmol of TEMPO, 10 mL of chlorobenzene, O$_2$ atmosphere. [b] H/D ratio determined by $^1$H NMR.

**Under stoichiometric TEMPO & inert atmosphere condition…**

**5.1**

**3.4**

*The same active species with/without oxygen Dehydrogenation by RuCl$_2$(PPh$_3$)$_3$ and TEMPO regenerates RuX$_2$ from RuH$_2$ ??*

# Mechanism of Ruthenium-TEMPO Catalysis

## - Mechanistic study

Sheldon, R. A. *et al. JACS* **2001**, *123*, 6826.
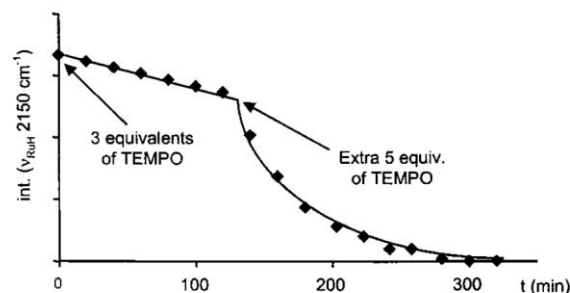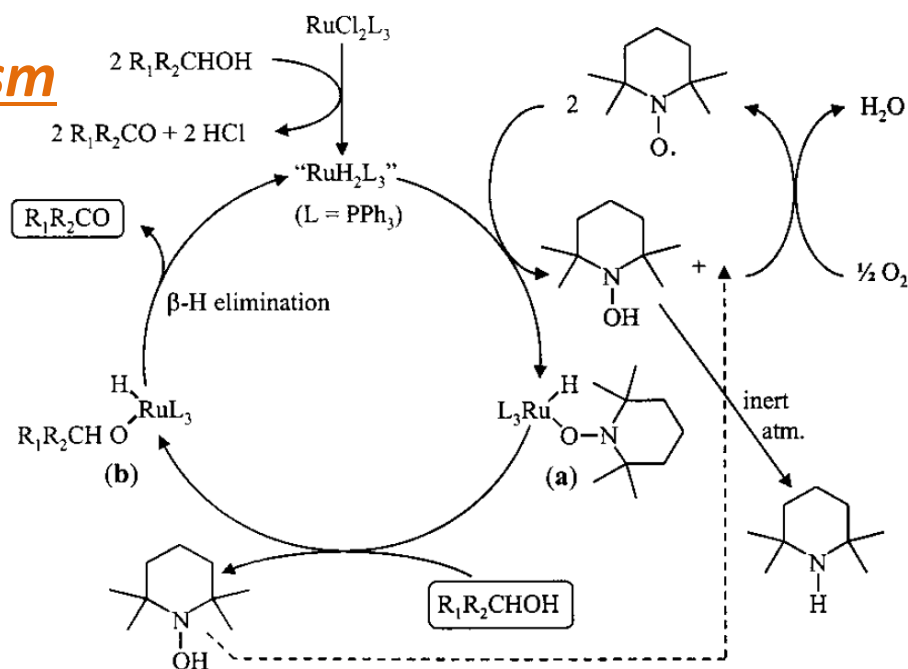
*RuH$_2$ reacts with TEMPO (observed in situ IR)*



**\*Ru-H vibration of RuH$_2$(PPh$_3$)$_3$ at 2150 cm$^{-1}$**

**Figure 8.** Stoichiometric reaction of "RuH$_2$(PPh$_3$)$_3$" with TEMPO in chlorobenzene under an inert atmosphere at 25 °C, followed by in situ IR.

➡️ *Conclusive mechanism*

# Metal-Free *N*-Oxy Radical Catalysis

## - TEMPO + stoichiometric oxidant

*Many reports…*

cat. TEMPO
oxidant

oxidant = *m*CPBA, NaOCl, $H_5IO_6$, oxone, etc.

## - The first non-metal aerobic oxidation catalyzed by TEMPO

*all catalytic amount*
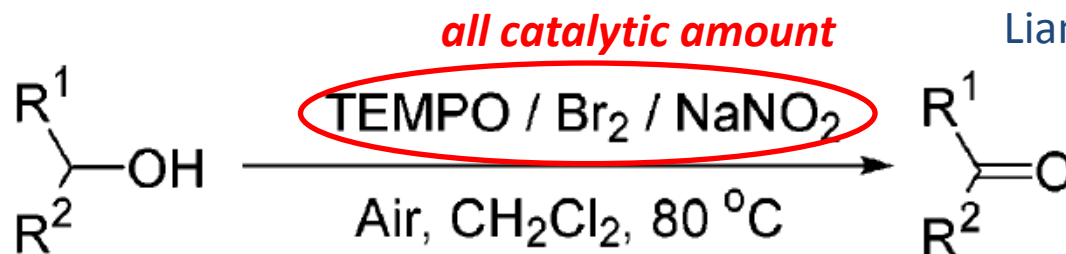
Liang, X.- M.; Hu, X.-Q. *et al.*
*JACS* **2004**, *126*, 4112.

TEMPO / $Br_2$ / $NaNO_2$

Air, $CH_2Cl_2$, 80 °C

**Scheme 1.** Overall Catalytic Mechanism
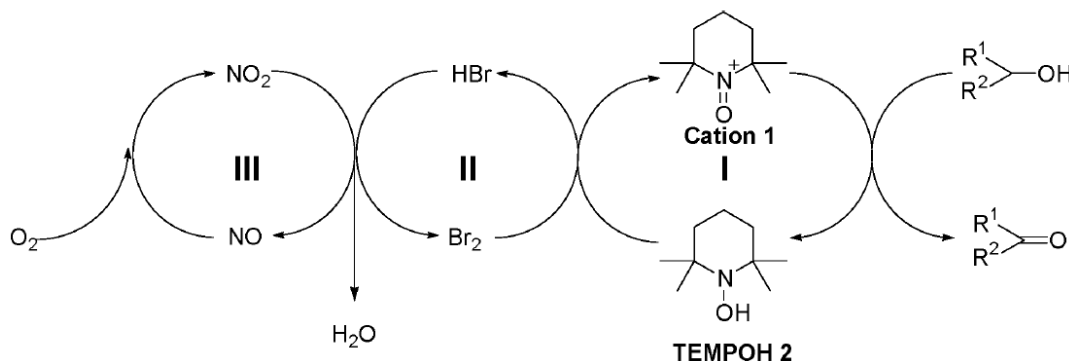
*But multiple components…*
*= Difficult application for complex molecule??*

# Metal-Free *N*-Oxy Radical Catalysis

## - Novel *N*-oxy radical AZADO for high efficiency

### *TEMPO: inefficient for hindered secondary alcohol*

➡ *Concept of their catalyst design:*

expanded accessibility

enhanced catalytic efficiency

### *AZADO exhibits great reactivity for alcohol oxidation*

**Table 1.** Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO under Anelli's Conditions

Ph⌁OH

TEMPO or 1-Me-AZADO
NaOCl (130 mol%), KBr (10 mol%),
Bu$_4$NBr (5 mol%)

CH$_2$Cl$_2$, aq. NaHCO$_3$, 0 °C, 20 min

→ Ph⌁⌁=O

| loading amount (mol%) | yield (%) | |
|---|---|---|
| | TEMPO | 1-Me-AZADO |
| 0.1 | 96 | 95 |
| 0.01 | 23 | 91 |
| 0.004 | n.d. | 88[a] |
| 0.001 | n.d. | 62[b] |

[a] The run time was 30 min. [b] The run time was 60 min.

**Table 2.** Comparison of Catalytic Efficiencies of TEMPO and 1-Me-AZADO under Margarita's Conditions

Ph⌁OH

TEMPO or 1-Me-AZADO

PhI(OAc)$_2$, CH$_2$Cl$_2$ (1M), rt

→ Ph⌁=O

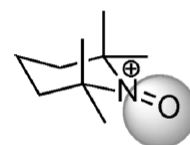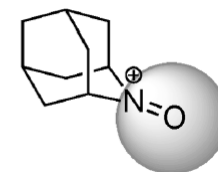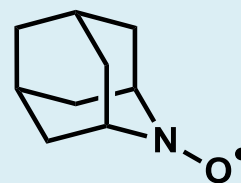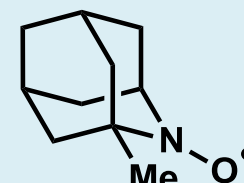| loading amount (mol%) | yield (%) / time (h) | |
|---|---|---|
| | TEMPO | 1-Me-AZADO |
| 10 | 95 / 1.5 | 96 / 0.1 |
| 1 | 42 / 6 | 93 / 0.7 |
| 0.1 | n.d. | 39 / 3 |

**AZADO**    **1-Me-AZADO**
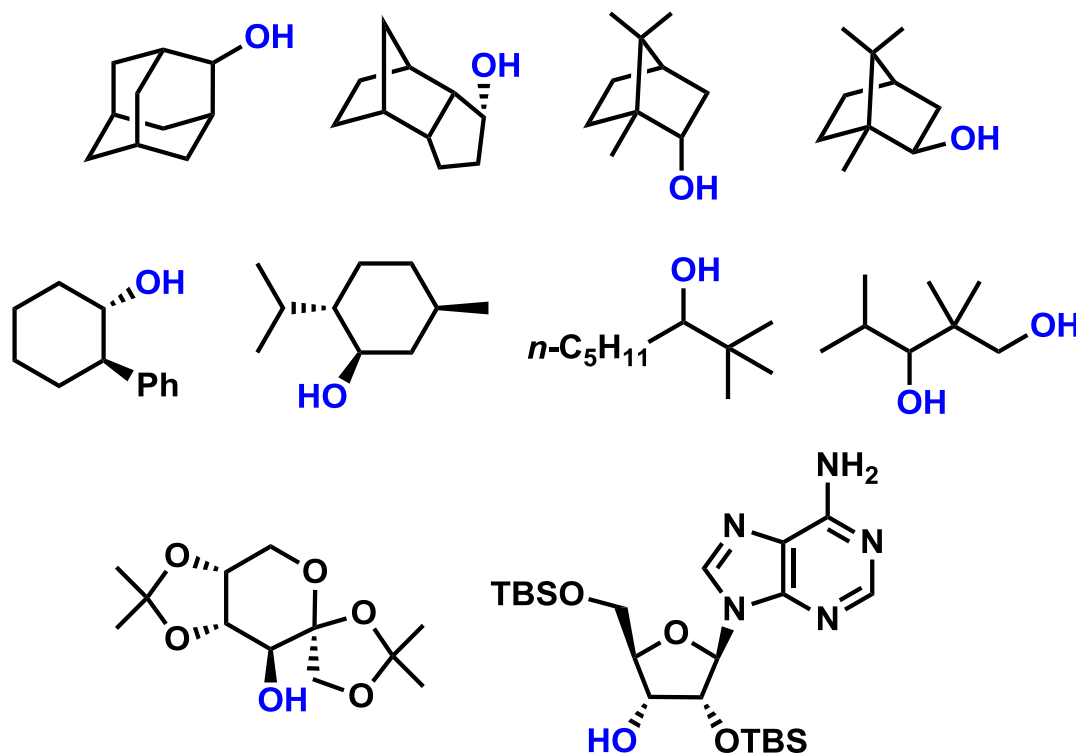
2-3. Metal-Free Catalysis

# Metal-Free *N*-Oxy Radical Catalysis

## - Novel *N*-oxy radical AZADO for high efficiency

Iwabuchi, Y. *et al.*
*JACS* **2006**, *128*, 8412.

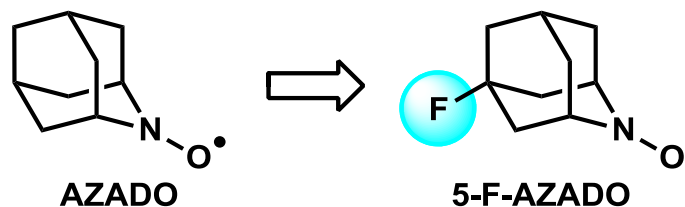*And various hindered alcohols can be oxidized.*
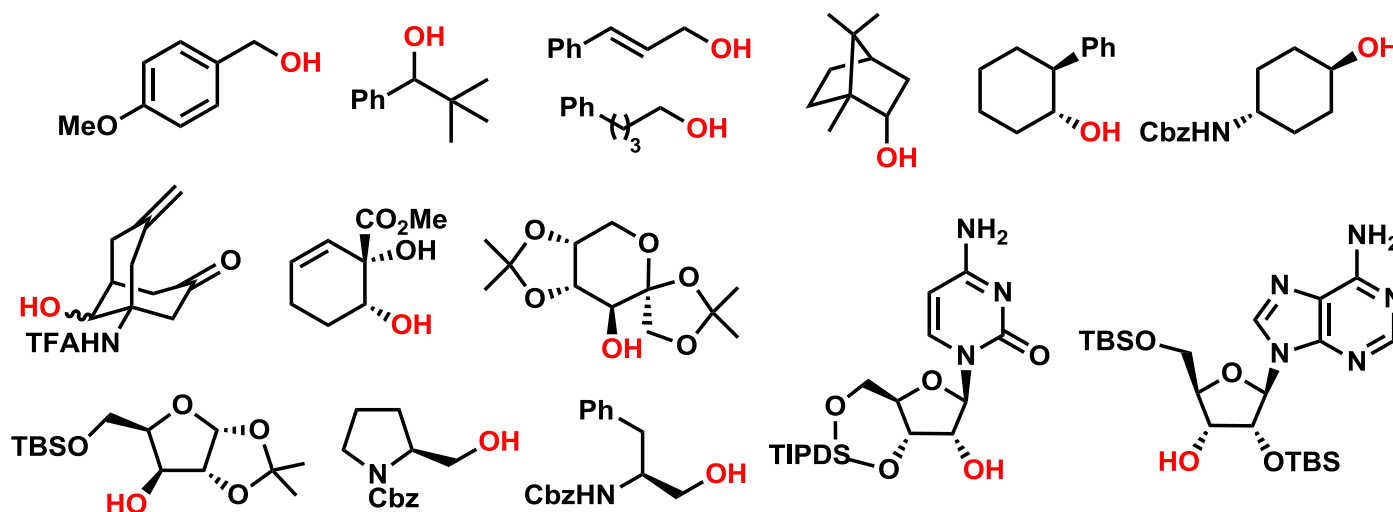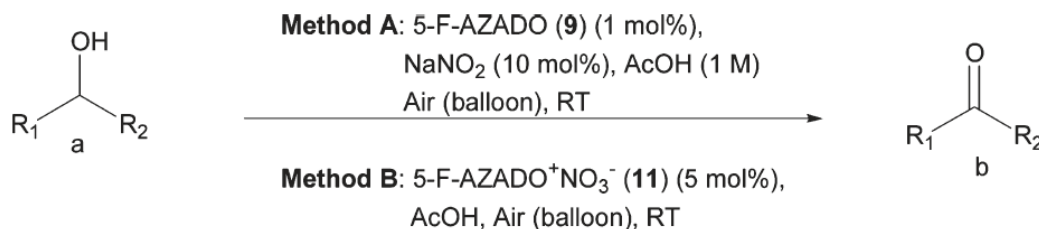
# Metal-Free *N*-Oxy Radical Catalysis

## - Aerobic version with more efficient catalyst

Iwabuchi, Y. *et al.*
*JACS* **2011**, *133*, 6497.

### Introduction of F at C$_5$ position



**AZADO** ⟹ **5-F-AZADO**

### Also wide substrate scope including hindered alcohol



**Method A**: 5-F-AZADO (**9**) (1 mol%),
NaNO$_2$ (10 mol%), AcOH (1 M)
Air (balloon), RT

**Method B**: 5-F-AZADO$^+$NO$_3^-$ (**11**) (5 mol%),
AcOH, Air (balloon), RT

# Metal-Free *N*-Oxy Radical Catalysis

## - Aerobic version with more efficient catalyst

*Proposed mechanism*
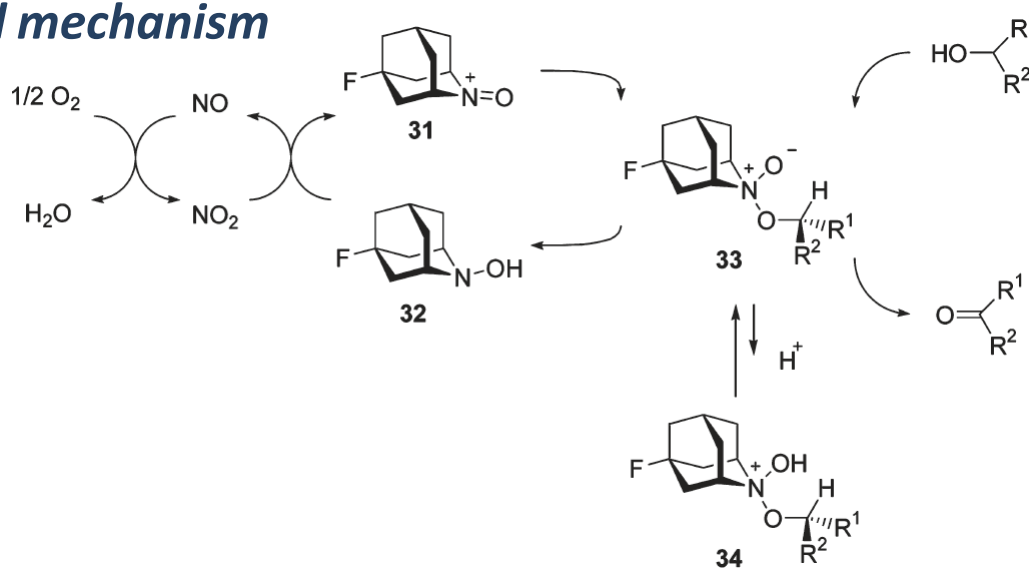


*I think oxoammonium cation is generated through disproportionation...*
*(Because solvent is AcOH)*
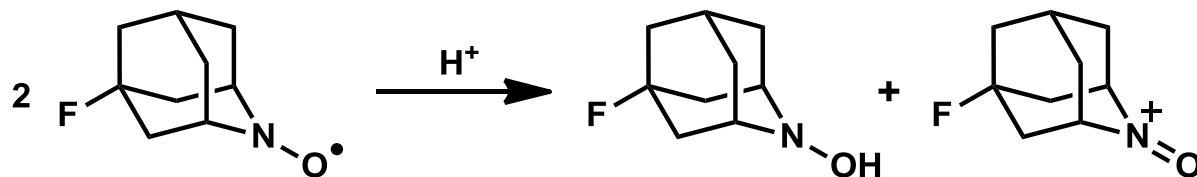
# Today's Contents

1. Fundamentals of *N*-Oxy Radical Species

2. Aminoxyl Radical-Mediated Reactions

**3. Imidoxyl Radical-Mediated Reactions**
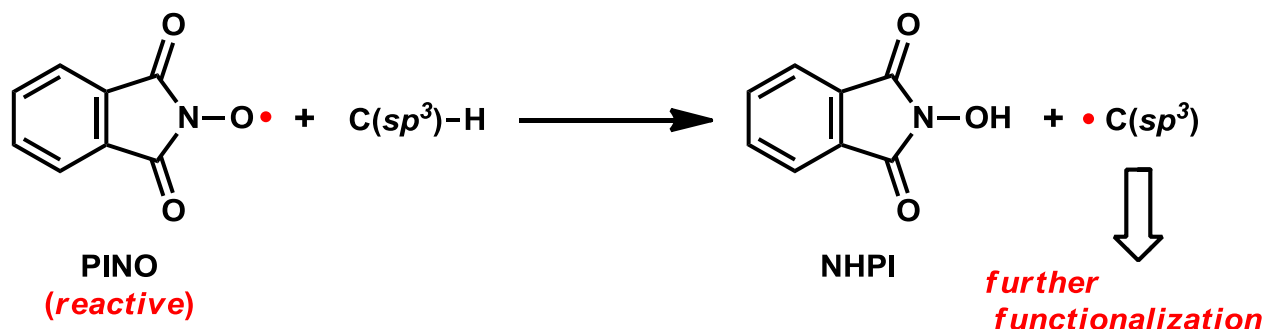
4. Iminoxyl Radical-Mediated Reactions

5. Perspectives
   – *For exploration of novel & efficient N-oxy radical catalysis*

# Imidoxyl Radical-Mediated Reactions

**Imidoxyl radical : High BDE makes the radical state unstable**

➡️ *Enables radicalic cleaveage of various C-H bonds*



**PINO**
(*reactive*)

**NHPI**

*further
functionalization*

*Reactions introduced today:*

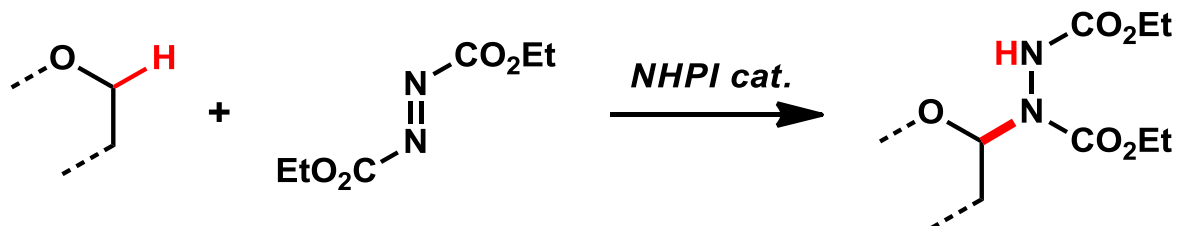**3-1. Alkane oxidation to alcohols/carboxylic acids**

**3-2. Ethers/Acetals oxidation**

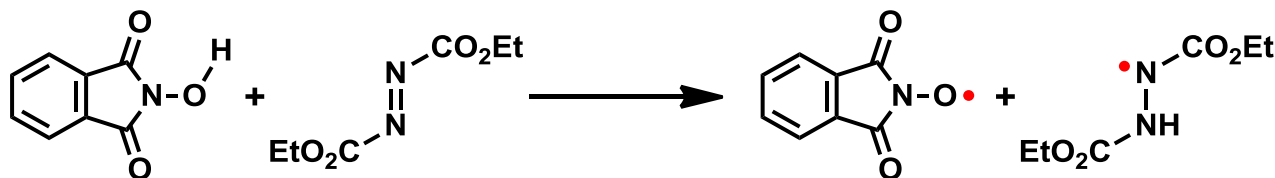**3-3. Application to C-C bond formation**

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# Early Works on NHPI-Mediated Reactions

## - Coupling between ethers and DEAD

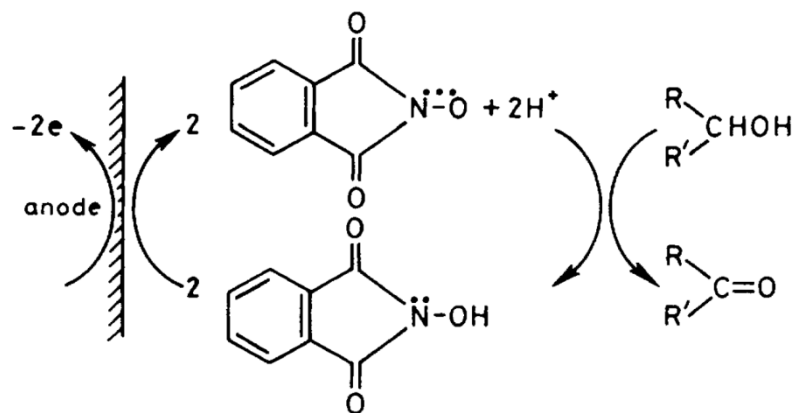Grochowski, E. *et al.*
*Synthesis* **1977**, 718.

*Initiation occurred by homolysis of N=N bond ?*
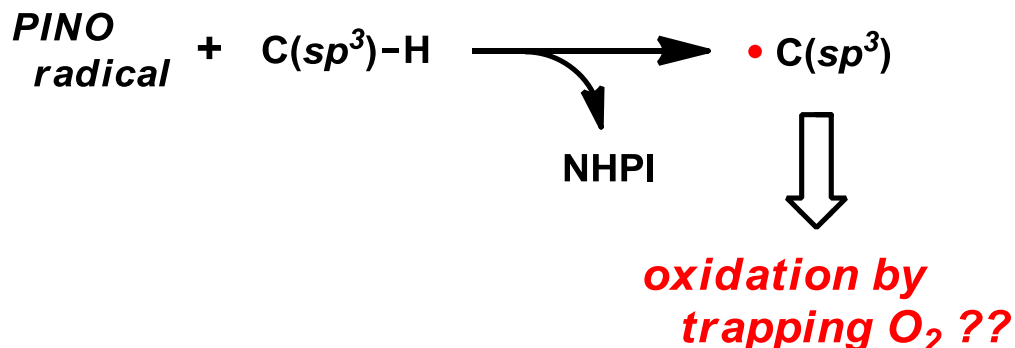
## - Electrochemical oxidation of alcohols

Masui, M. *et al.*
*Chem. Commun.* **1983**, 479.

# Alkane C($sp^3$)-H Oxidation – *Focusing on Prof. Ishii's Work*

**Key person: Prof. Ishii**

**Alkane oxidation using $O_2$**

**⬇**

**_Green_ oxidation of bulk chemicals ??**

*PINO radical* + C($sp^3$)–H → • C($sp^3$)

NHPI

*oxidation by trapping $O_2$ ??*

*Yasutaka Ishii* was born in Osaka, Japan, in 1941, graduated from Kansai University (Department of Engineering) in 1964. He received his Ph.D. degree under the supervision of Prof. Masaya Ogawa. In 1967, he was appointed assistant professor at Kansai University. He was a postdoctoral fellow at Colorado State University in 1980–1981. Since 1990 he has a full professor at Kansai University. He has received the Japan Petroleum Institute Award for Distinguished Papers in 1987, Divisional Award (Organic Synthesis) of the Chemical Society of Japan in 1999, and Award of the Synthetic Organic Chemistry, Japan (Yu-uki Gosei Kagaku Kyokai) in 1999. His current research interests include the development of practical oxidation reactions using molecular oxygen and hydrogen peroxide, homogeneous catalysis, petrochemistry, organometallic chemistry directed towards organic synthesis.
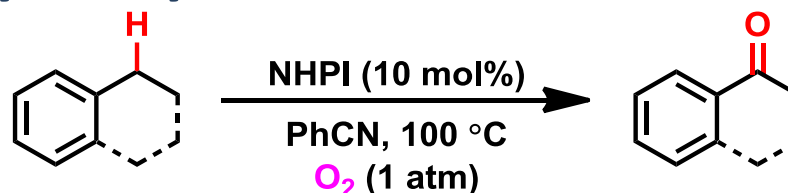
(*Adv. Synth. Catal.* **2001**, *343*, 393.)

# Alkane C($sp^3$)-H Oxidation – *Focusing on Prof. Ishii's Work*

## - Oxidation catalyzed by NHPI

*But conversions of simple alkanes are low...*



*generally conv. <50%*
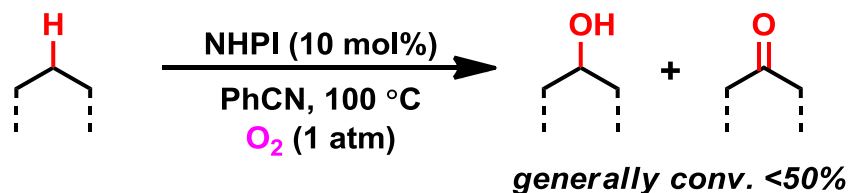
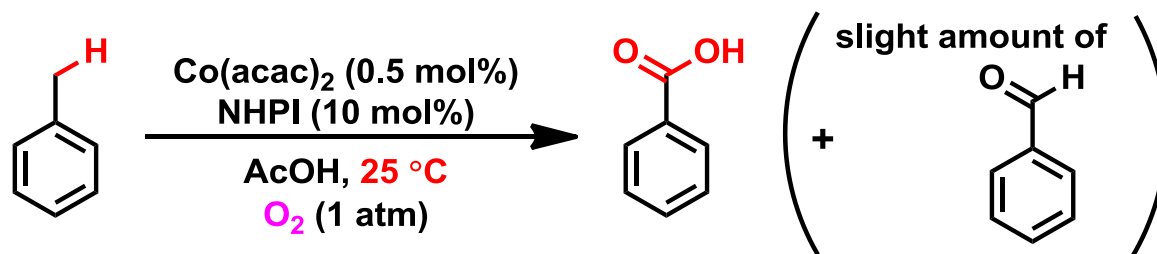## - Co-NHPI combined catalysis

*With broad substrate scope of simple alkane*
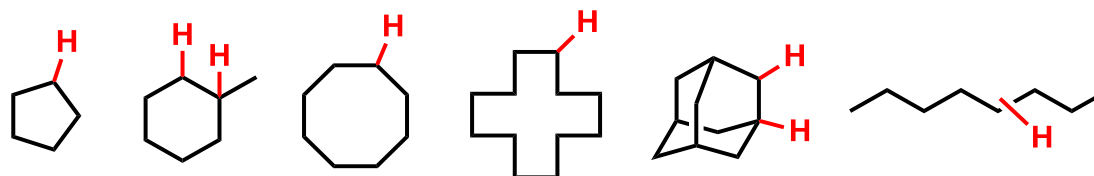
# Alkane C(*sp³*)-H Oxidation – *Focusing on Prof. Ishii's Work*
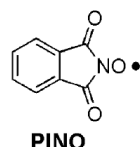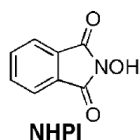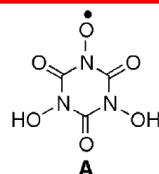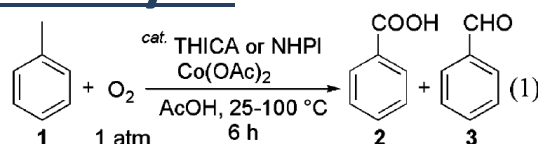
## - Co-NHPI catalysis at <u>room temp.</u>

Ishii, Y. *et al. JOC* **1997**, *62*, 6810.



Co(acac)$_2$ (0.5 mol%)
NHPI (10 mol%)

AcOH, **25 °C**
**O$_2$** (1 atm)

slight amount of

*First example of catalytic aerobic oxidation of toluene at rt.*

## - THICA catalysis

Ishii, Y. *et al. JOC* **2003**, *68*, 6587.



| run | catalyst (mol %) | temp (°C) | conversn (%) | yield (%) | |
|-----|------------------|-----------|--------------|-----------|-----|
| | | | | **2** | **3** |
| 1 | THICA (1) | 80 | 71 | 68 | 3 |
| 2 | NHPI (1) | 80 | 25 | 20 | 5 |
| 3 | NHPI (3) | 80 | 53 | 47 | 3 |
| 4 | THICA (3) | 80 | >99 | 93 | 2 |
| 5 | THICA (5) | 80 | >99 | >99 | nd |
| 6 | THICA (3) | 100 | >99 | >99 | nd |
| 7[b] | THICA (5) | 25 | 1 | nd | trace |
| 8[b] | NHPI (5) | 25 | 39 | 34 | 5 |

[a] **1** (3 mmol) was reacted under O$_2$ (1 atm) in the presence of THICA or NHPI and Co(OAc)$_2$ (0.5 mol %) in AcOH (5 mL) at 25−100 °C for 6 h. [b] 20 h.

*THICA allows low cat. loading due to stability of its radical*
*(PINO is subject to the decomposition)*

# What's The Mechanism of NHPI Catalysis ??

## - <u>O$_2$ uptake experiment</u>

Ishii, Y. *et al. JOC* **1996**, *61*, 4520.
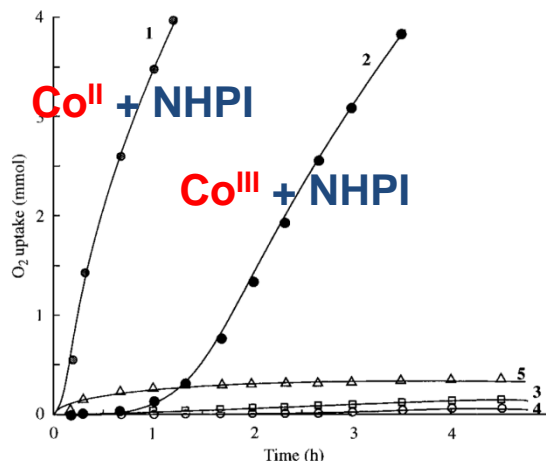
Co$^{II}$ + NHPI

Co$^{III}$ + NHPI

**Figure 1.** Time dependence curves of O$_2$ uptakes for the oxidation of ethylbenzene (**32**) under atmospheric pressure of dioxygen by various catalysts. Conditions: Ethylbenzene (**32**) (10 mmol) was allowed to react with dioxygen (1 atm) in acetic acid (25 mL) at 80 °C. (**1**) NHPI (10 mol %), Co(acac)$_2$ (0.5 mol %); (**2**) NHPI (10 mol %), Co(acac)$_3$ (0.5 mol %); (**3**) NHPI (10 mol %); (**4**) Co(acac)$_2$ (0.5 mol %); (**5**) AIBN (5 mol %), Co(acac)$_2$ (0.5 mol %).

*Co$^{II}$ is the active catalyst ??*
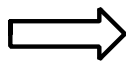*(Co$^{III}$ somehow reduced in situ.)*

## - <u>ESR measurement</u>

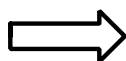Ishii, Y. *et al. JOC* **1997**, *62*, 6810.
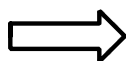
NHPI in PhCN, 80 °C ⟹ **PINO's peak observed**

NHPI in PhCN, 80 °C ⟹ **ESR silent**

NHPI in MeCN, rt ⟹ **ESR silent**

NHPI + Co(OAc)$_2$ in MeCN, rt ⟹ **PINO's peak observed**
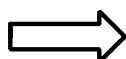
NHPI + Co(acac)$_3$ in MeCN, rt ⟹ **ESR silent**
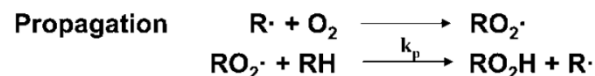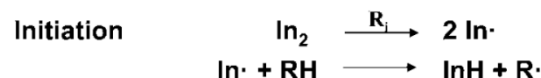**(And NR with Co(acac)$_3$)**
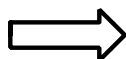
*PINO's ESR spectra*
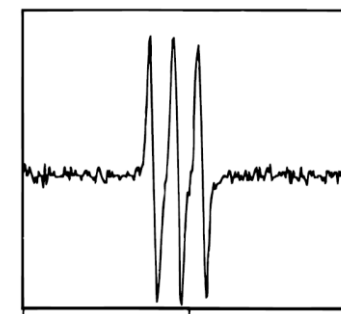
g=2.0073, A$_N$=0.423 mT

*Co$^{II}$ accelerates generation of PINO*

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# What's The Mechanism of NHPI Catalysis ??

## - General mechanism of free radical chain aerobic oxidation

**Initiation**
$$In_2 \xrightarrow{R_i} 2\,In\cdot$$
$$In\cdot + RH \longrightarrow InH + R\cdot$$

**Propagation**
$$R\cdot + O_2 \longrightarrow RO_2\cdot$$
$$RO_2\cdot + RH \xrightarrow{k_p} RO_2H + R\cdot$$

**Termination**
$$2\,RO_2\cdot \xrightarrow{k_t} RO_4R \longrightarrow ketone + alcohol + O_2$$

$$-d[RH]/dt = -d[O_2]/dt = k_p[RH] \times [R_i/2k_t]^{1/2}$$

$\Rightarrow$ *$Co^{II}$ acts as the initiator ??*

### *Key to efficient catalytic cycle:*

*1. Increase of the propagation rate*

*2. Decreasing of the termination rate*

**Table 2.** Rate constants per active hydrogen for hydrogen abstraction from RH.

| RH | Rate constant ($M^{-1}s^{-1}$) at 25 °C | | | |
|---|---|---|---|---|
| | $t$-BuOO$\cdot$ | ROO$\cdot$ | PINO | |
| PhCH$_3$ | 0.012 | 0.08 | 0.21[a] | 0.13[b] |
| PhCH$_2$CH$_3$ | 0.10 | 0.65 | 2.7[a] | 1.1[b] |
| PhCH(CH$_3$)$_2$ | 0.22 | 0.18 | 26.6[a] | 3.25[b] |
| PhCH$_2$OH | 0.065 | 2.4 | 5.7[a] | 14.2[b] |
| c-C$_6$H$_{12}$ | 0.003 | 0.53[c] | 0.05[a] | 0.002[b] |

[a] In PhH/10% CH$_3$CN.[13]
[b] In HOAc.[14]
[c] At 60 °C.
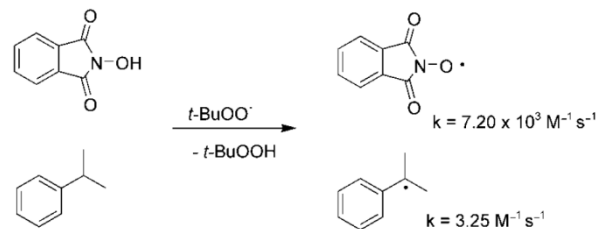
**Figure 9.** Rate constants for reaction of $t$-BuOO$\cdot$ with NHPI *vs.* cumene.

$k = 7.20 \times 10^3\ M^{-1}s^{-1}$

$k = 3.25\ M^{-1}s^{-1}$

$\Rightarrow$ *NHPI mediates radical propagation cycle ??*

# What's The Mechanism of NHPI Catalysis ??

## - Plausible mechanism (for toluene oxidation)

Ishii, Y. *et al.*
*JOC* **1997**, *62*, 6810.



**initiation**

**propagation**
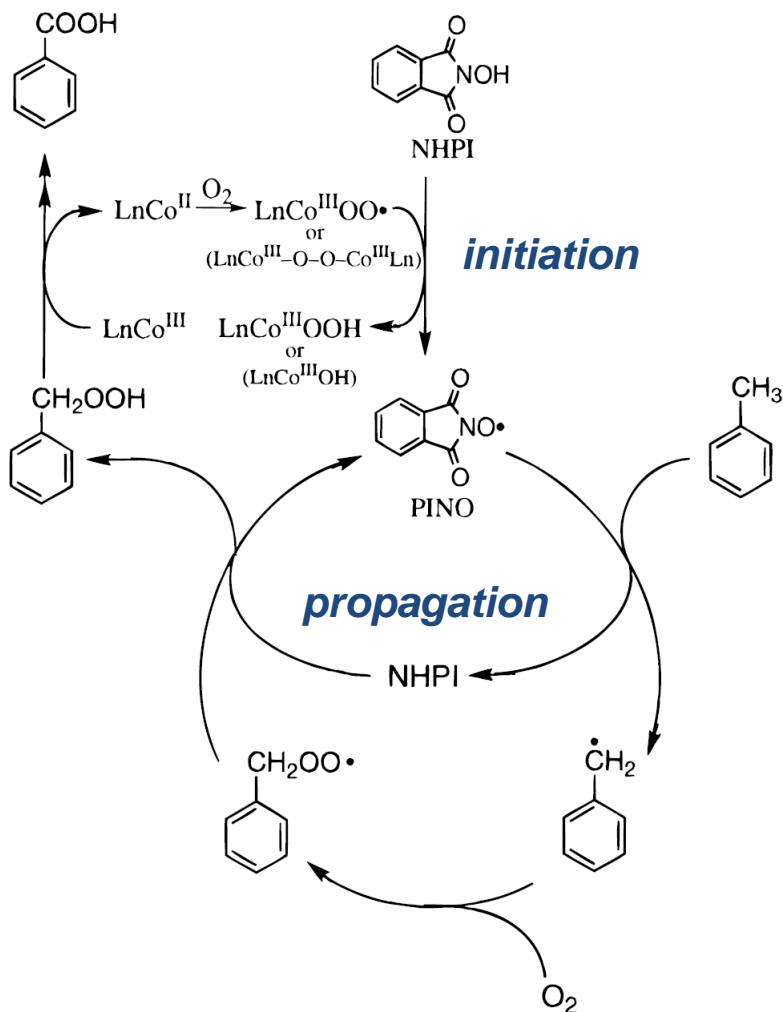
<span style="color:red">***But***</span>

*some questionable points remain...*

*How is alcohol product generated ??*
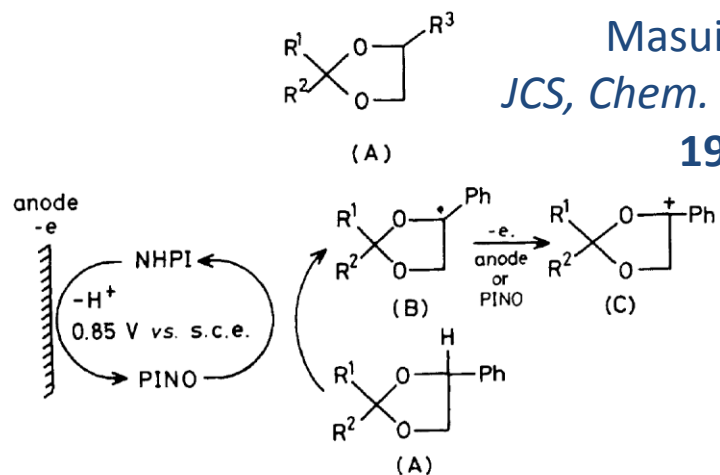*Reduction by Co[II] ??*

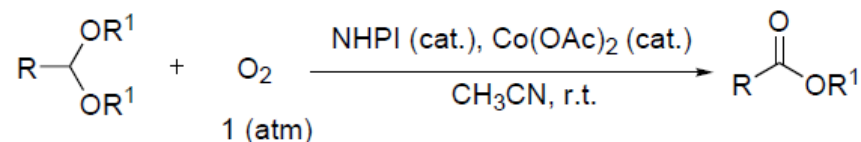*Peroxide really oxidized by Co[III] ??*
*Not via formation of aldehyde ??*

*etc.*

# Ethers/Acetals Oxidation

*BDE of a-C-H bond of ethers/acetals is weak (xx kcal/mol)*
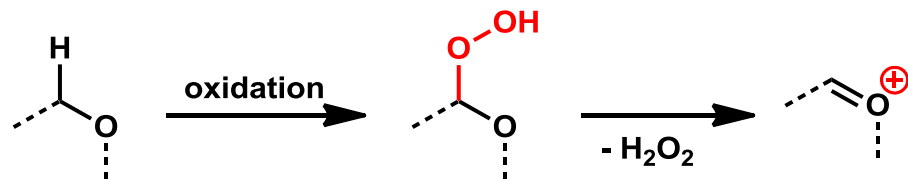
*Facile radicalic C-H cleavage by PINO*

Masui, M. *et al.*
*JCS, Chem. Commun.*
**1985**, 1484.

Karimi. B. *et al.*
*Synthesis* **2003**, 2373.



**Scheme 1**

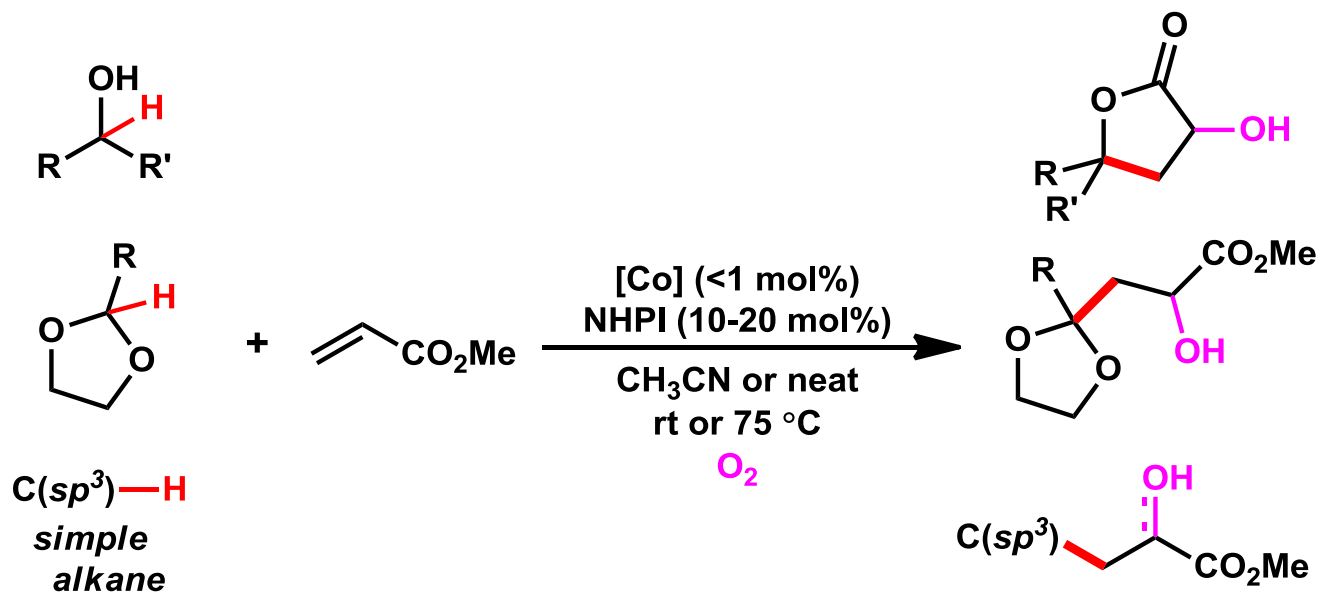**Oxidation affords
cation equivalent**

# Application for C-C Bond Formation

## - Radicalic C-C bond formation

*Trap the formed carbon radical by carbon electrophile (e.g. Michael acceptor) before trapped by oxygen*
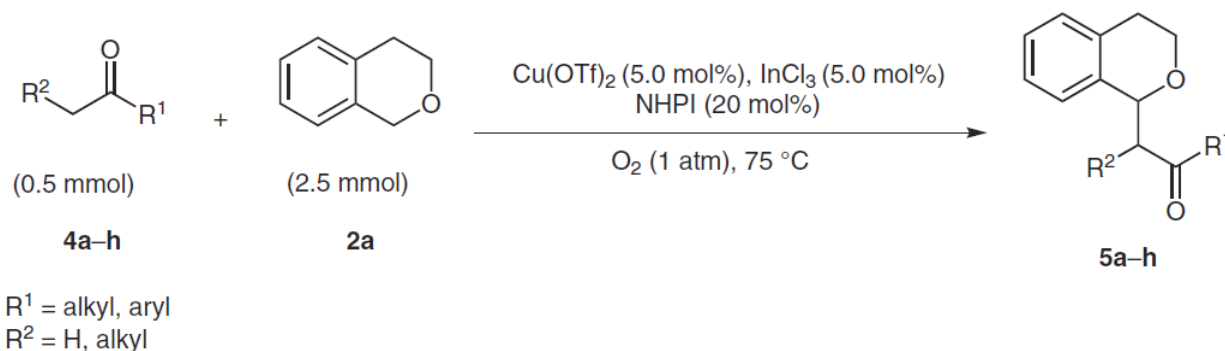
➡ *Radicalic C-C bond formation ??*

Ishii, Y. *et al. Chem. Commun.* **2000**, 613; *Chem. Commun.* **2000**, 2457; *JOC* **2001**, *66*, 6425.

# Application for C-C Bond Formation
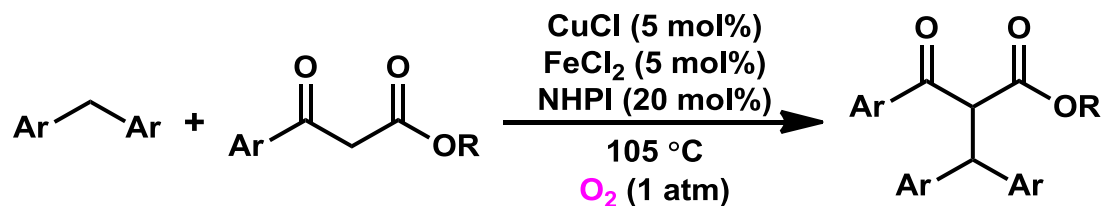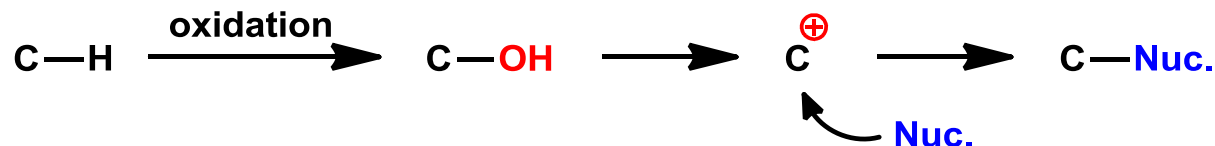
## - Cross-dehydrogenative coupling (CDC)

Li, C.-J. *et al. Synlett* **2009**, 138.



$R^1$ = alkyl, aryl
$R^2$ = H, alkyl

Li, C.-J. *et al. TL* **2010**, *51*, 1172.



*Reaction proceeds via formation of cation intermediate ??*

# Today's Contents

1. Fundamentals of *N*-Oxy Radical Species

2. Aminoxyl Radical-Mediated Reactions

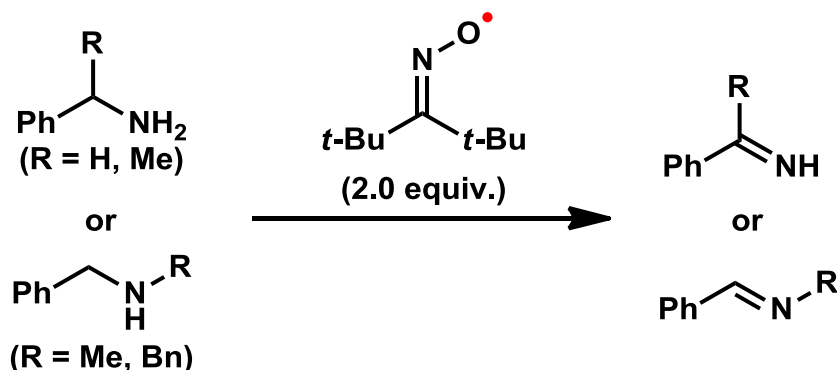3. Imidoxyl Radical-Mediated Reactions

4. Iminoxyl Radical-Mediated Reactions

5. Perspectives
   – *For exploration of novel & efficient N-oxy radical catalysis*

# Iminoxyl Radical-Mediated Reactions

## - Amine oxidation with stoichiometric iminoxyl radical

Mendenhall, G. D. *et al.*
*JOC* **1985**, *50*, 5382.



## - Phenol oxidation with stoichiometric iminoxyl radical

Mendenhall, G. D. *et al.*
*JOC* **1986**, *51*, 5390.



*No reports on use of iminoxyl radical as catalyst. Why…??*

# Today's Contents

1. Fundamentals of *N*-Oxy Radical Species

2. Aminoxyl Radical-Mediated Reactions

3. Imidoxyl Radical-Mediated Reactions

4. Iminoxyl Radical-Mediated Reactions

5. Perspectives
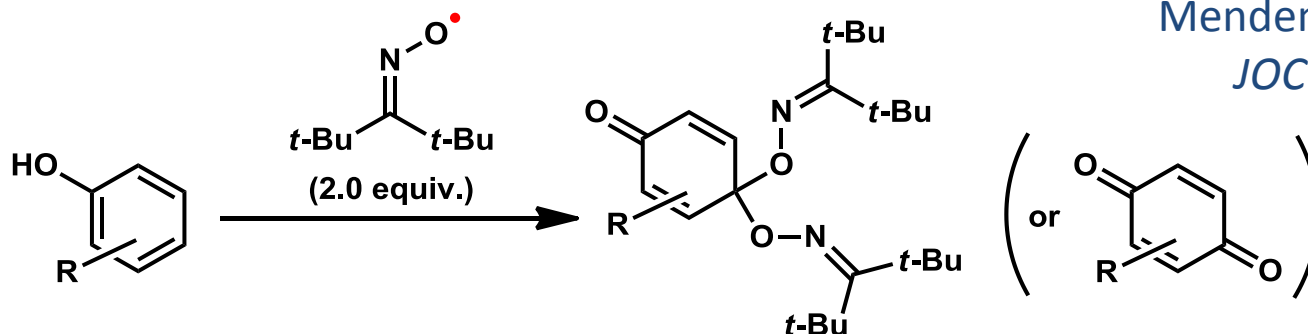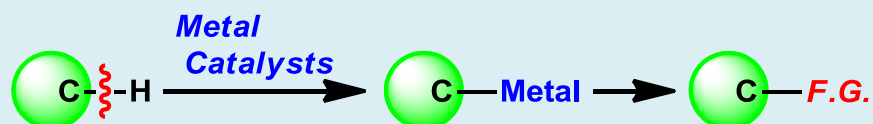    – *For exploration of novel & efficient N-oxy radical catalysis*

# Toward C-H Bond Functionalization
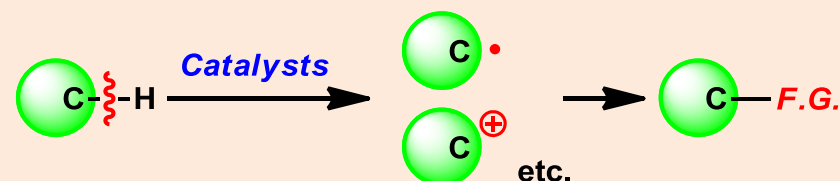
## Inner-sphere C-H functionalization

C—§—H → **Metal Catalysts** → C—**Metal** → C—*F.G.*

### Advantages

- **Many catalysis & reaction mode**
- **Selectivity**

### Disadvantages

- **Harsh conditions**
- **Directing group**
- **Noble metal catalysts**
- **Only unhindered C-H bond**

## Outer-sphere C-H functionalization

C—§—H → **Catalysts** → C• / C⊕ etc. → C—*F.G.*

### Advantages

- **Cheap metal/organocatalysts**
- **Applicable for hindered C-H bond**

### Disadvantages

- **Harsh conditions**
- **Selectivity**
- **Only limited examples**

➡ *Can we realize efficient outer-sphere C-H functionalization by overcoming current disadvantages ??*

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# How to Overcome Disadvantages ??

*For utilization of N-oxy radical toward outer-sphere C-H functionalization...*

- Harsh condition is often necessary

- Chemoselectivity between several C-Hs

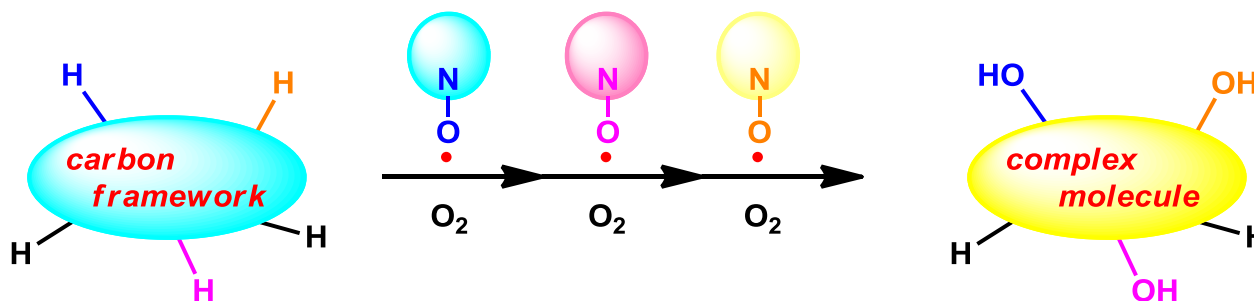        ➡ New *N*-oxy radical having <u>**more suitable BDE**</u>

New catalyst design based on strict strategy
(*e.g.* BDE theory) is important...??

# Future Potentiality 1 – *Sequential C-H Oxidation*

**In highly oxidized, complex molecule synthesis...**

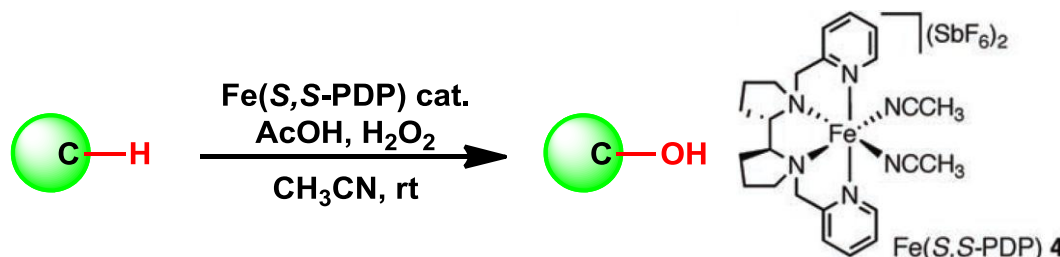*Introduction of FGs <u>at the late stage</u> is ideal.*

**Concept:**



**Each C-H has each BDE** ➡️ *Selectively cleaved by N-O catalyst having similar BDE in kinetically controlled reaction ??*
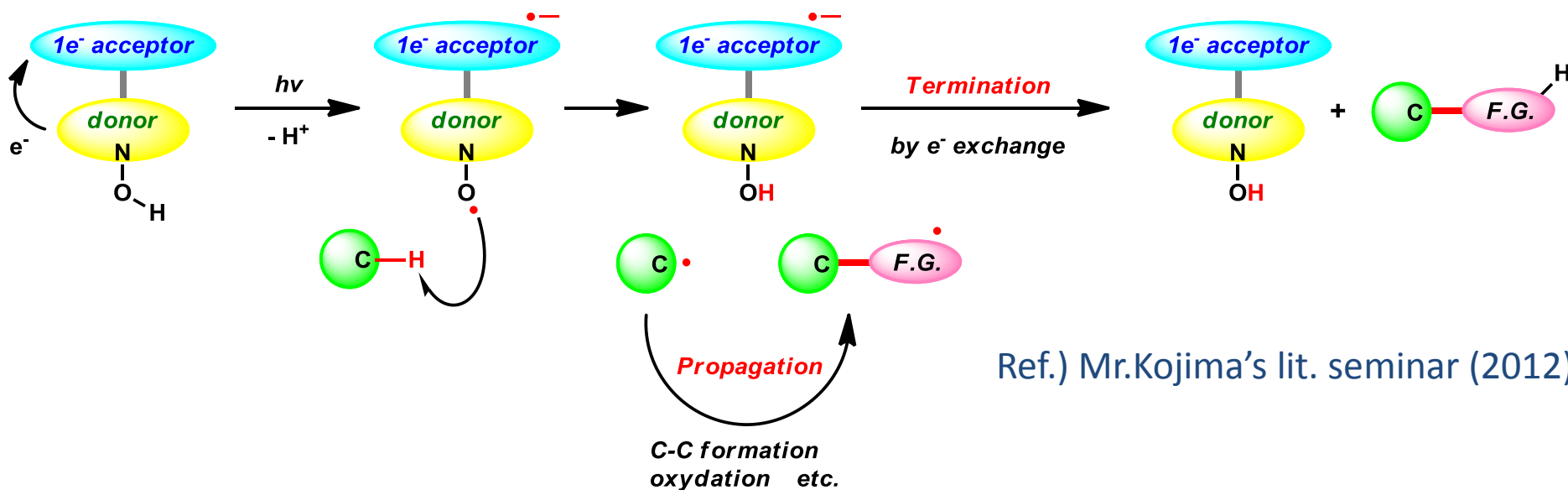
**Related work:**    White, M. C. *et al. Science*, **2007**, *318*, 783

# Future Potentiality 2 – *Photoredox N-Oxy Radical Catalyst*

**Activation of unreactive C-H bonds**

*= thermodinamically unfavorable process*

**This is the cause of need of harsh conditions…??**

➡ *Can we use photoenergy as energy source ??*

*Concept:*



Ref.) Mr.Kojima's lit. seminar (2012)

# References (Reviews)

"What's new in stable radical chemisty?"
Hicks, R. G. *Org. Biomol. Chem.* **2007**, *5*, 1321.

"Organocatalytic Oxidations Mediated by Nitroxyl Radicals"
Sheldon, R. A. *et al. Adv. Synth. Catal.* **2004**, *346*, 1051.

"Free Radical Functionalization of Organic Compounds Catalyzed by *N*-Hydroxyphtalimide"
Recupero, F. *et al. Chem. Rev.* **2007**, *107*, 3800.