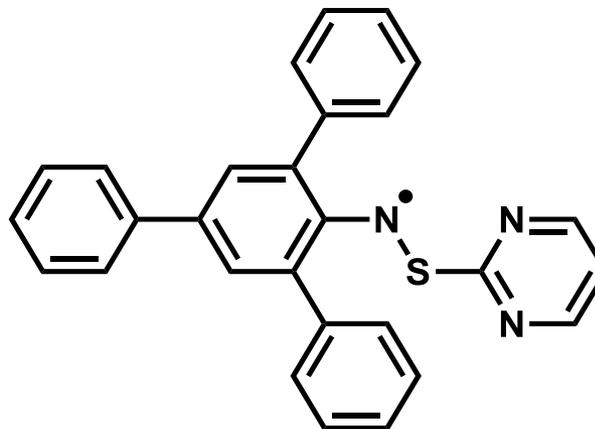
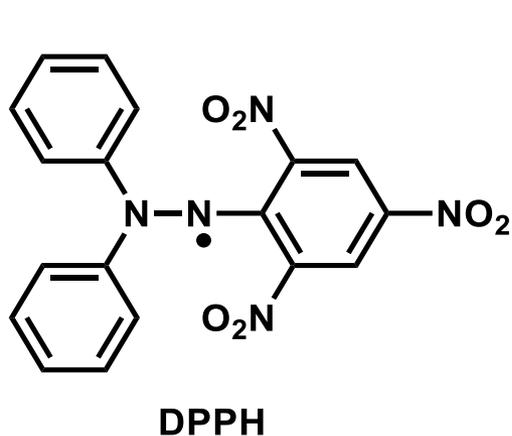


Nitrogen Centered Radical Ligands

2015. 7. 4.
Nagashima Nozomu

1. Introduction

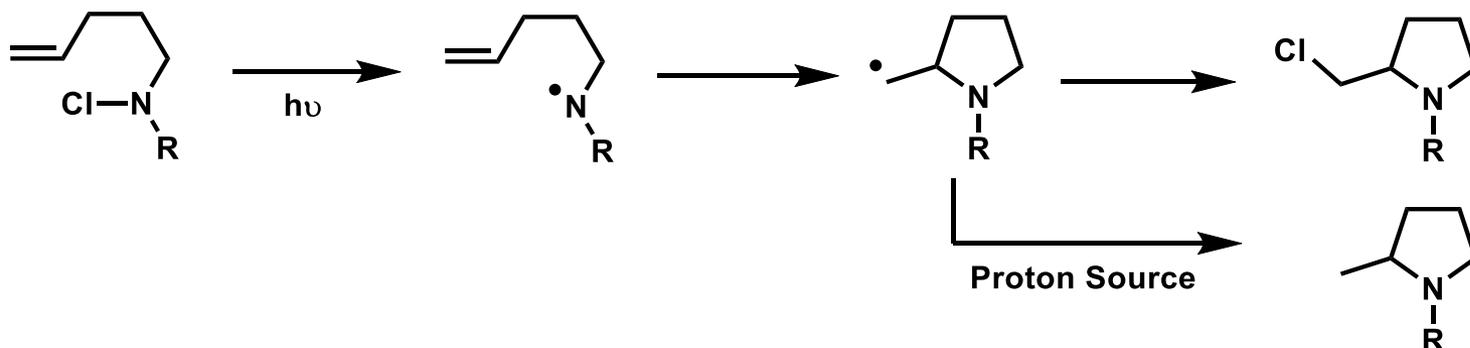
Aminyl radical



- 1) D. E. Williams, JACS, 1966, 88, 5665
- 2) Y. Teki et al. JOC, 2000, 65, 7889

- Sterically protected aminyl radicals were reported and play an important role in chemical processes.
- Resonance effect by electron donating group stabilizes N radical.

Preparation and Reactivity of N radical



- Reactive aminyl radicals are also formed thermally or photolytically by homolytic bond cleavage or by N oxidation.
- These N radicals are high reactive and short-lived intermediate

L. Stella *et al.* *ACIE*, 1983, 22, 337

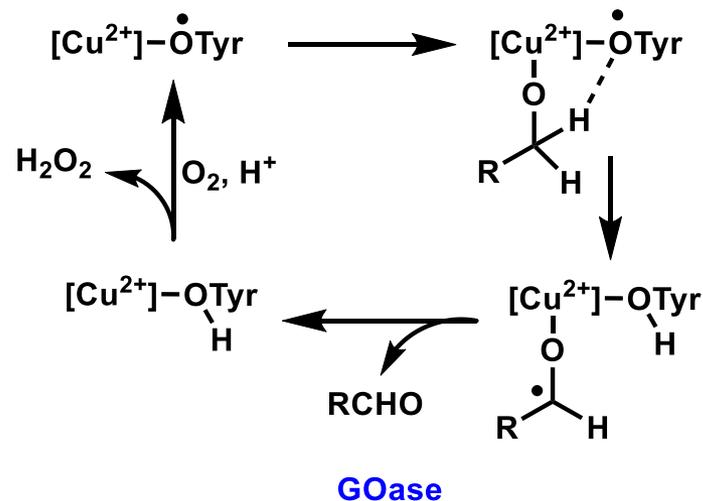
{
 Sterically protected N radical
 Short-Lived N radical (Formed in reaction)
Metal-Coordinated N Radical

Metal coordinated N radicals should show New Reactivity

Metal Coordinated N radical

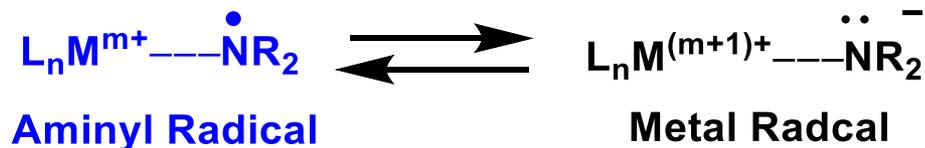
- Advantage

1. Sometimes becomes Catalysis.
2. Bioinspired Reactivity.
3. N-Radical is more reactive than O-radical.



Arch. Biochem. Biophys. **2005**, 433, 227

- N radical is really formed?



- Electron is sometimes localized at the metal.
→ Metal Radical can not react as N radical.
- Metal should stabilize N radical by electron transfer.

Some analyses (EPR, DFT, X-ray analysis etc..) are needed.

Electron Paramagnetic Resonance (EPR)

- Method for studying materials with unpaired electrons.
- EPR is like NMR for electron spin.

□ g value

$$\Delta E = g\mu_B B_0$$



$$g = \Delta E / \mu_B B_0$$

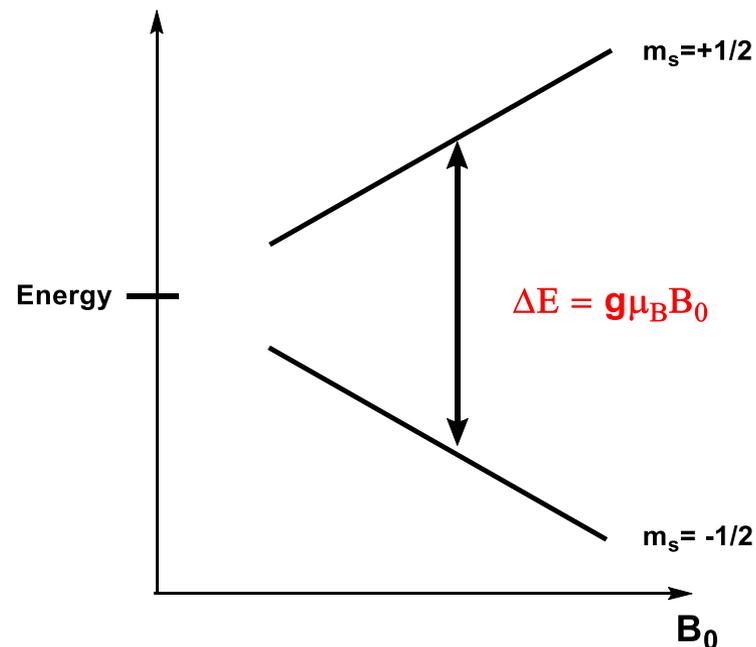
μ_B : Bohr magneton

B_0 : Magnetic strength

Free Radical: $g = 2.0023$

Organic Radical: $g \doteq 2$

Organometallic Radical $0 < g < 6$



- g value is parameter for evaluating where radical is localized.

Electron Paramagnetic Resonance (EPR)

- Method for studying materials with unpaired electrons.
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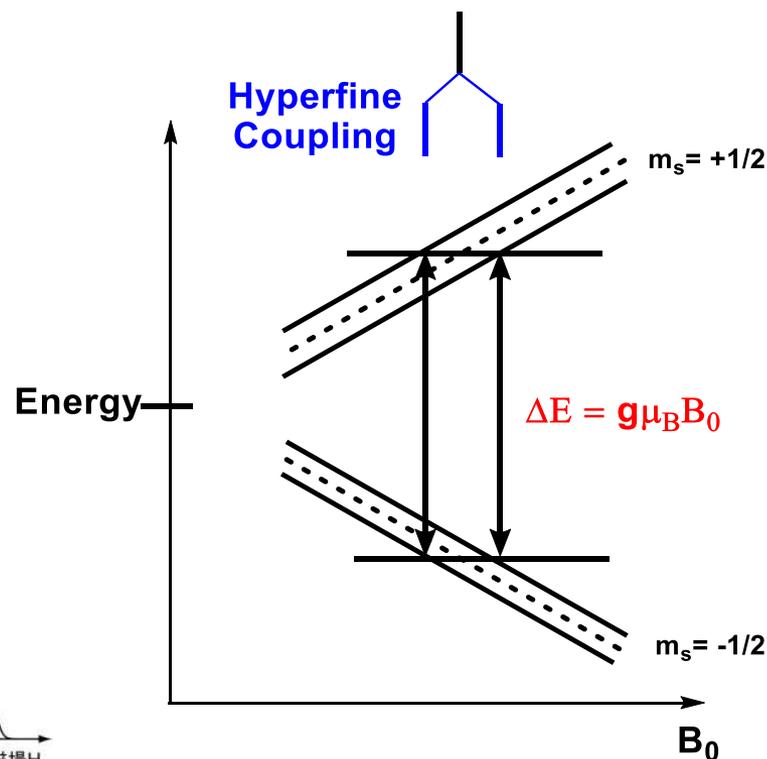
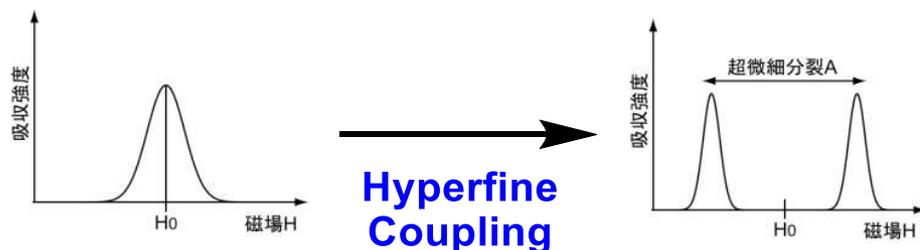
□ g value

$$\Delta E = g\mu_B B_0$$

$$g = \Delta E / \mu_B B_0$$

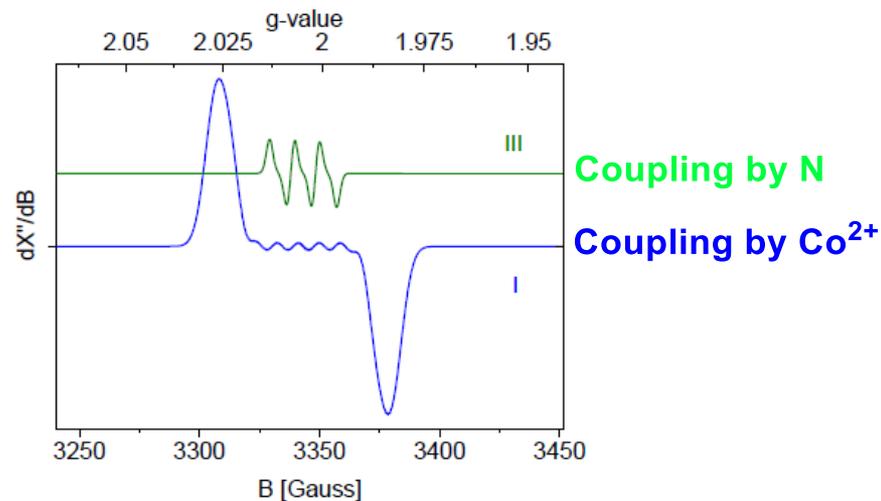
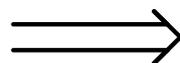
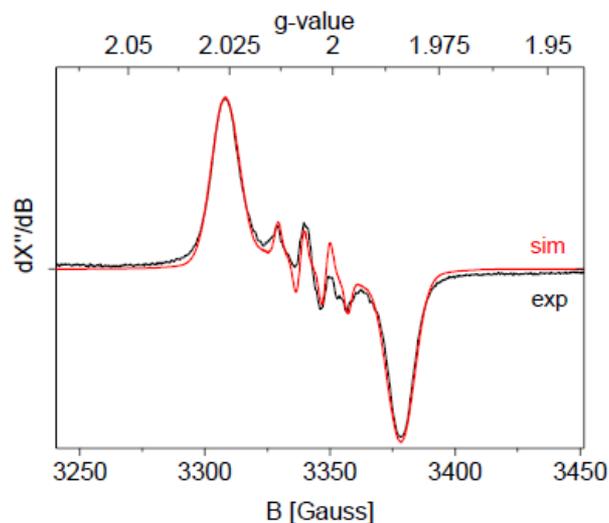
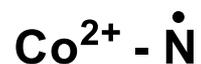
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Free Radical: $g = 2.0023$
 Organic Radical: $g \doteq 2$
 Organometallic Radical $0 < g < 6$



- g value is parameter for evaluating where radical is localized.

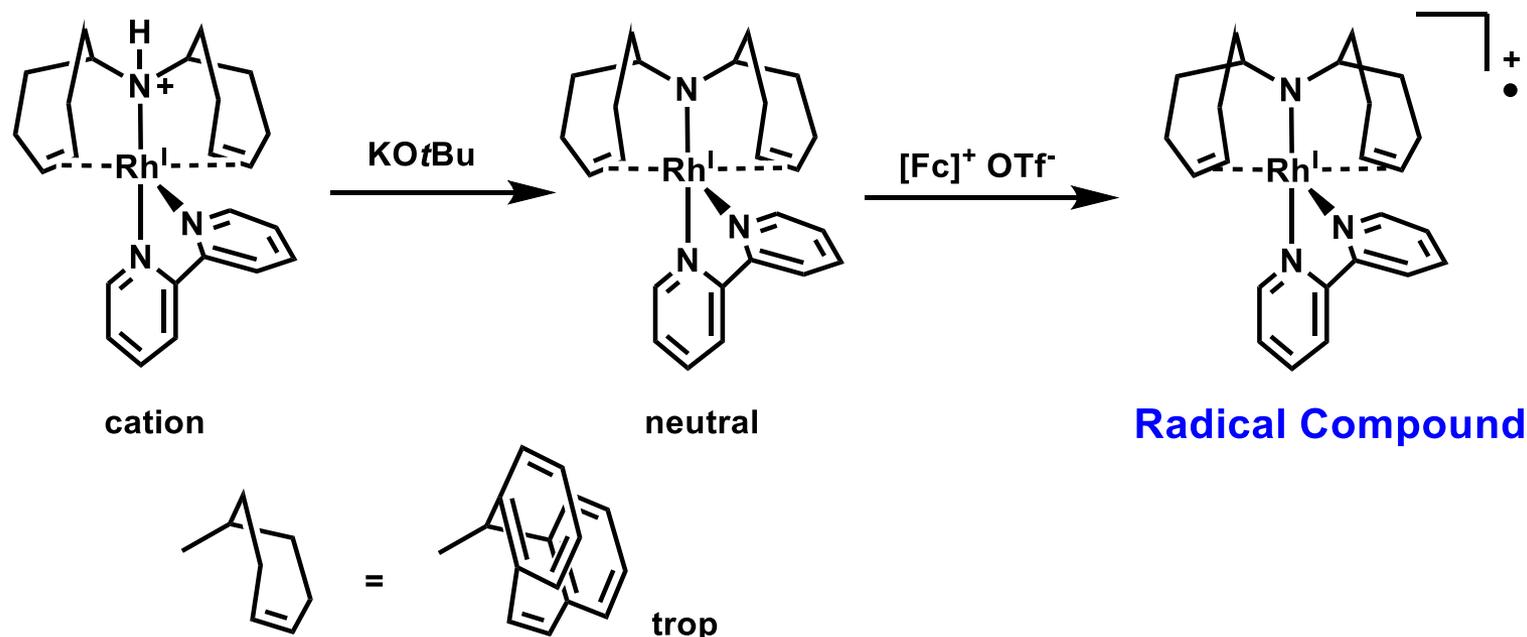
Examples of EPR Spectra



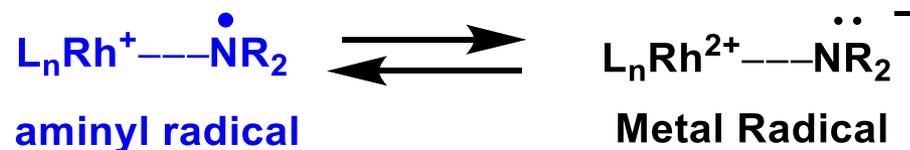
- It is difficult to evaluate EPR spectrum because each peak overlaps.
- Method: Compare calculated spectra and experimental data.

2. Aminyl Radical Observation

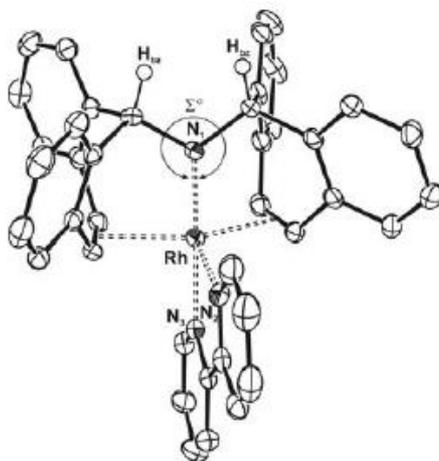
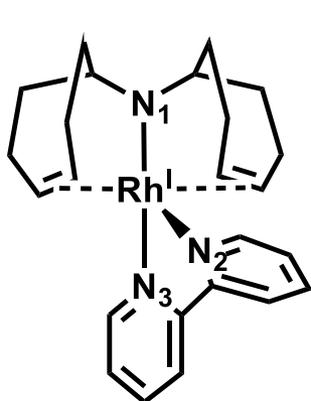
First Example of Synthesis of Stable Aminyl Radical



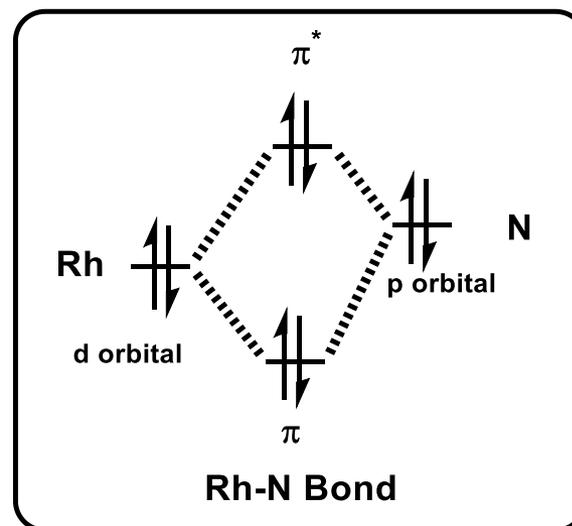
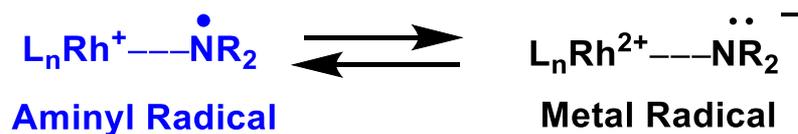
- Aminyl radical compound was synthesized through deprotonation and oxidation.
- d⁸-Rh(I) is suitable for stabilizing N radical.
- Trop moiety contributes as Shield of N radical.
- Aminyl radical is really formed??



Aminyl radical or Amido? (1)

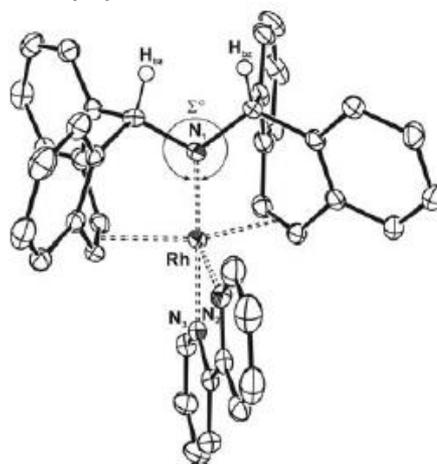
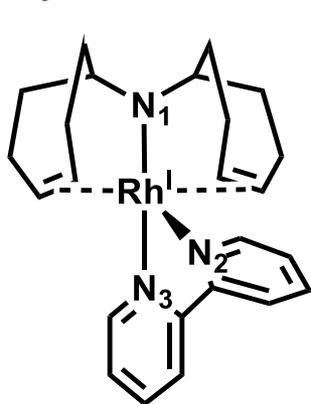


	Rh-N ₁ (Å)	Σ°
cation	2.090	345.1°
neutral	2.045	341.5°
radical	1.936	358.9°

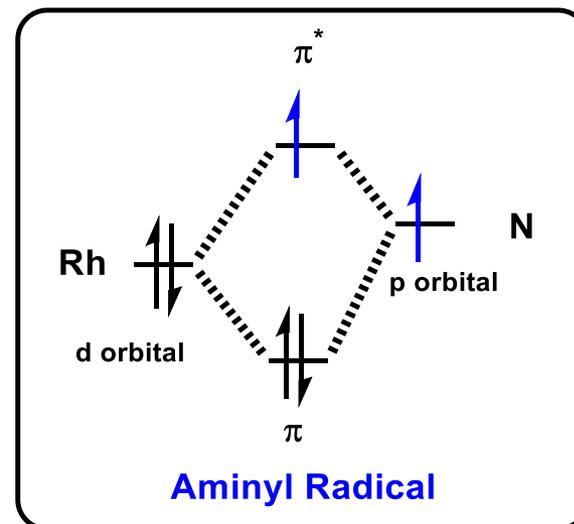
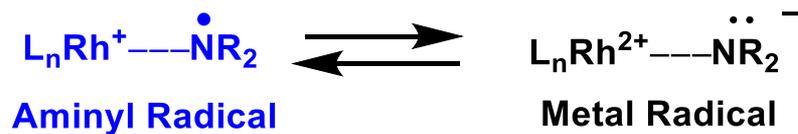


- Almost trigonal planar around N1 suggests the oxidation mainly occurs at N1 atom.
- Shortening of Rh-N1 implies aminyl radical complex.

Aminyl radical or Amido? (1)



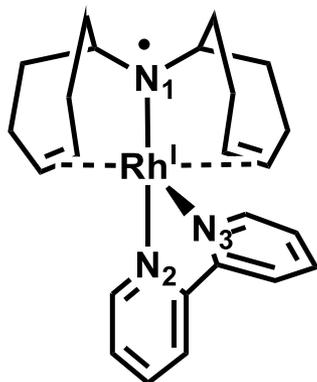
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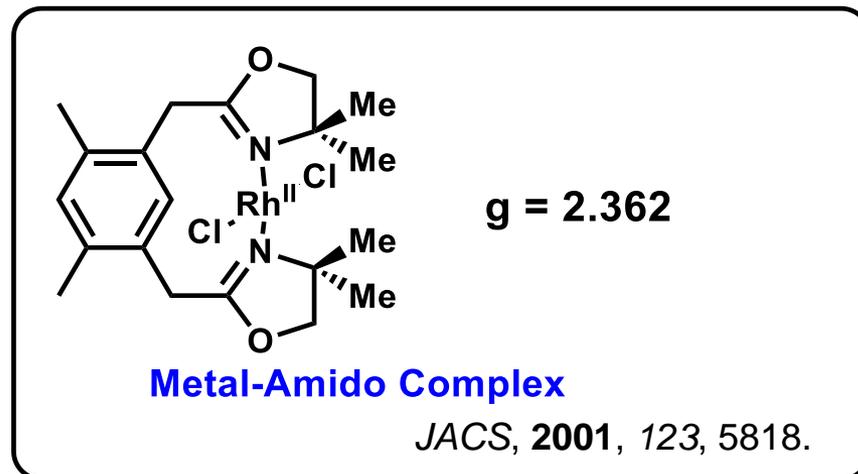
Aminyl radical or Amido? (2)

□ EPR spectrum

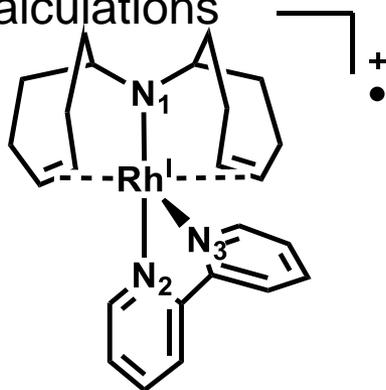


$g = 2.0512$

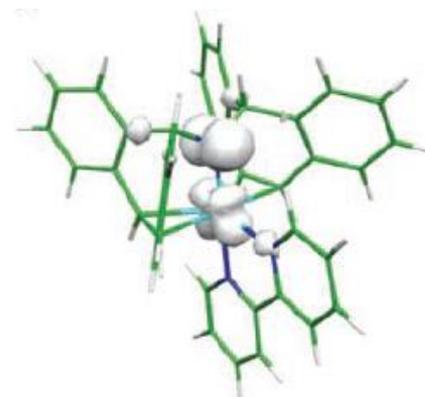
- g value is near to 2.00 → Radical is also delocalized on N?



□ DFT calculations



≡



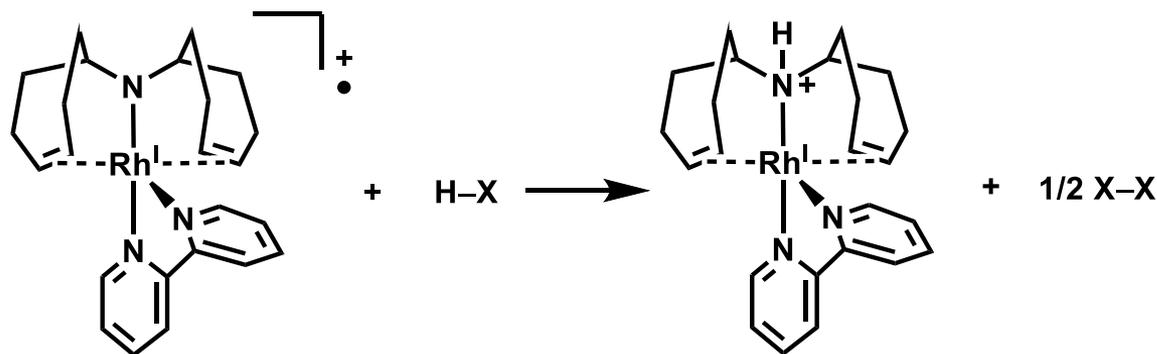
Spin density

$N_1 = 56\%$

$Rh = 30\%$

- More than half of radicals are on N_1

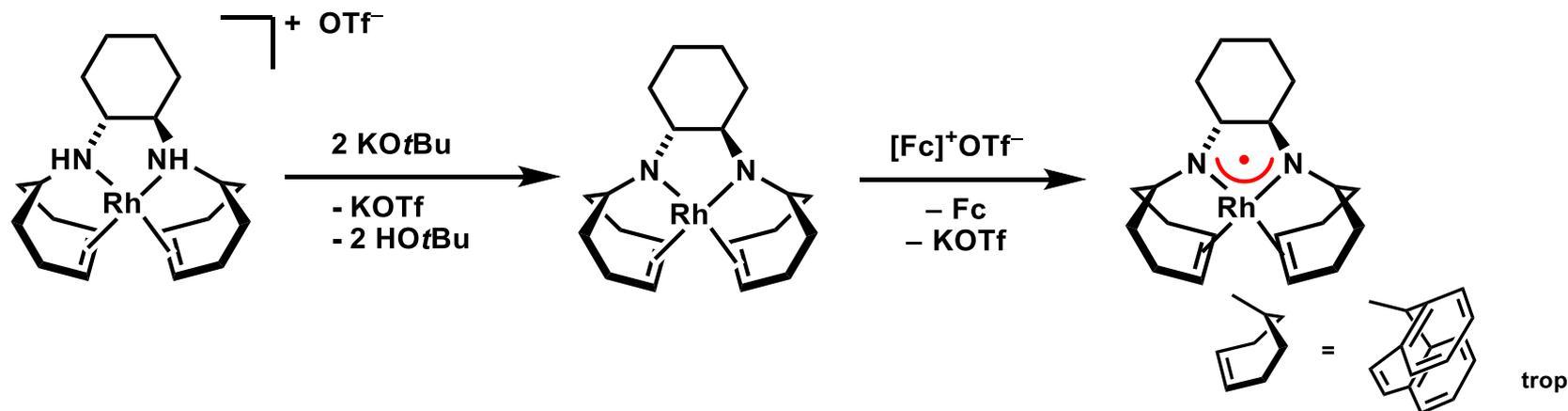
Reactivity of Aminyl Radical



Entry	HX	BDE (X-H)	Reaction	Product X-X
1	Bu ₃ Sn-H	308.5	Yes (fast)	Bu ₃ Sn-SnBu ₃
2	PhS-H	348.7	Yes (fast)	PhS-SPh
3	<i>t</i> BuS-H	>380.0	Yes (slow)	<i>t</i> BuS-StBu
4	MeOOCCH ₂ S-H	>380.0	Yes (slow)	MeOOCCH ₂ S-SCH ₂ COOMe
5	PhO-H	376.0	No	No
6	Ph ₃ Si-H	356.0	No	No
7	Ph ₂ CH-H	343.0	No	No
8	Ph ₃ C-H	339.0	No	No

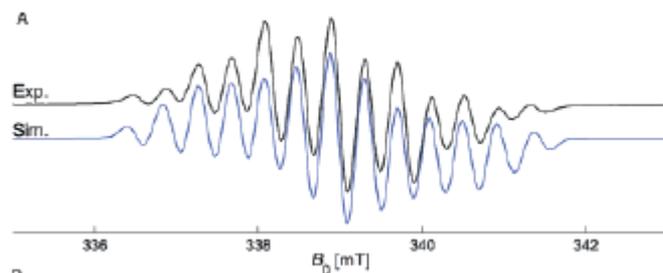
- Aminyl radical reacts with Sn-H bond and S-H bond.
- This aminyl radical is nucleophilic radical because thiyl radical is known as electrophilic radical.

Observation of 16 electron Rh --- N radical



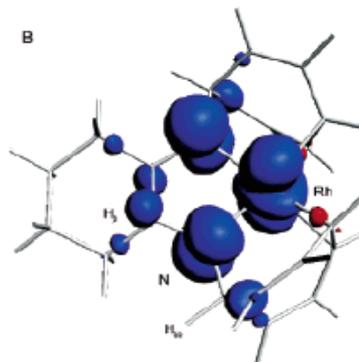
- This Rh catalyst also includes Trop substituents which stabilize aminyl radical.

EPR Parameters



$$g = 1.996$$

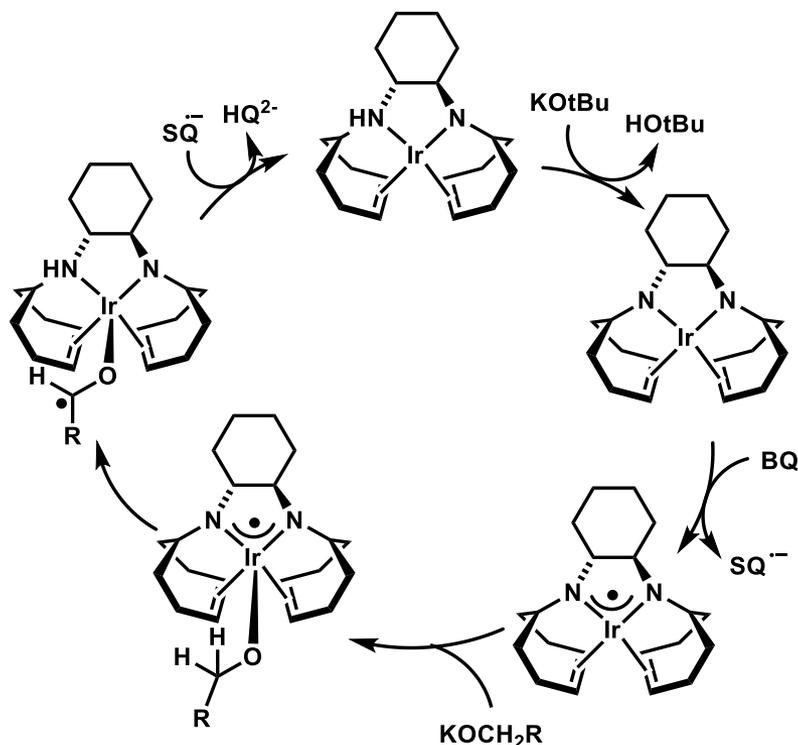
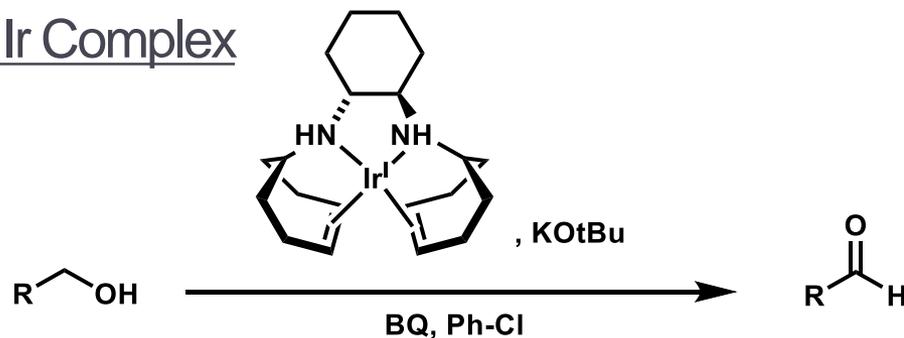
DFT calculations



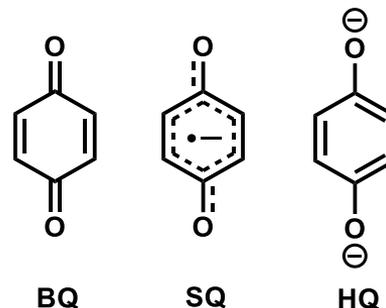
Spin density
N = 56% (28%*2)
Rh = 41%

Radical is delocalized on N.

Oxidation Reaction by Ir Complex



1. No reaction with only BQ, SQ, and HQ2-
2. No reaction without $KOTBu$
3. Violet SQ radical was detected in all the reactions.



Compounds which have affinity to metal can react with aminyl radical.

Substrate Scope

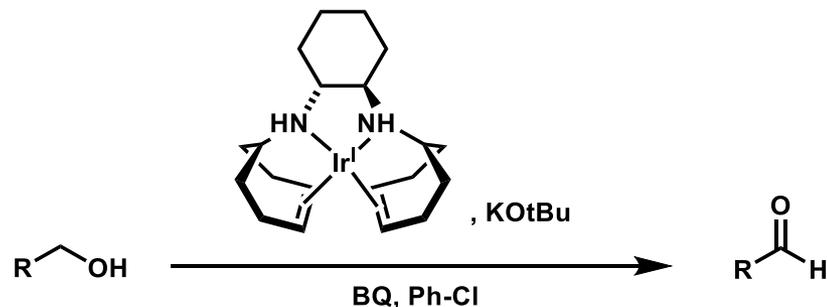


Table 1: Catalytic dehydrogenation of alcohols to aldehydes.^[a]

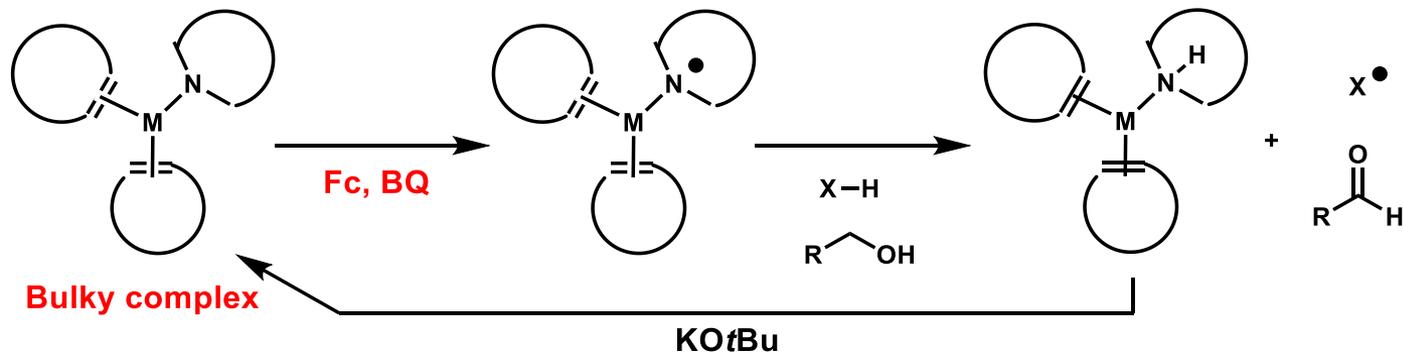
Entry	Substrate	Product ^[b]	Yield [%]	t	Entry	Substrate	Product ^[b]	Yield [%]	t
1			94	3 min	7			> 98	10 min
2			> 98	16 h ^[c]	8			> 98	12 h
3			70	1 h	9			> 98	2 h ^[c]
4			> 98	3 h ^[c]	10			> 98	1 h
5	CH ₃ OH	CH ₂ =O	64	4 h	11			> 98	10 min ^[d]
6	MeCH ₂ OH	MeCH=O	94	4 h	12			> 98	5 min

[a] With **BQ** as the H₂ scavenger, 0.01 mol% **2**, and 0.03 mol% KOtBu in chlorobenzene at 80 °C. [b] The identity of each product was verified by gas GC, MS, and ¹H NMR spectroscopy through comparison with a reference sample. [c] In chlorobenzene at 25 °C. [d] In chlorobenzene/THF (3:1) at 100 °C.

- Aliphatic alcohols are also dehydrogenated.
- Primary alcohols are converted into aldehydes

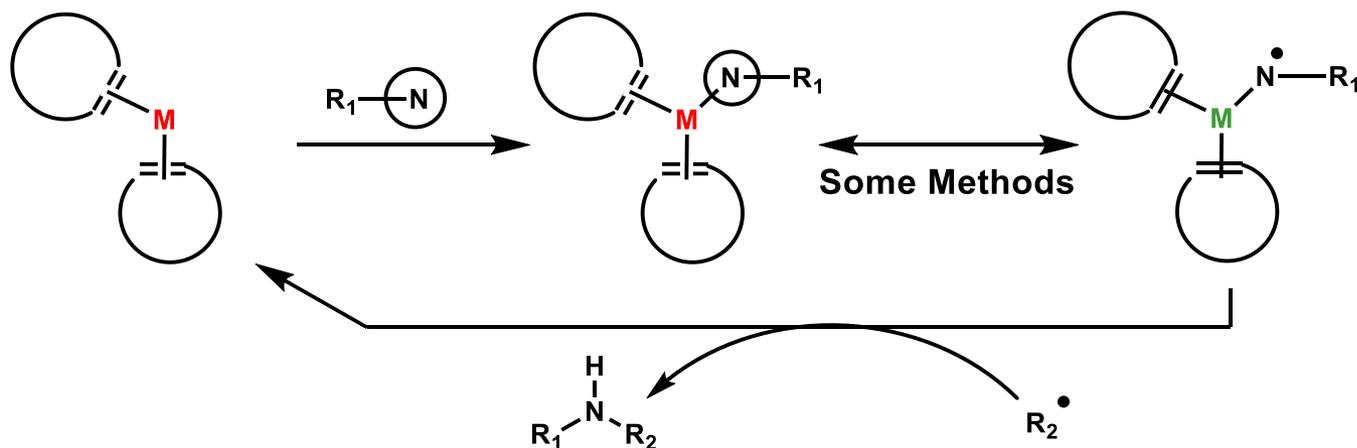
Other reactions by N radical

Grutzmacher's method



Reaction is limited to only dehydrogenation.

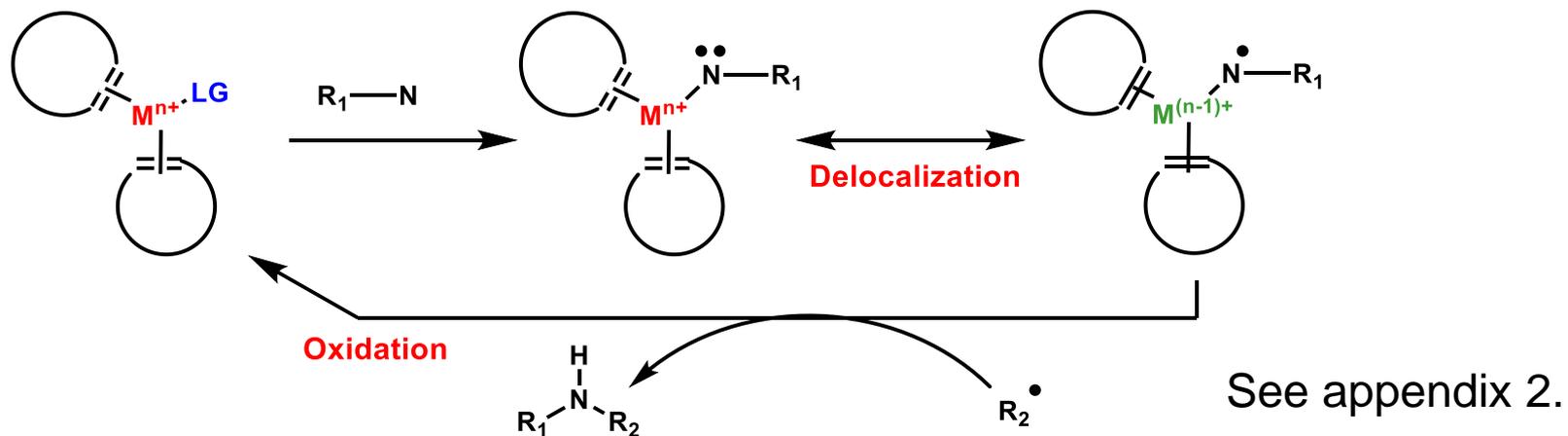
Potentials of other reactions



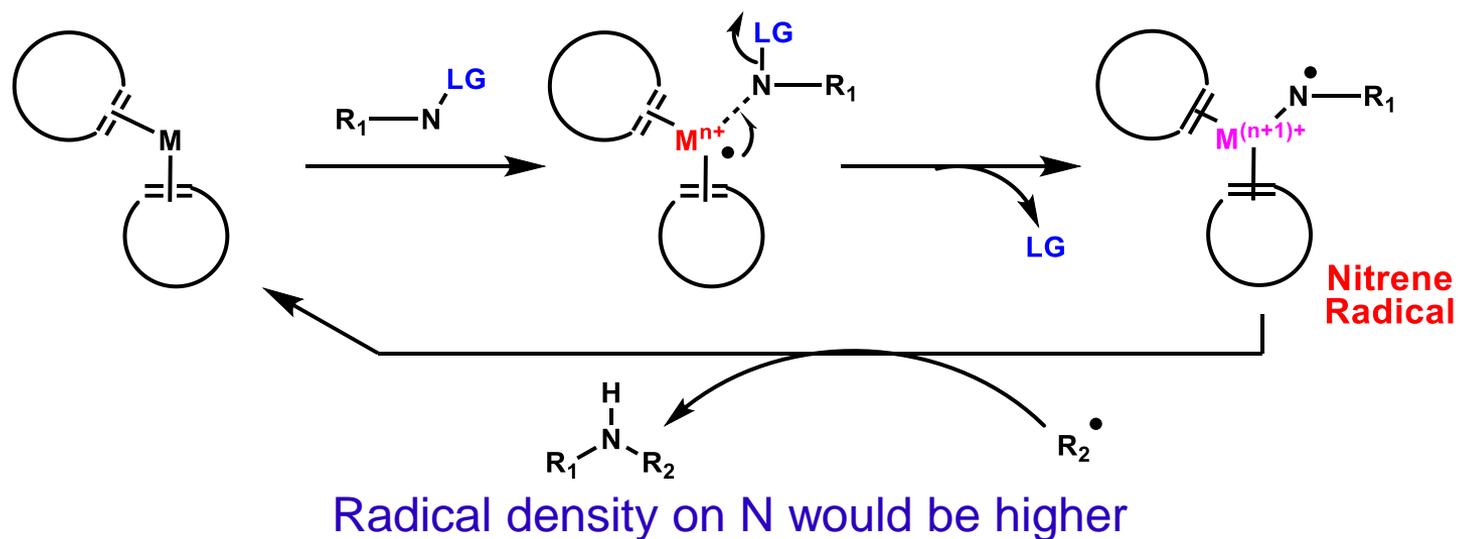
Amination would also proceed by introducing N as SM.

Other routes to get Ligand-Centered Radical

Aminyl Radical

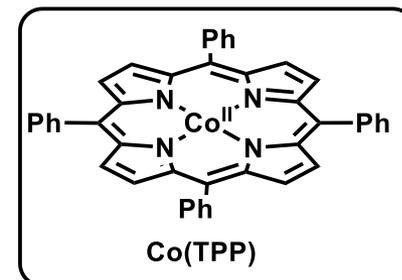
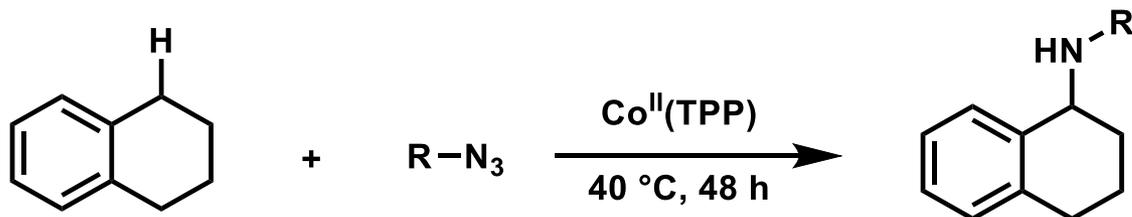


Nitrene Radical

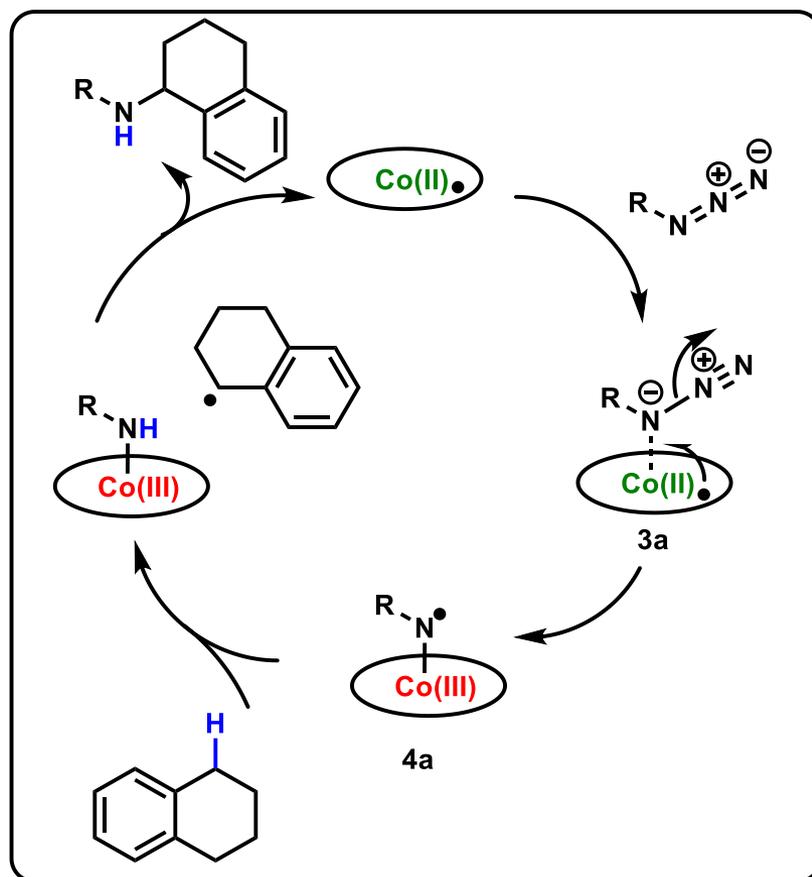


3. Nitrene Radical

Benzylic C-H amination



Reaction Mechanism



R-N ₃	yield ^b
	32%
	85%

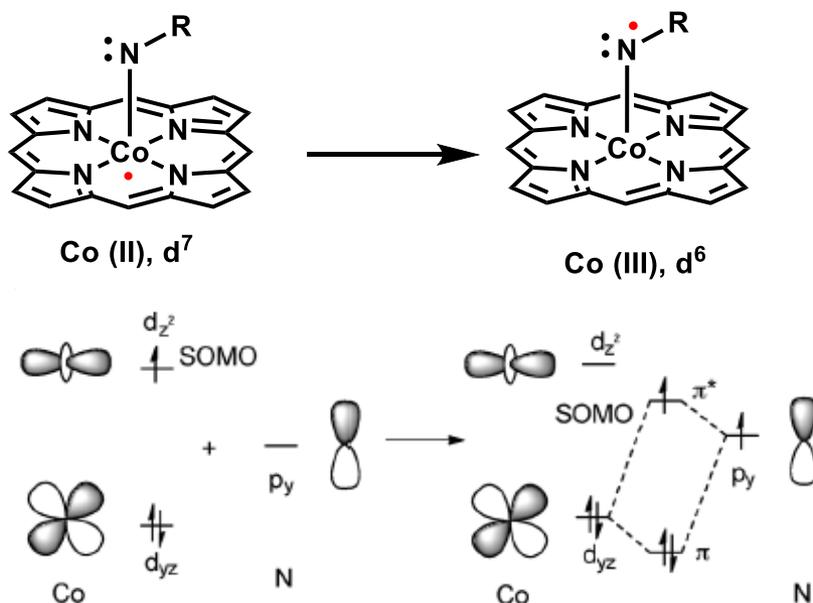
- Electron Transfer stabilizes nitrene and promotes nitrene formation. (**3a** to **4a**)
- Only Troc-Azide and Ts-Azide proceeded C-H amination reaction.

X. P. Zhang *et al.* *Organometallics*, **2010**, 29, 389

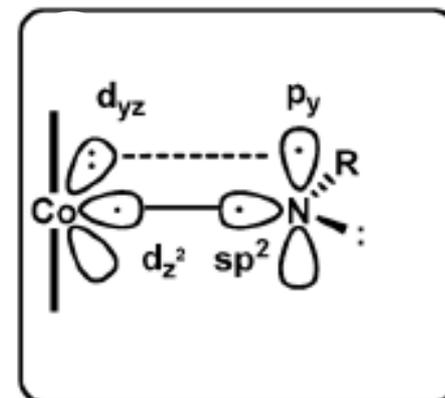
B. de Bruin *et al.* *JACS*, **2011**, 133, 12264.

The Formation of Nitrene Radical

Singlet Nitrene **4a**



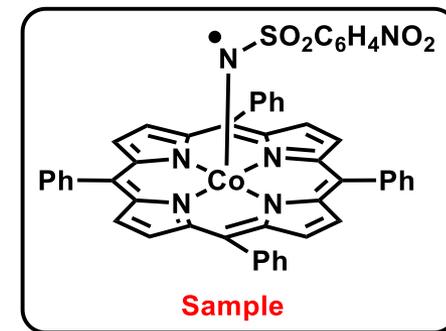
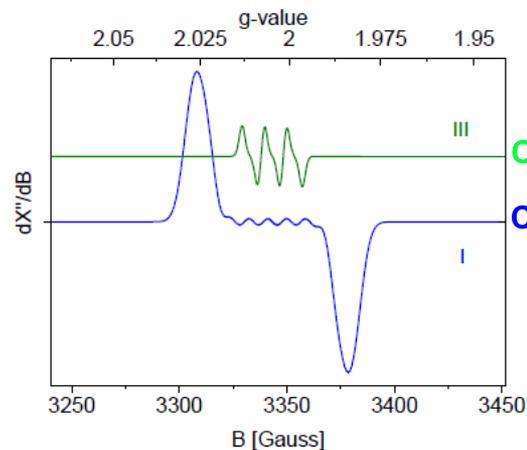
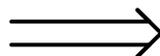
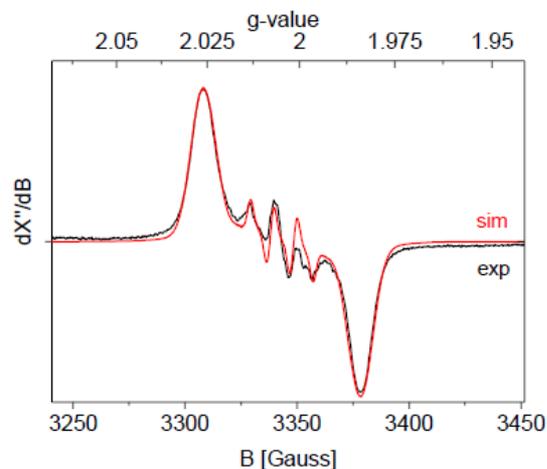
Triplet Nitrene **4a**



- Electron transfer from **d** orbital of Co to **p** orbital of N makes N radical. (Singlet Nitrene)
- **d** orbital of Co and **sp²** orbital of N makes covalent bond (Triplet Nitrene)

Radical is Really Generated on N?

- EPR spectrum shows N radical generation.

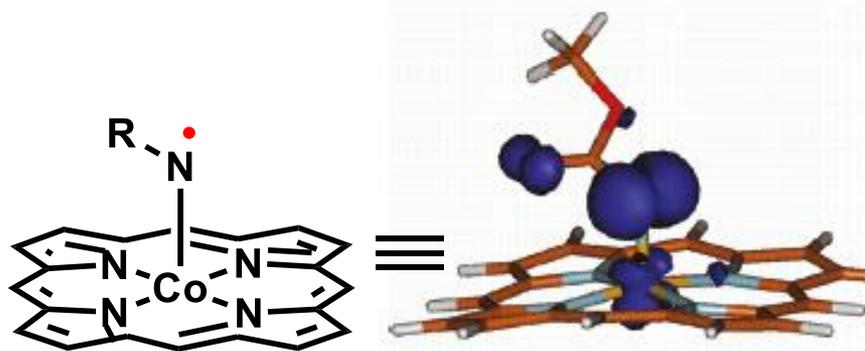


Coupling by N

Coupling by Co

$$g = 2.008$$

- Intermediate DFT calculation

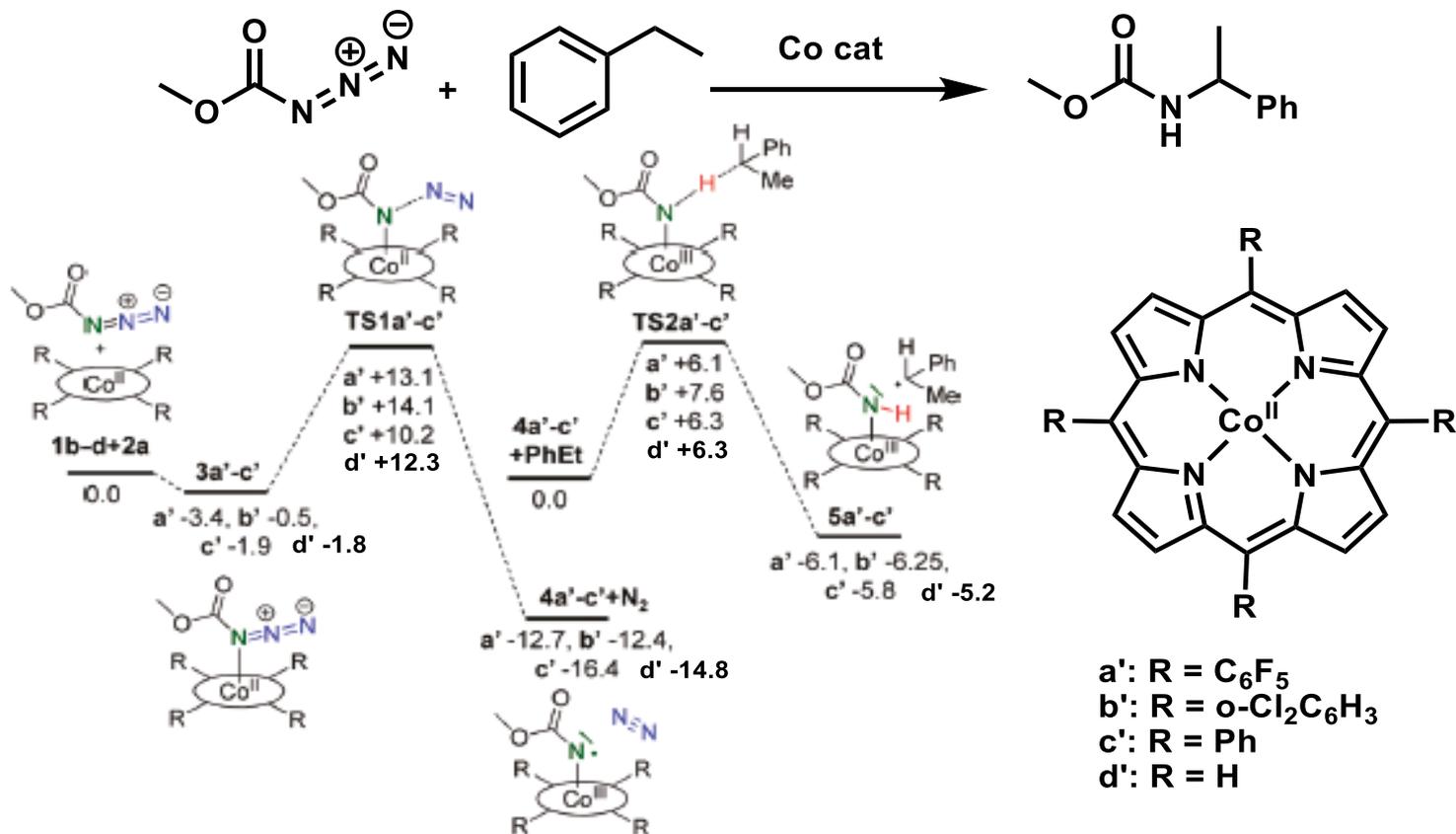


R	BP86 / def-TZVP		b3-lyp / def-TZVP	
	N	Co	N	Co
MeOC(O)-	74%	18%	95%	-6%
PhSO ₂ -	65%	27%	87%	2%

- Unpaired electron mainly resides on the nitrene nitrogen.

Reaction Profile by Substituents on Catalyst

Computational Model Reaction

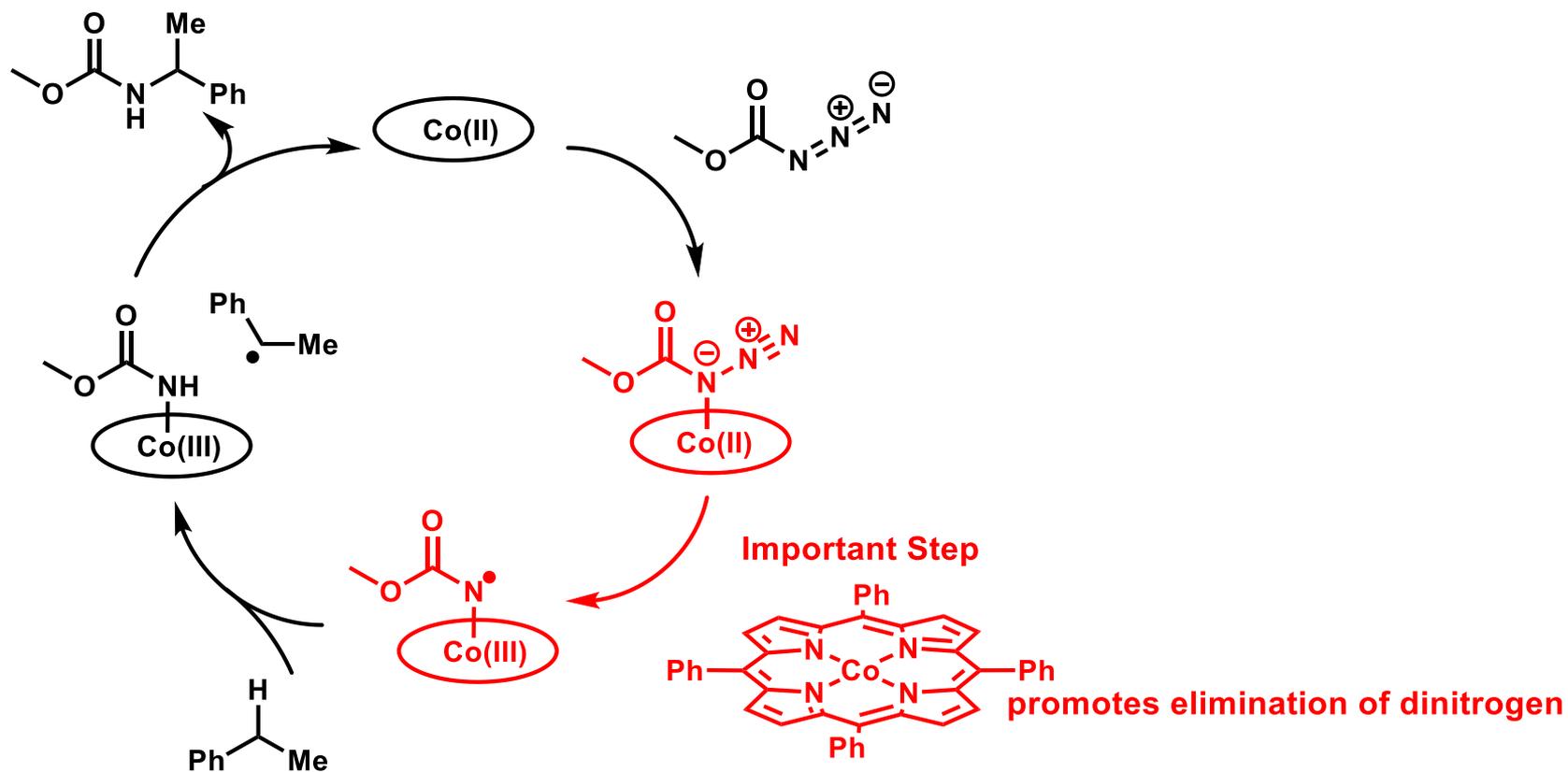


ΔH for the reaction of methyl azidoformate with ethyl benzene.

□ Mild electron-withdrawing substituent is best

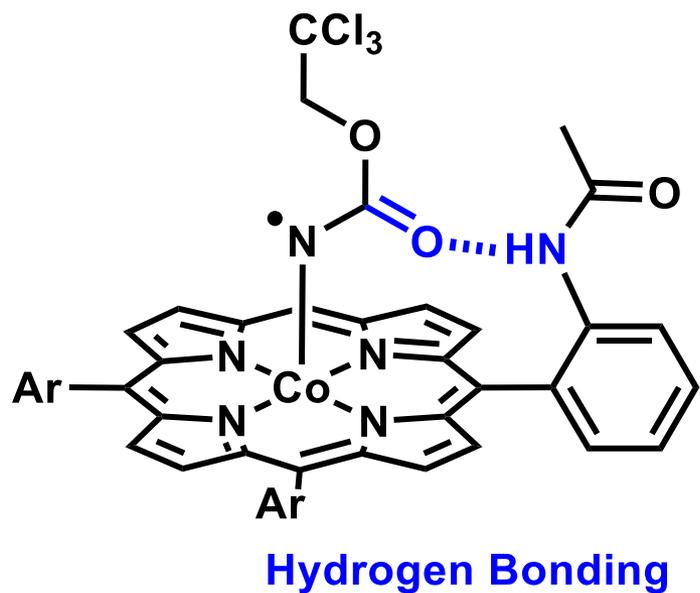
Electron withdrawing group weakens the N α -N β bond of the azide.
TS1 also involves oxidation of metal center by electron transfer.

Important Step in Reaction

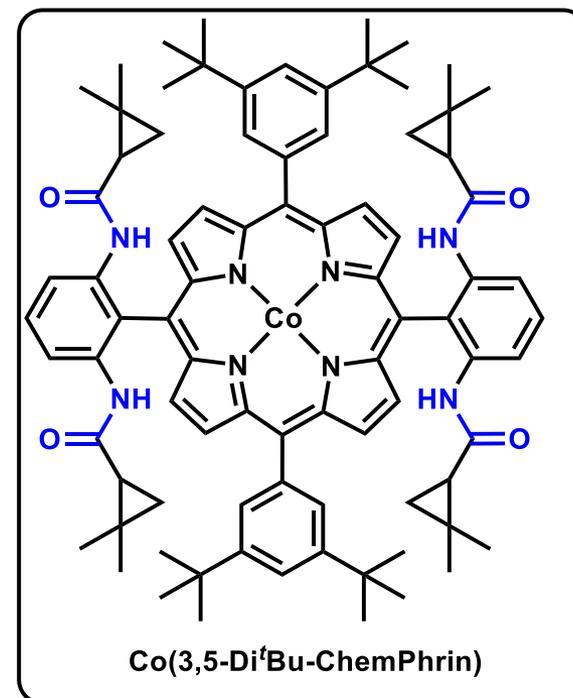


- Can this reaction proceed more efficiently by changing catalyst design?

How promote the Co-N Bond Formation?



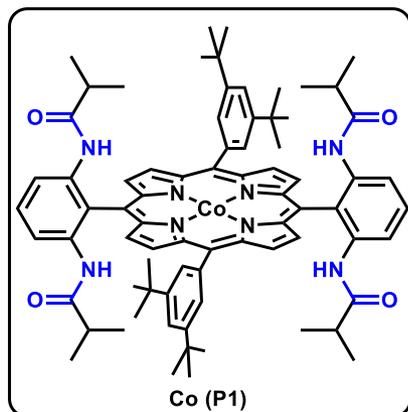
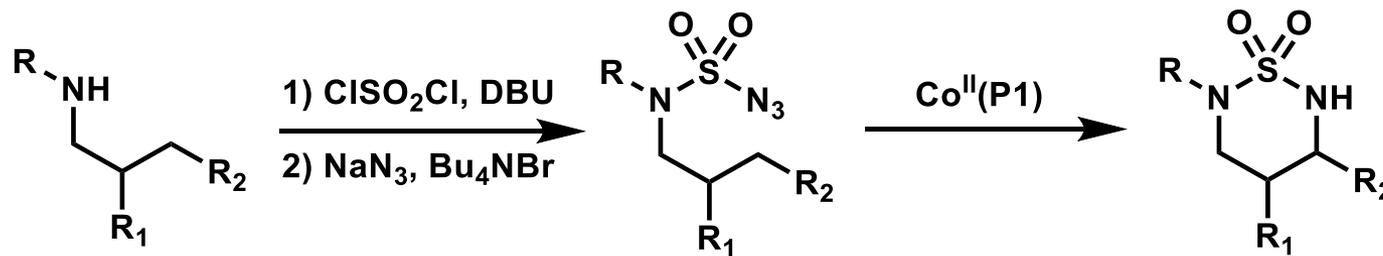
**Catalyst
Design**



- The bond formation between N and Co is promoted through hydrogen bonding.
- Catalytic reactions with this catalyst are much faster than those with (TPP)Co.

Intramolecular C-H Amination (1)

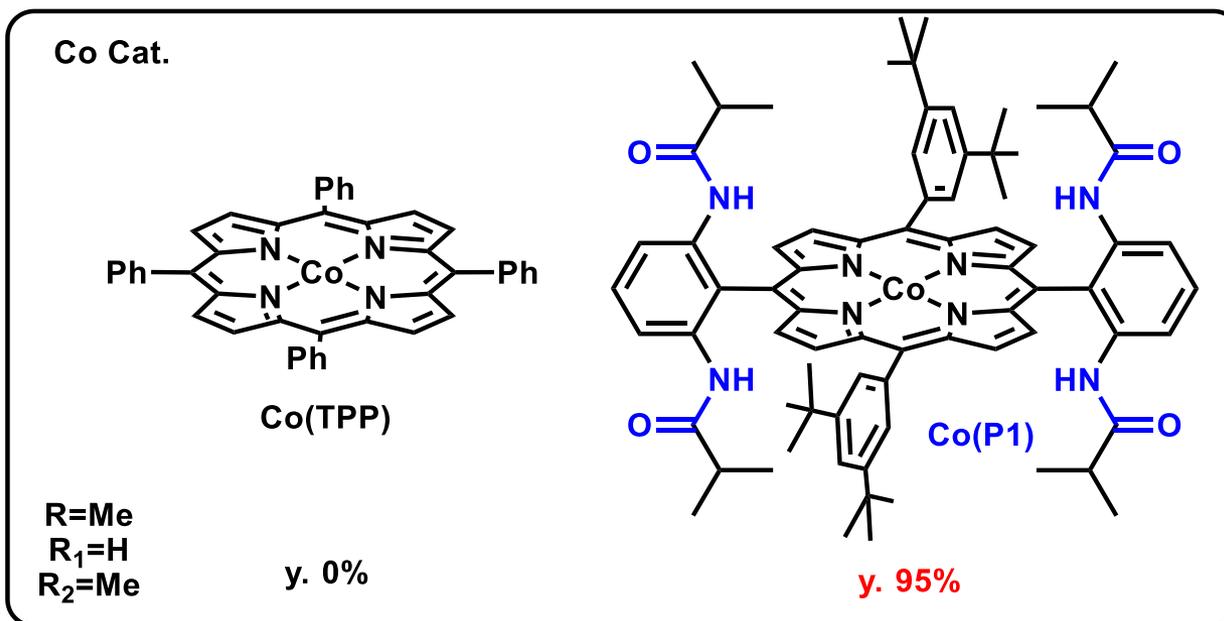
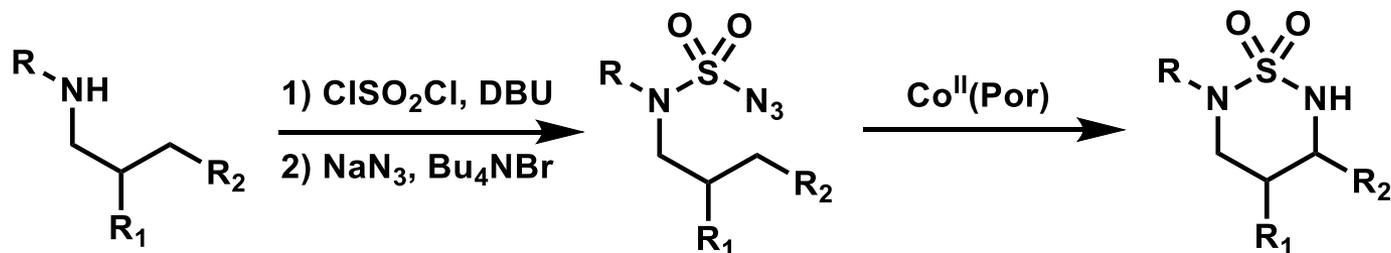
□ Example to promote reaction by using Hydrogen Bonding



- Sulfamoyl azides are synthesized from secondary amine.
- The reaction proceeded not only with benzylic position but also with aliphatic position.

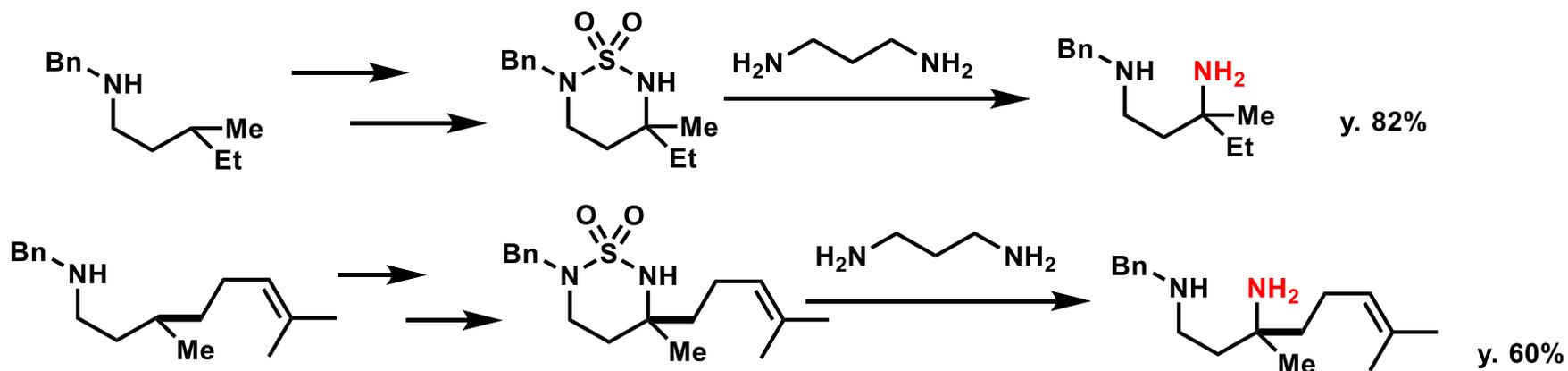
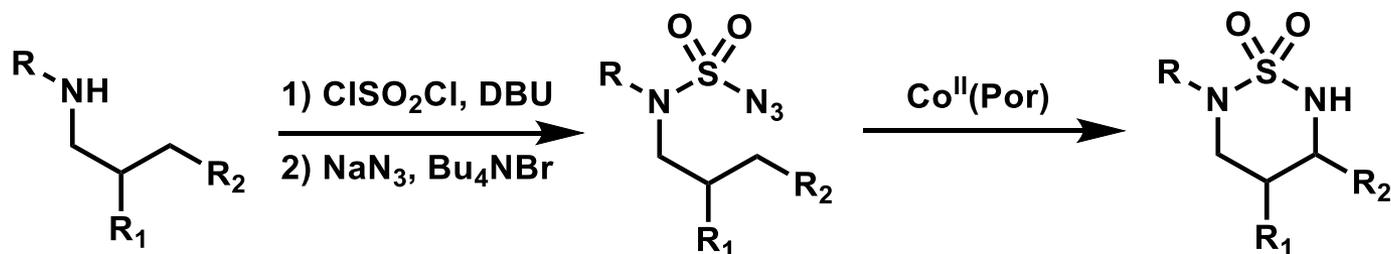
Sulfamoyl azide	Cyclic sulfamide	Yield [%] ^[b]
 2a R = Me	 3a	95
 2e R = Et	 3e	94
 2g	 3g	90

Intramolecular C-H Amination (2)



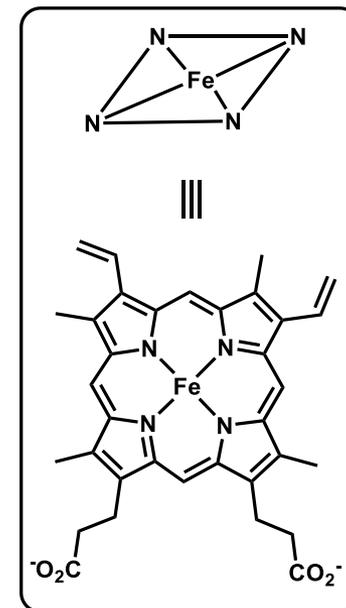
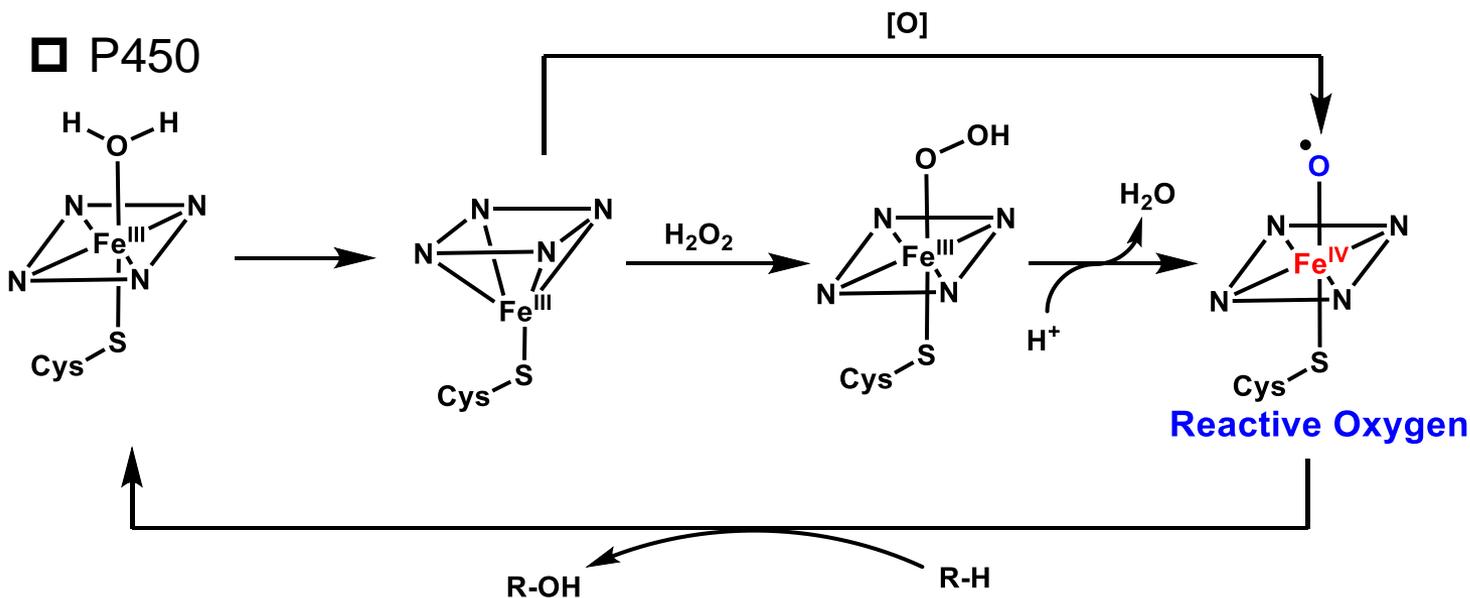
- Hydrogen Bonding promotes the formation of Co-N Bond

Intramolecular C-H Amination ()



1.3- diamination through C-H amination by using Nitrene Radical proceeds.

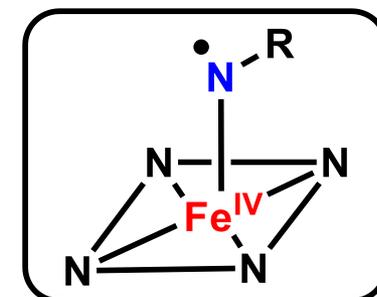
Bioinspired radical reaction



- Cytochrome P450 makes reactive oxygen.
- Fe (IV) shows high-spin ground state.
- P450 also activates aliphatic C-H Bond.

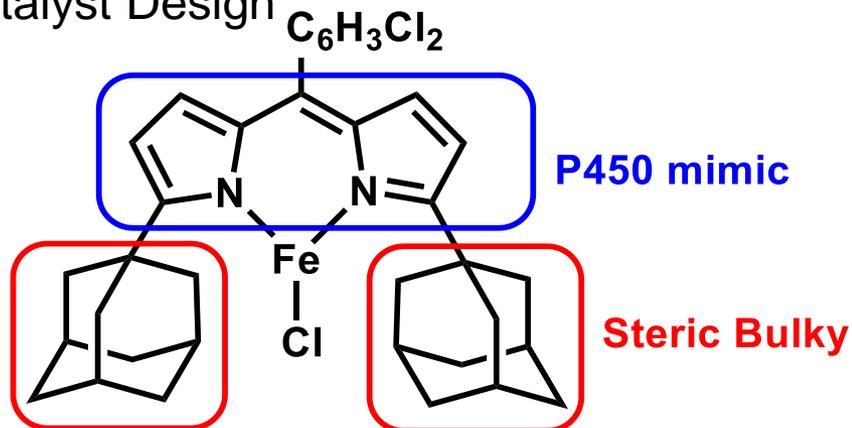
J. H. Dawson *et al.* *Chem. Rev.* **1996**, 96, 2841.

Nitrene radical which conjugates with Fe(IV) also shows high reactivity?



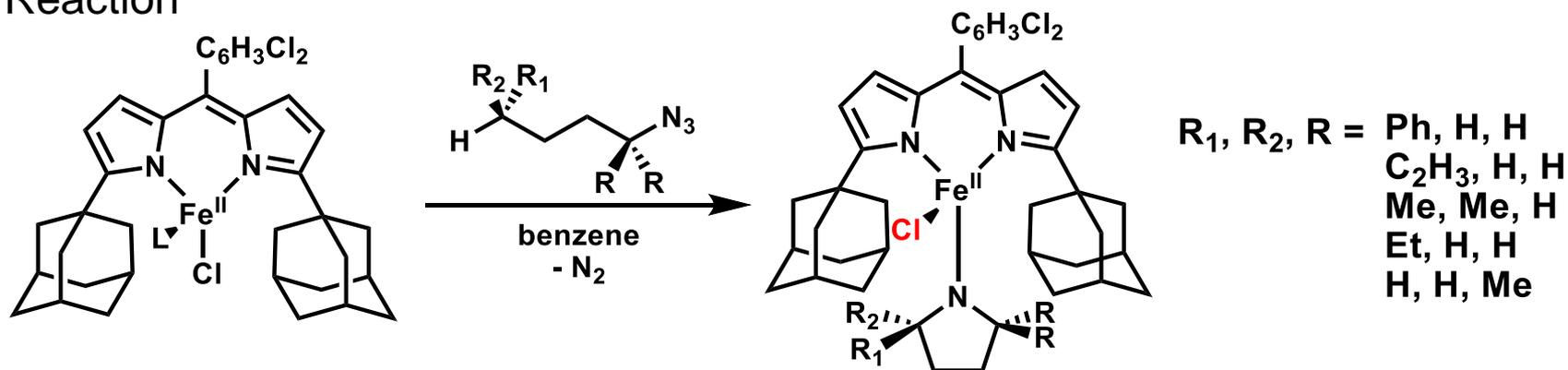
Bioinspired Nitrene radical reaction (1)

□ Catalyst Design



Lack C-H Bond which is easily activated by N radical

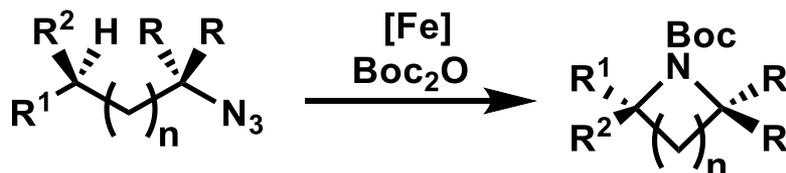
□ Reaction



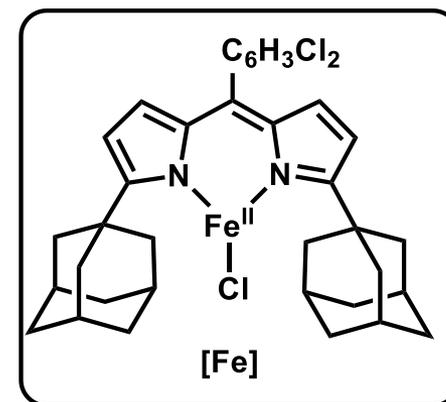
- Azide cyclization proceeds to make 5 membered ring.

Bioinspired Nitrene radical reaction (2)

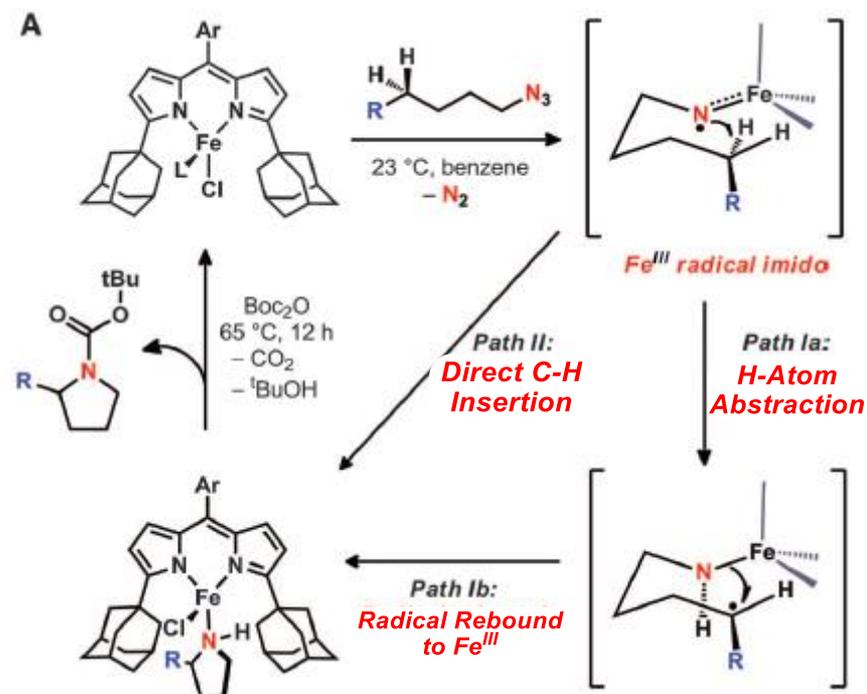
□ Reaction



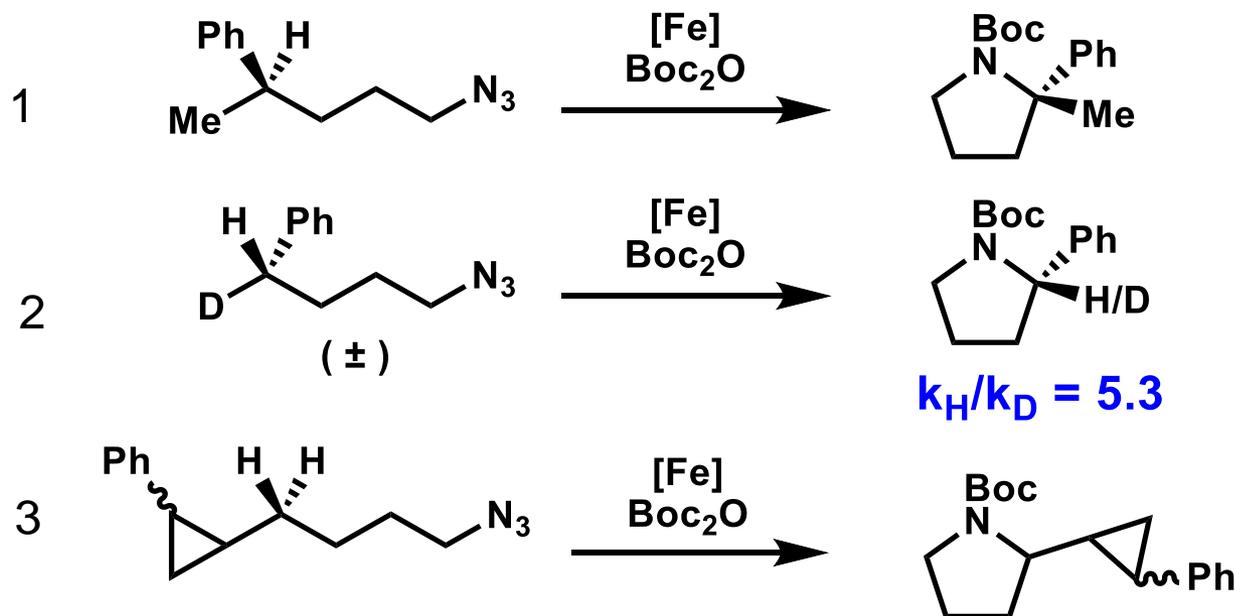
- Reaction proceeds to make 5 membered ring.
- If there is allyl C-H near N radical, it reacts with allyl C-H Bond.



Entry	Azide	Pyrrolidine	Yield (%) [*]
1			98 ^{†S} (PG = Fmoc) 93 ^{†S} 57 ^{†S} (PG = Boc)
2			60 ^S 49 ^{†S}
3			67
4			45
5			82



Bioinspired Nitrene radical reaction (3)

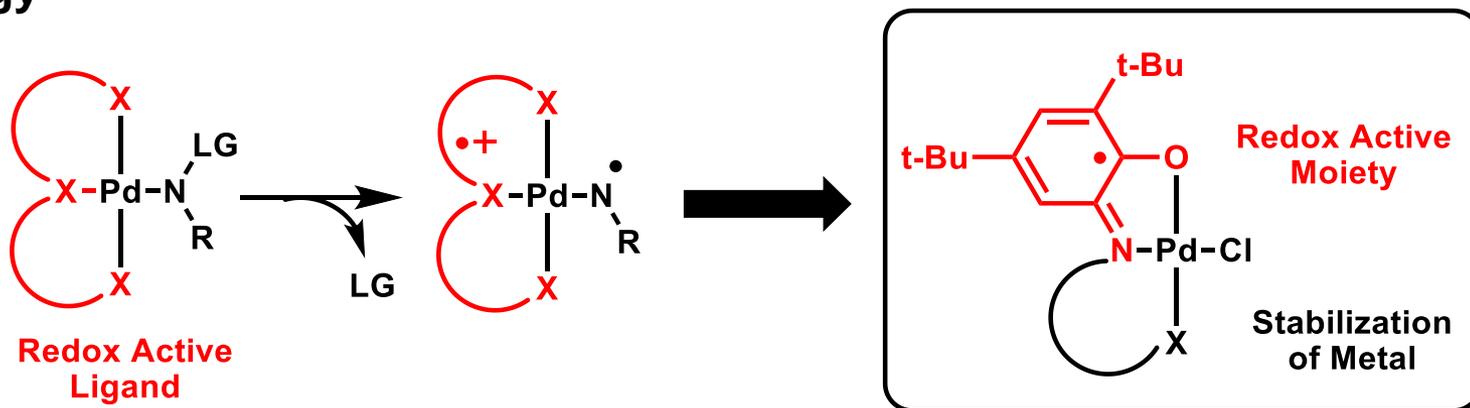


1. Stereochemistry is retained in this cyclization. → Ad inhibits racemization.
2. C-H breakage is big rate determining step. → Radical Stepwise Mechanism
3. Radical is not generated. → Concerted Direct C-H Insertion

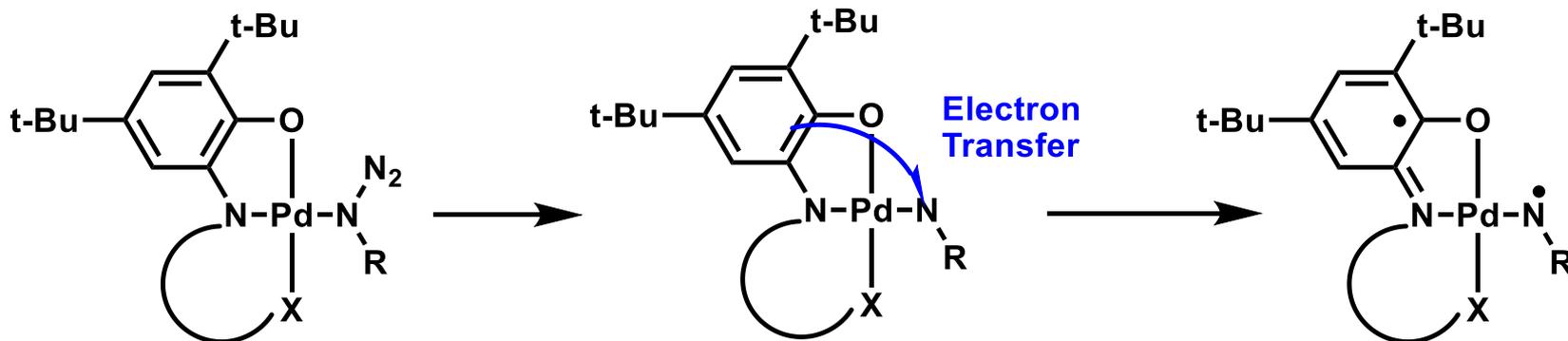
- Benzylic substrate → **Stepwise Mechanism**
- Stronger C-H substrate → **Direct C-H Insertion**

Another strategy to make Nitrene Radical

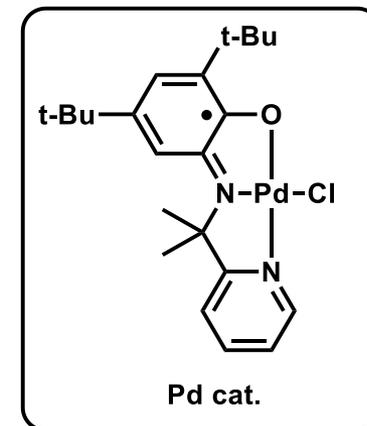
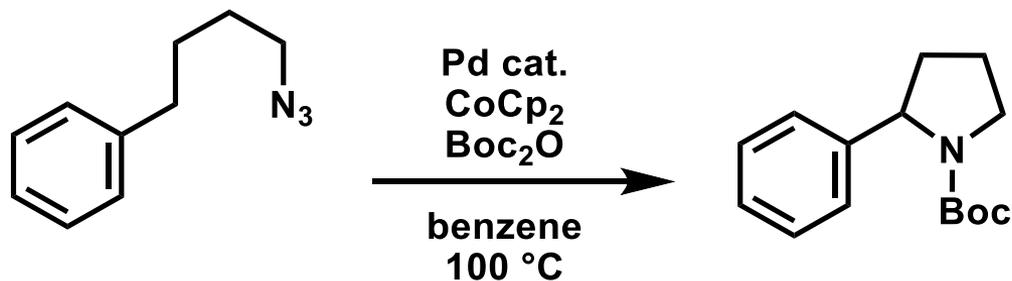
Strategy



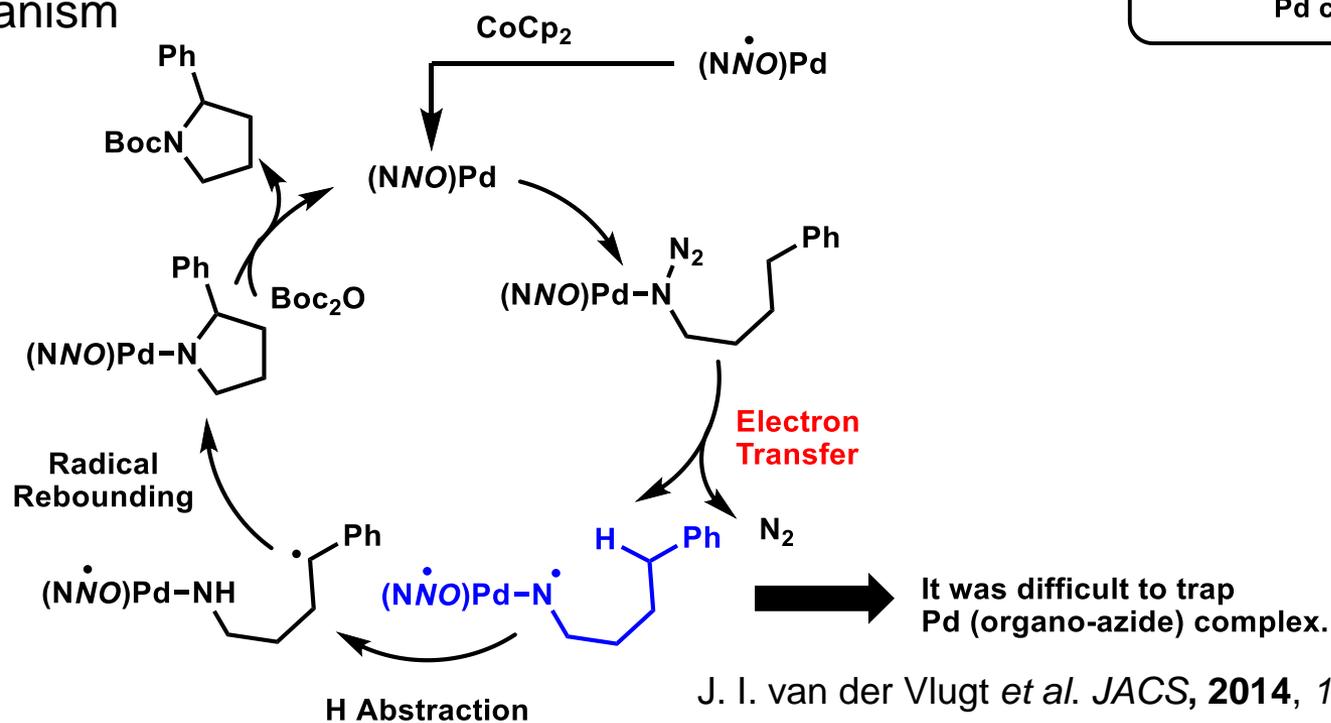
Mechanism



Another strategy to make Nitrene Radical



□ Mechanism

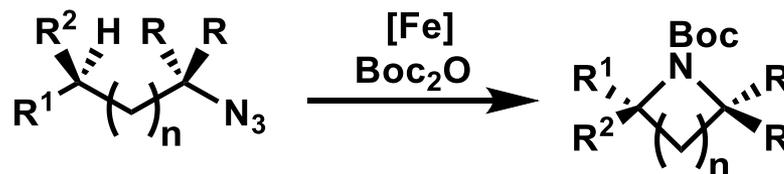


J. I. van der Vlugt *et al.* *JACS*, **2014**, *136*, 11574.

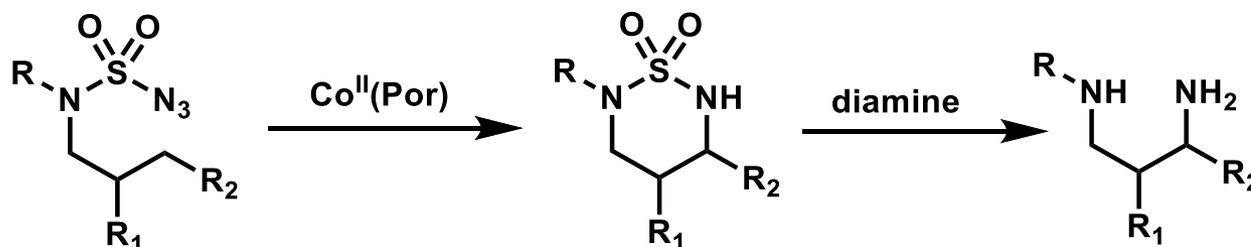
4. Summary and Future of N radical

Reactivity of N Radicals

□ Intramolecular Reaction

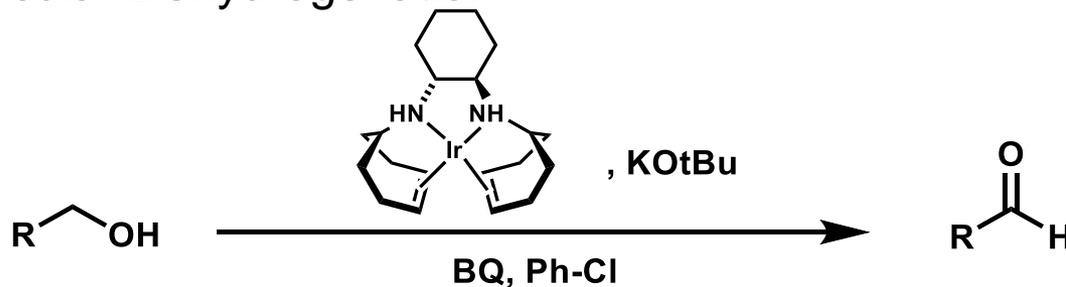


T. A. Betley *et al.* *Science*, **2013**, 340, 591.



X. P. Zhang *et al.* *ACIE*, **2010**, 49, 10192

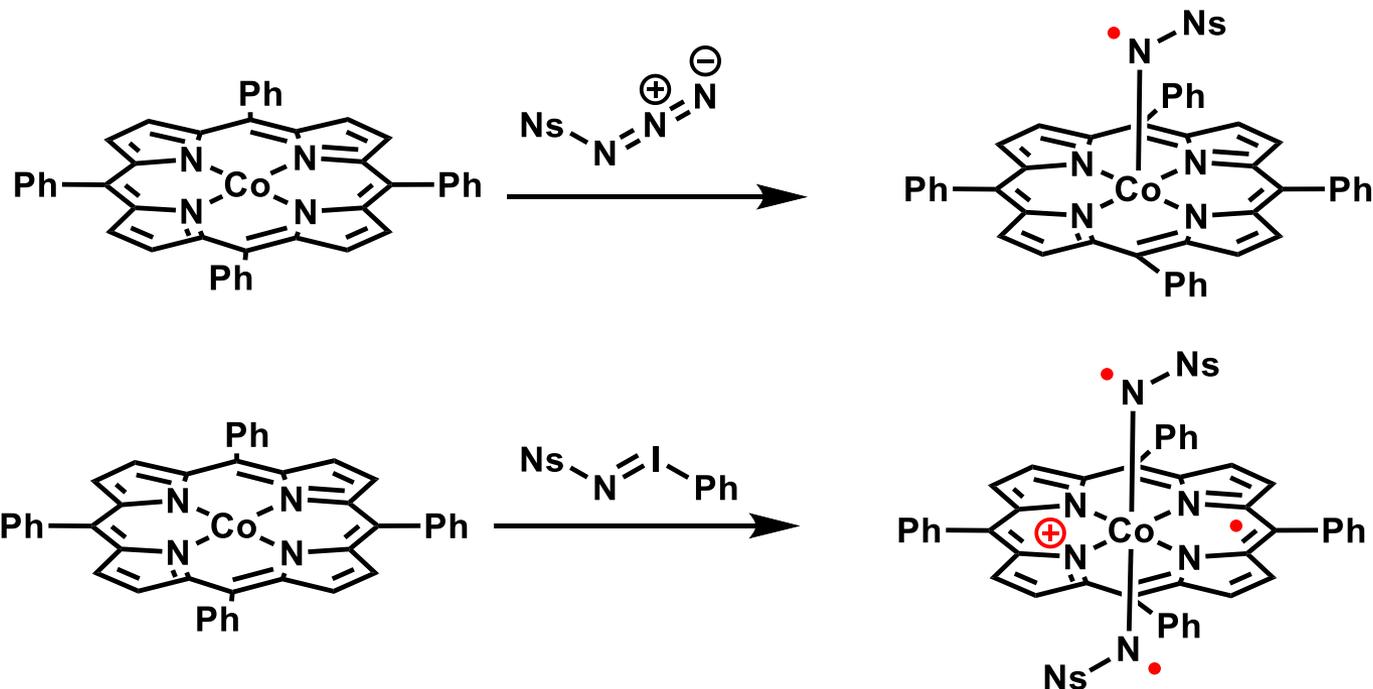
□ Intermolecular Dehydrogenation



Are there more reactive N radicals?

H. Grutzmacher *et al.* *ACIE*, **2007**, 46, 3567.

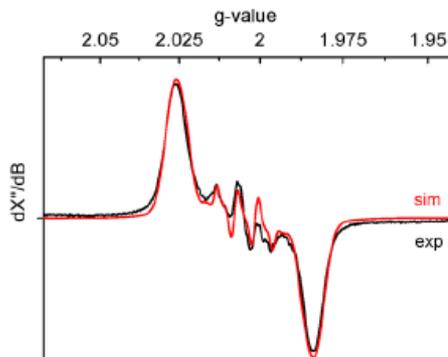
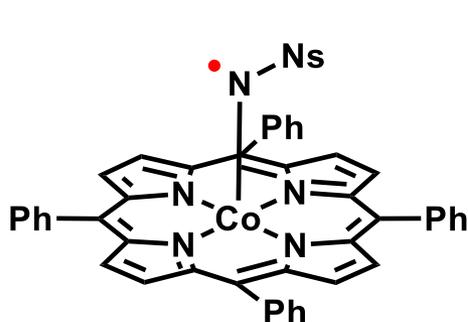
Bis-Nitrene Complex (N Radical Future)



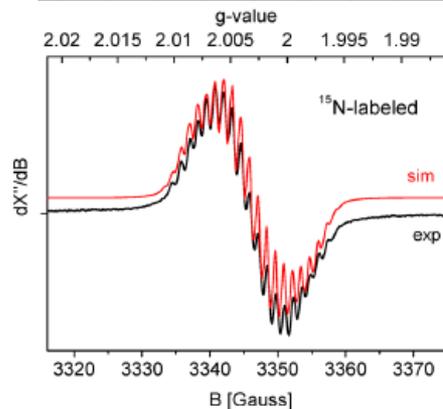
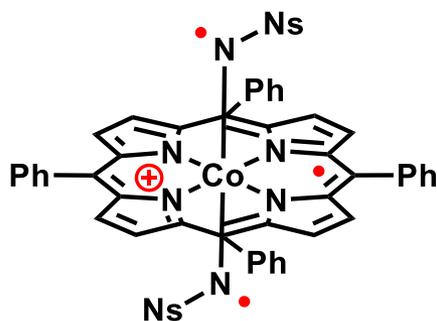
- Stronger Oxidizing nature of iminoiodane promotes bis-nitrene species.
- This nitrene radical species would show higher reactivity

B. de Bruin *et al.* *JACS*, **2015**, *137*, 5468.

More Reactive N Radicals (N Radical Future)



$$\left\{ \begin{array}{l} g = 2.011 \\ A_{Co} = -25.0 \\ A_N = 10.0 \end{array} \right.$$



$$\left\{ \begin{array}{l} g = 2.003 \\ A_{Co} = -2.0 \\ A_{N\text{-nitrene}} = 10.0 \\ A_{N\text{-por}} = 3.5 \end{array} \right.$$

- Hyperfine Coupling from 2 eq. N_{nitrene} atoms and 4 eq. N_{por} atoms indicates bis-nitrene species.

B. de Bruin *et al.* *JACS*, 2015, 137, 5468.

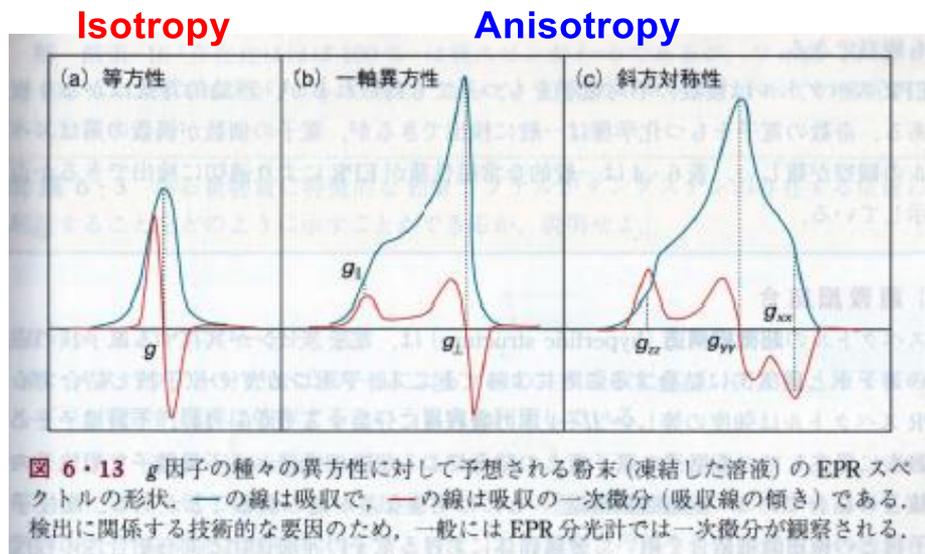


Is it possible to activate unreactive C-H Bond in the future?

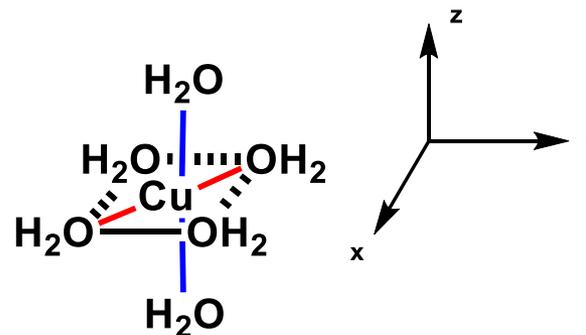
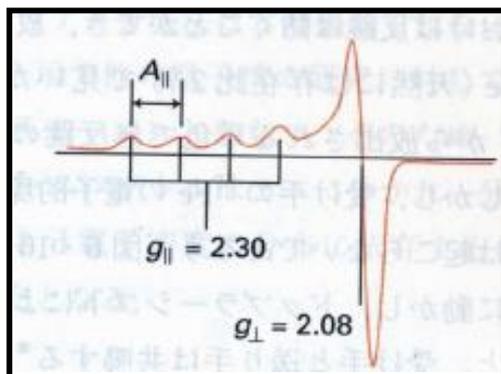
Appendix

Appendix 1 (Isotropy and Anisotropy in EPR spectra)

Organic Radical: isotropy
Metallic Radical: anisotropy



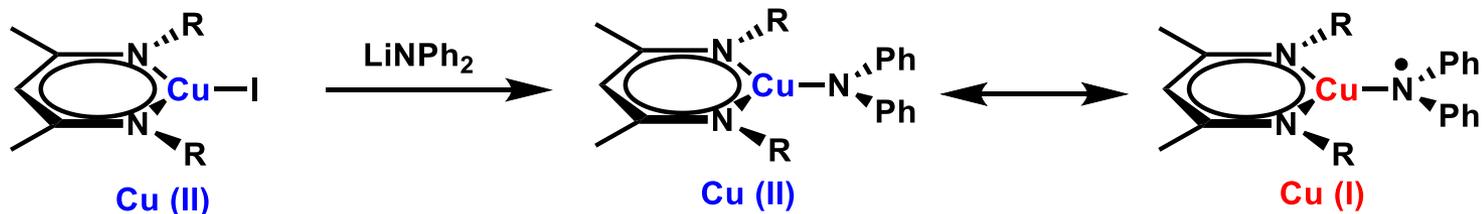
ex) Cu^{2+} aq.



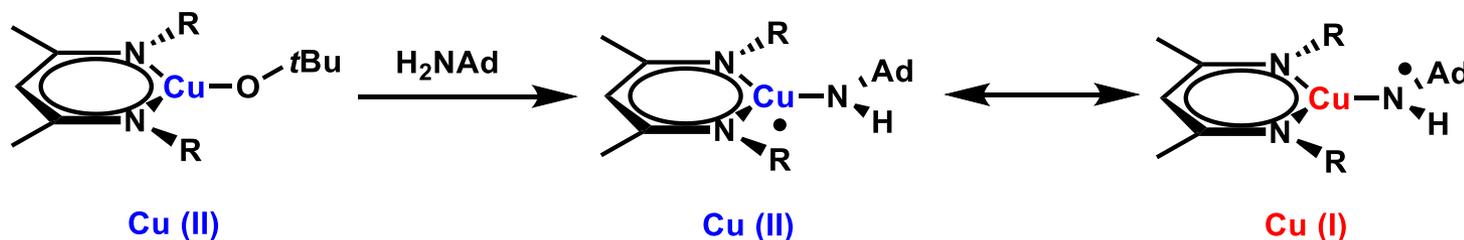
Tetragonal Distortion

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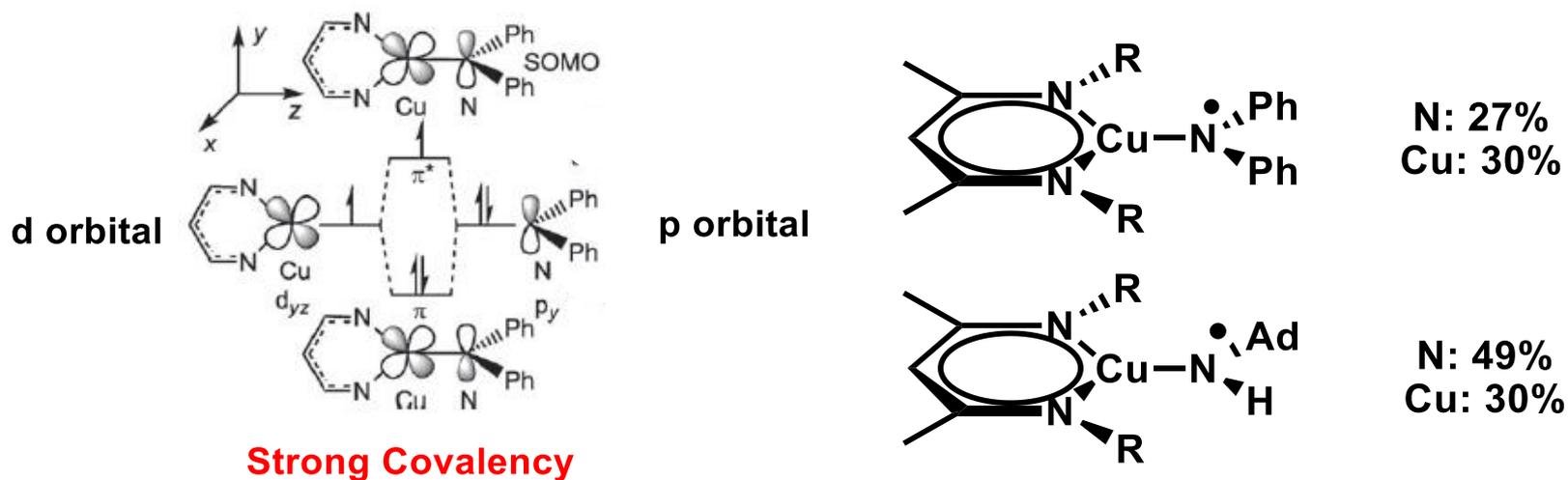
Appendix 2A (Aminyl Radical Generation by using Leaving Group)



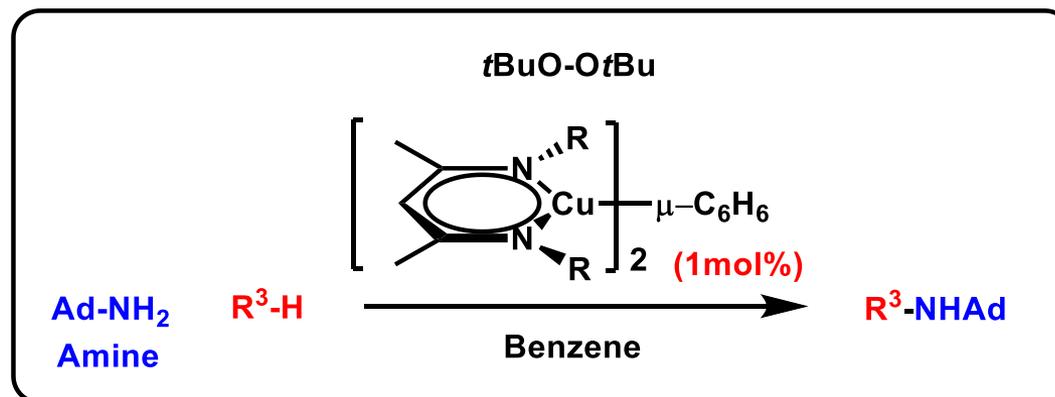
T. H. Warren *et al.*, *ACIE*, 2010, 49, 904.



T. H. Warren *et al.*, *ACIE*, 2010, 49, 8850.



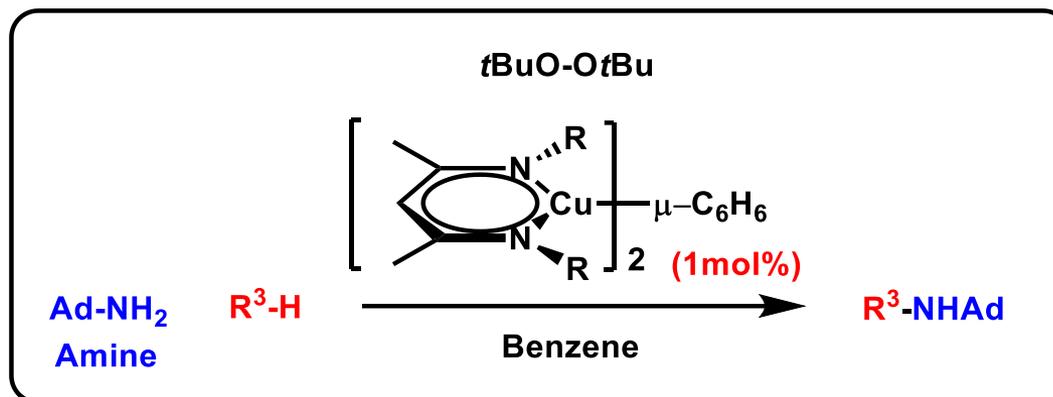
Appendix 2B (C-H Amination through Copper Amides)



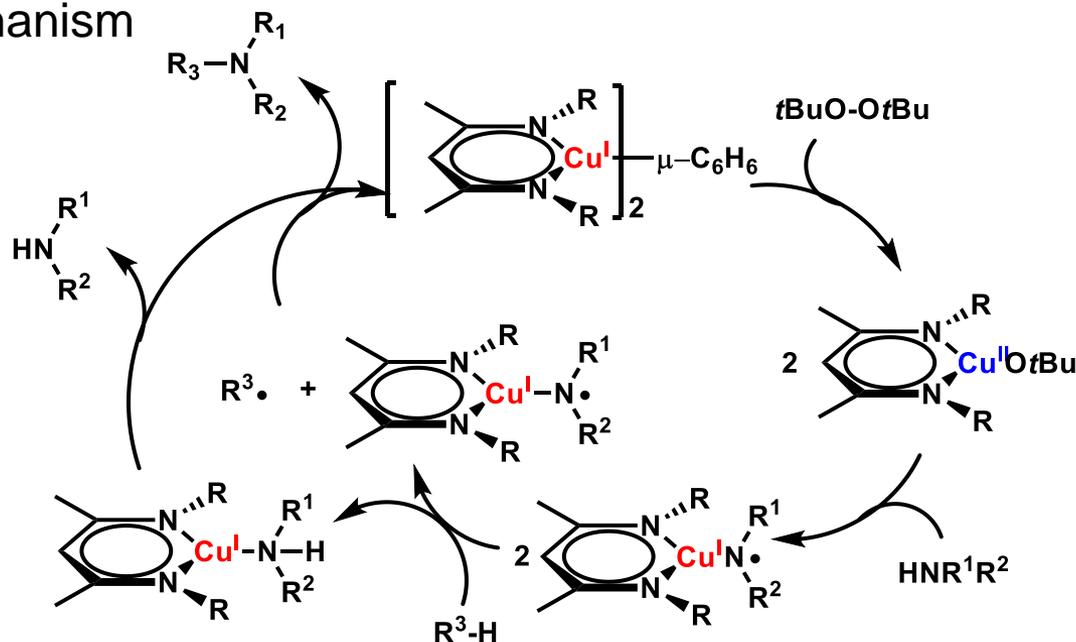
R ₁ R ₂ NH ₂ Amine substrates ↓	Amination products; yields [%]		
H ₂ NAd	98 (83)	93 (65)	91 ^[c]
H ₂ NCy	97 (65)	73 (52)	70 ^[c]
H ₂ NCH ₂ CH ₂ Ph	74 (59)	81 (49)	61 ^[c]
	79 (40) ^[b]	53 (40) ^[b]	2 ^[c,d]

- Aminyl radical promotes benzyl and also cyclohexane C-H bond cleavage.

Appendix 2C (C-H Amination through Copper Amides)

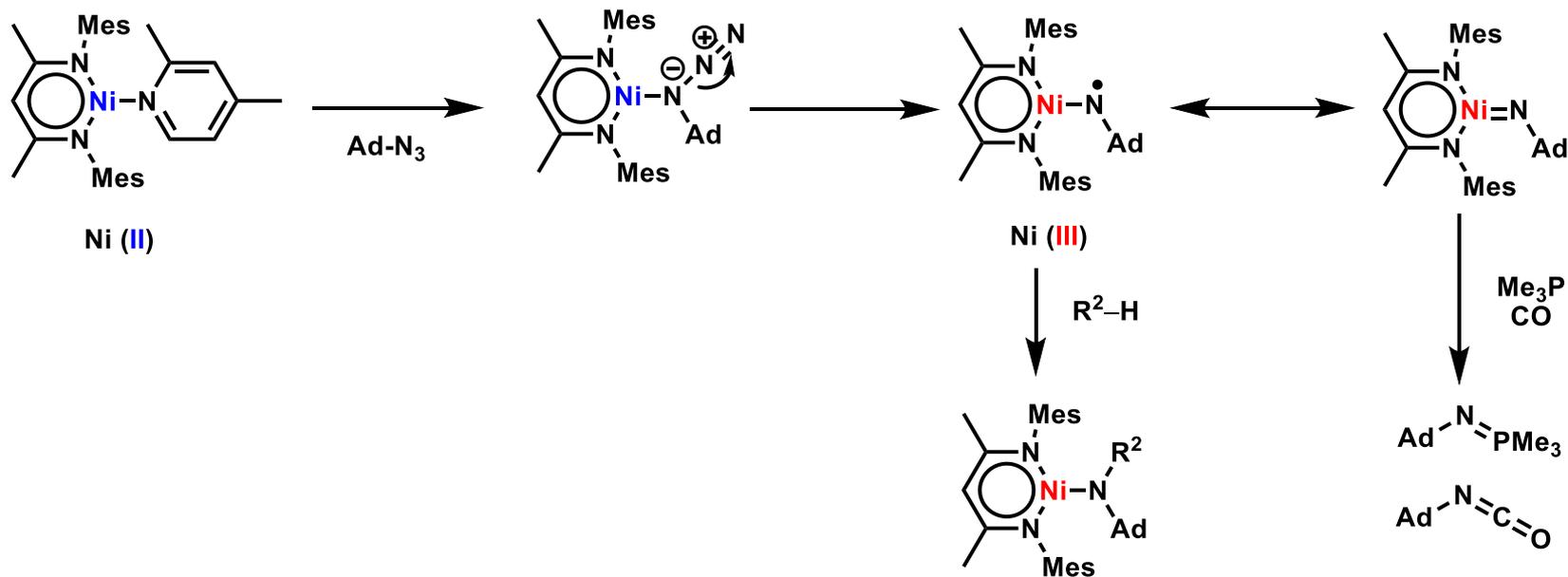


● Proposed Mechanism



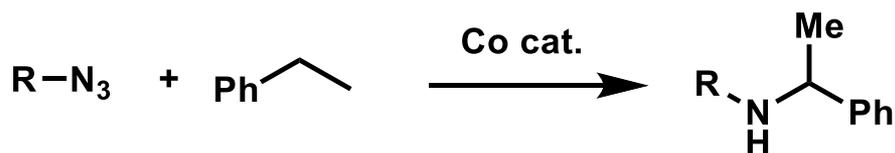
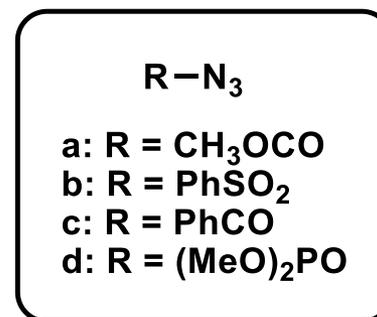
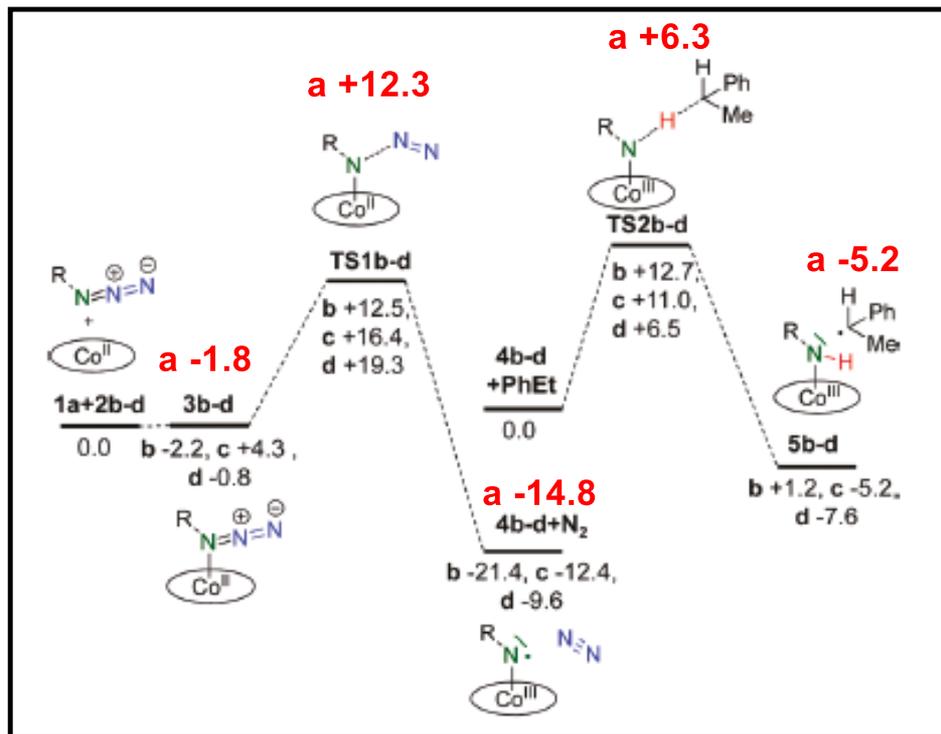
Benzyl C-H Bond is activated by Aminyl Radical.

Appendix 3 (First Example of Nitrene Radical)



- Nitrene moiety gets electron from Metal and made radical complex
- Nitrene is stabilized by electron donation from metal.

Appendix 4 (Computational Study for substrate Scope (Slide 20))



	yield
a: R = CH ₃ OCO	85%
b: R = PhSO ₂	32%
c: R = PhCO	no reaction
d: R = (MeO) ₂ PO	no reaction

c, d: High N α -N β bond energy disturbs reaction. (TS1)

b: Electron withdrawing PhSO₂ group decreases radical reactivity. (TS2)

Appendix 5A (EPR spectra with hydrogen bond)

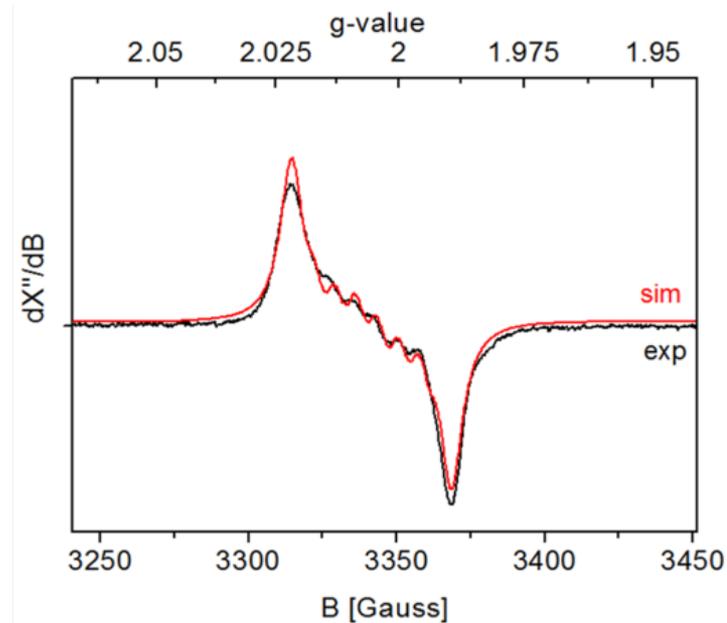
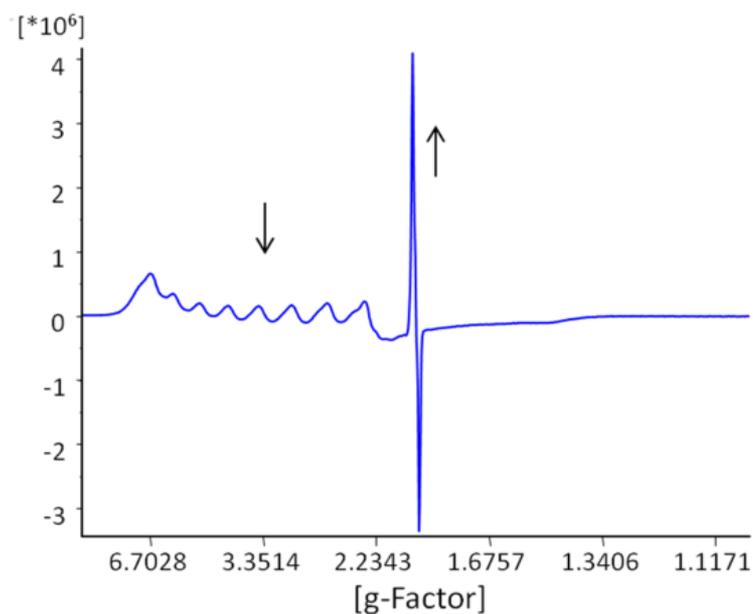
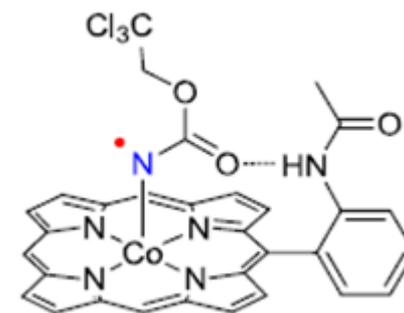
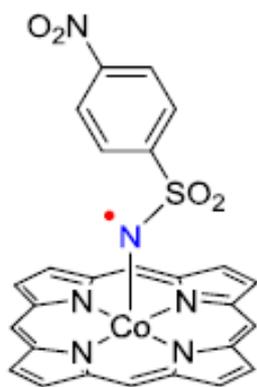


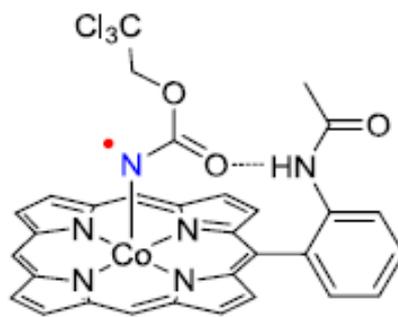
Figure . Left: Disappearance of signals of **1P2** with simultaneous appearance of new signals characteristic for **3P2troc**. Right: Spectrum around $g = 2.00$ showing the cobalt and nitrogen hyperfine structure of species **3P2troc** in benzene- d_6 .

Appendix 5B (EPR spectra with hydrogen bond)

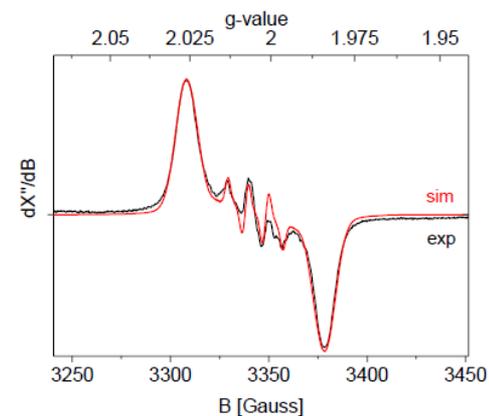
- Spin Density on N radical evaluated by hyperfine coupling



I



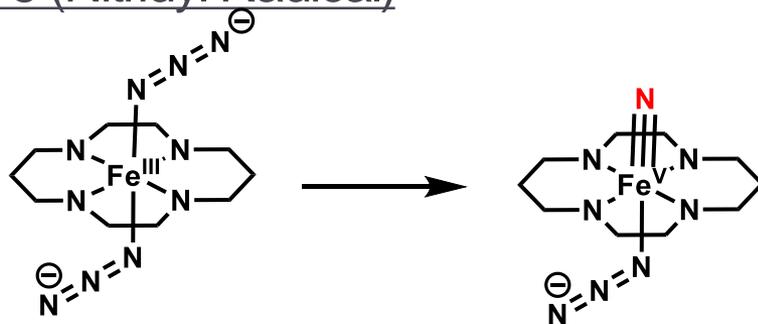
II



Compound	g_{iso}	$A_{\text{iso}}^{\text{Co}}$ (c)	$A_{\text{iso}}^{\text{N}}$ (c)	$A_{\text{iso}}^{\text{D}}$ (d)	ρ_{Co} (e)	ρ_{N} (e)
I ^(b)	2.008	20.0	14.8		4%	82%
II ^(b)	2.000	26.8	22.1		0.3%	90%

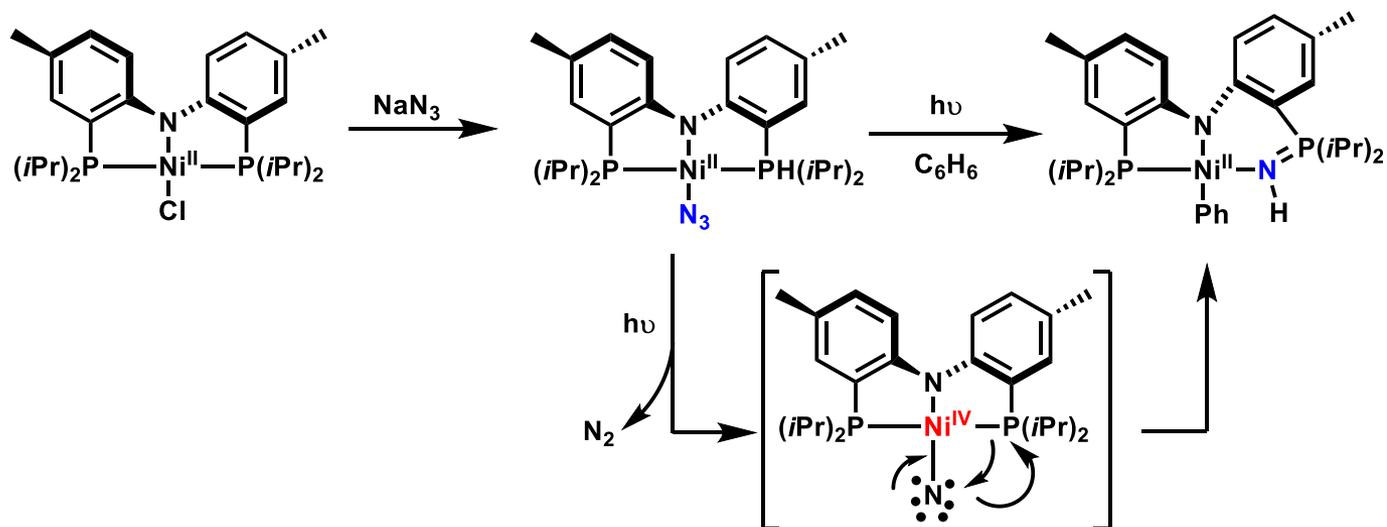
- By using hydrogen bonding, radical density on N increases.

Appendix 6 (Nitridyl Radical)



Nitridyl Radical

K. Wieghardt *et al.* *JACS*, **1999**, 121, 4859.



Nitridyl Radical

J. I. van der Vlugt *et al.* *ACIE*, **2015**, 54, 7055.