# Synthesis of Polypyridine Ligands and Polypyridine-Containing Metal Complexes Directed Towards Water-Soluble Catalysts for Organophosphate Decomposition

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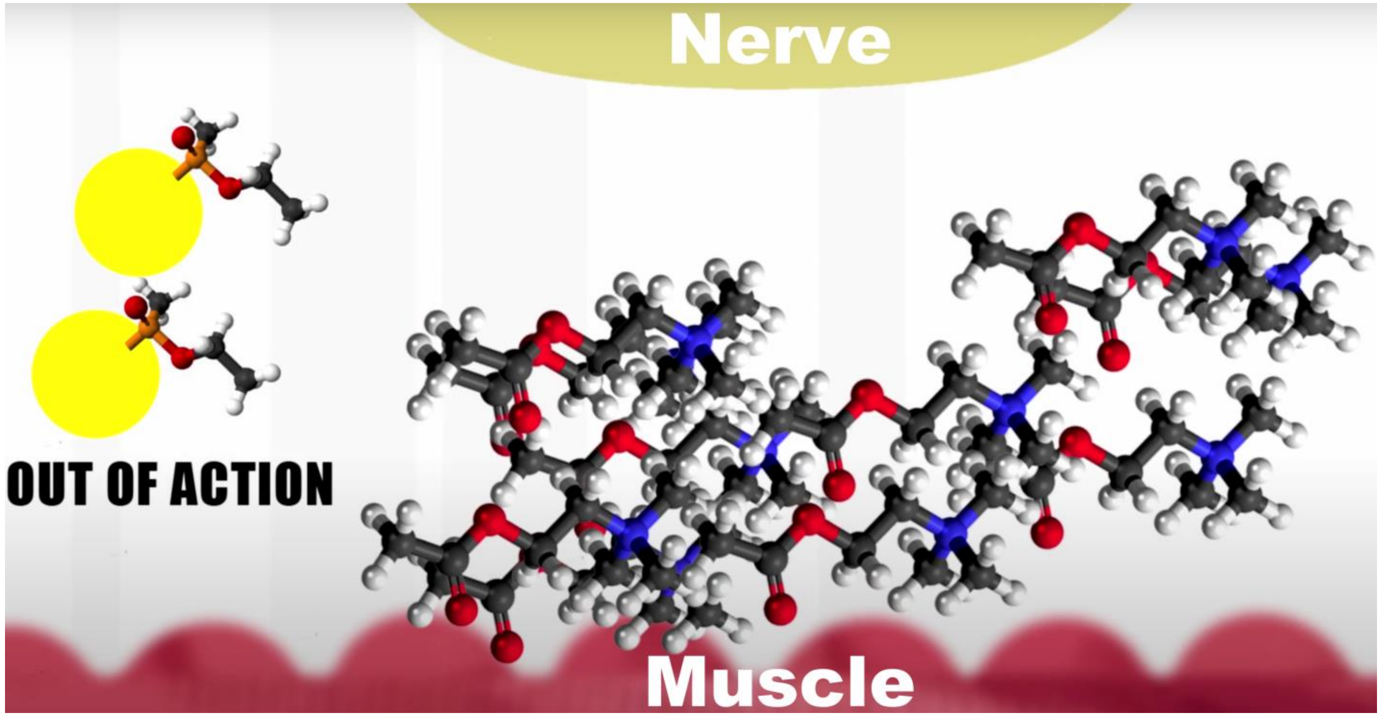
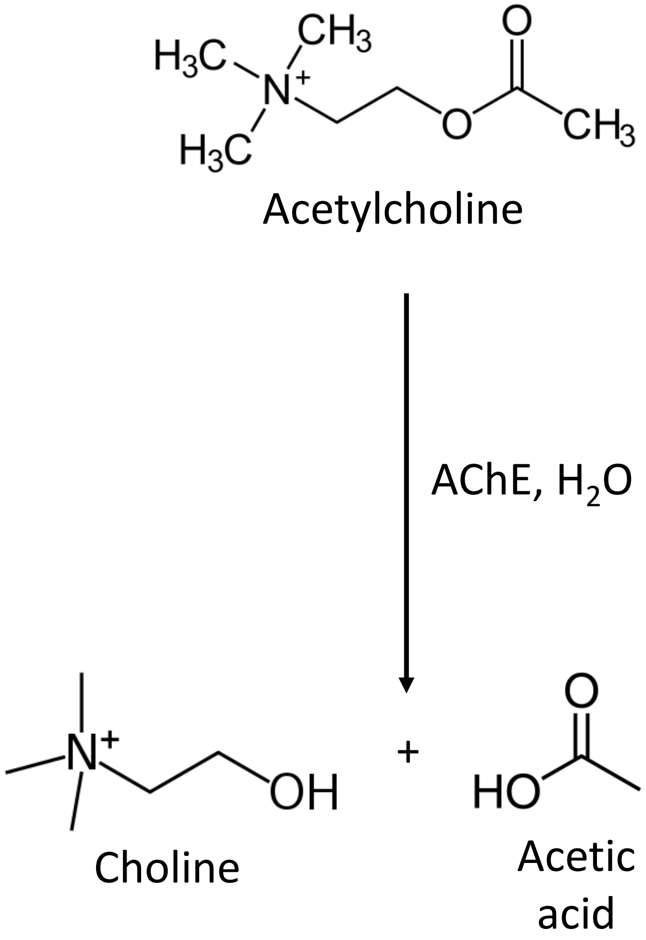
Goucher College Symposium: May 11th, 2021

# Acetylcholinesterase inhibitors (AChEIs)

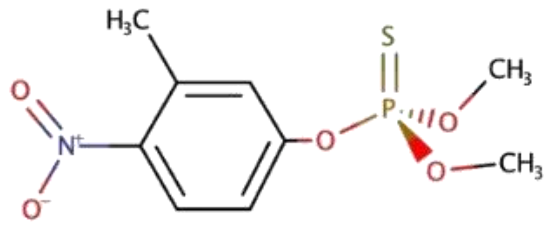
- Acetylcholine secreted by motor neurons to activate muscles
- Must constantly be secreted and quickly broken down by acetylcholinesterase (AChE)
- AChEIs inhibit AChE
- Inhibition of AChE leads to build-up of acetylcholine → muscles continuously activated



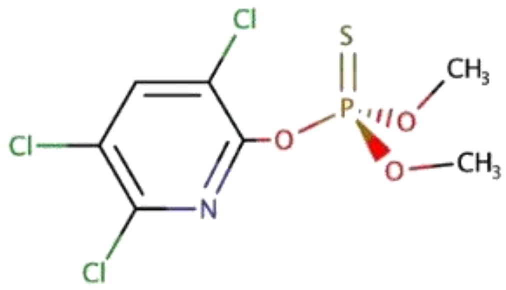


https://www.youtube.com/watch?v=62fPW-5TR-M

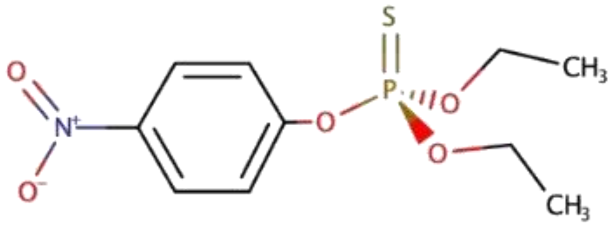
# Why care about organophosphate (OP) decomposition?



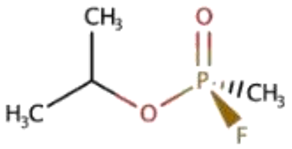
Fenitrothion



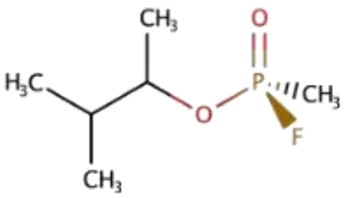
Chlorpyrifos methyl



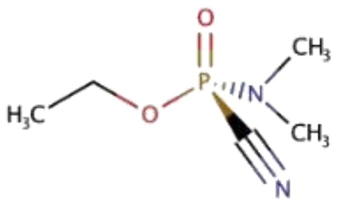
Parathion



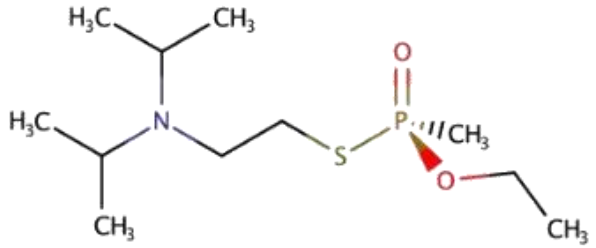
Sarin



Soman



Tabun



VX

- Many pesticides and nerve agents are organophosphates
- Mode of action is AChE inhibition
- Pesticides: strong pollutants and ecological threat
- Nerve agents: potential danger emerging from aging stockpiles

> “…smooth muscles and secretions go crazy. The nerves to those areas keep firing...The nose runs, the eyes cry, the mouth drools and vomits, and bowels and bladder evacuate themselves.”
>
> —Dr. James Hamblin, Yale University

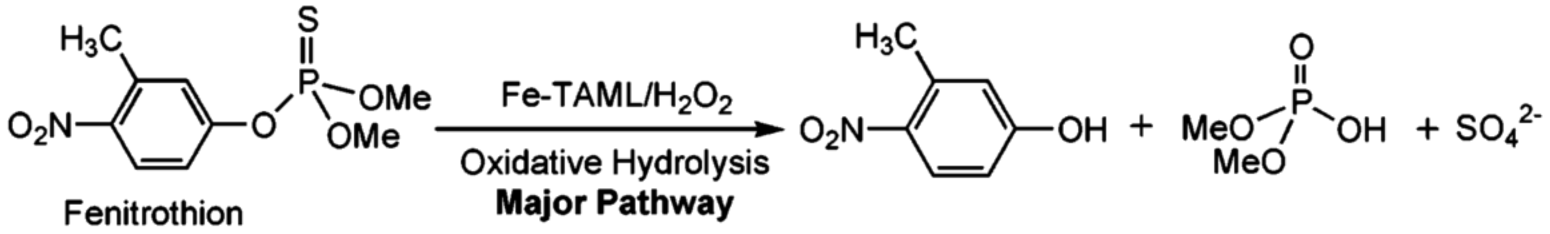
*Int. J. Pure Appl. Sci. Technol.*, 20(2) (2014), pp. 79-94

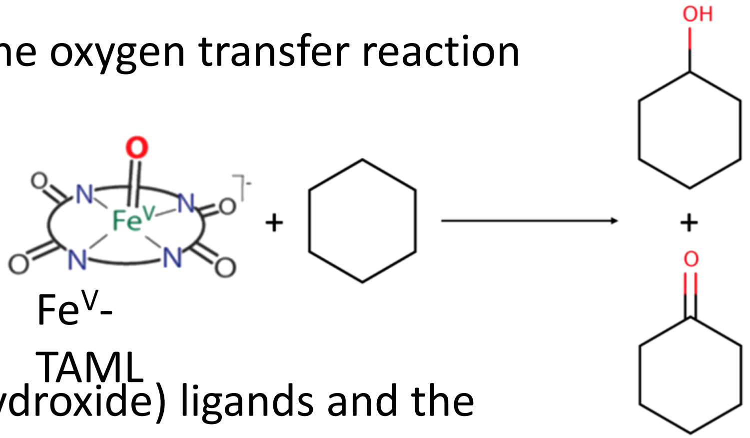
*Angew. Chem. Int. Ed.* **2000**, *39*, No. 17

# Q: How do you decompose an OP w/ a metal complex?

# A: Two ways:

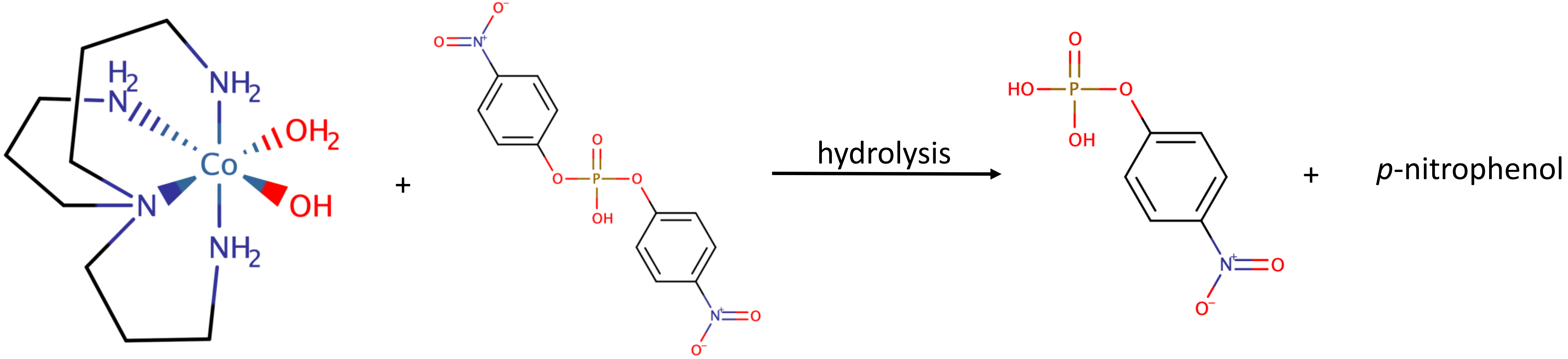
1. Oxidation: requires a high oxidation state transition metal oxo complex to facilitate the oxygen transfer reaction





$Fe^V$-TAML

2. Hydrolysis: must have two *cis* coordination sites that can be occupied by water (or hydroxide) ligands and the proper sterics/electronics/geometry for the reaction to proceed

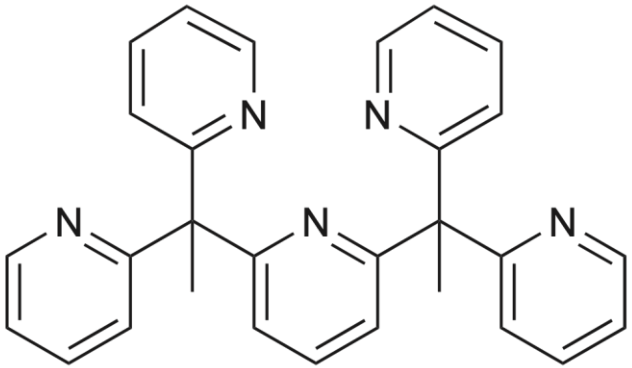


*cis*-diaquotetraazacobalt(III) complexes can catalyze the hydrolysis of OP

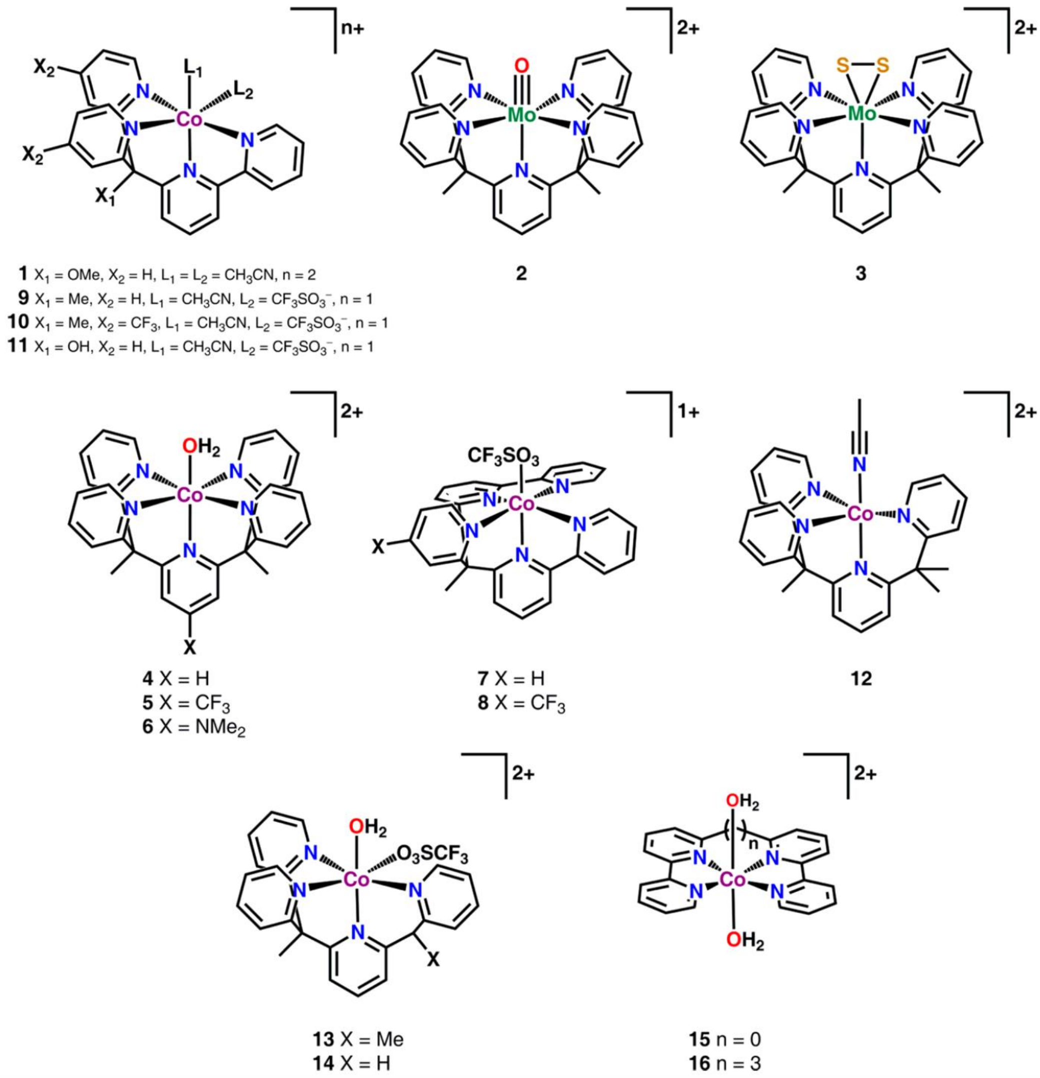
*J. Am. Chem. Soc.* **1989**, *111* (1), 186–190 *J. Am. Chem. Soc.* **2006**, *128* (37), 12058–12059 *Chemical Reviews* **2017**, 117 (13), 9140-9162

# A little background on polypyridine ligands

- First pentapyridine ligand [PY5(OMe)$_2$] reported by Stack in 1997 → synthetically challenging
- In 2007, Nam reported polypyridine ligands that can support high-oxidation state Fe(IV) oxo complexes
- In 2010, Long developed a straightforward synthetic route to PY5Me$_2$ on a multigram scale
- Chang and Long later reported the synthesis of a variety of similar PY4/PY5 ligands and metal complexes supported by these ligands



PY5Me$_2$



**1** $X_1$ = OMe, $X_2$ = H, $L_1 = L_2 = CH_3CN$, n = 2
**9** $X_1$ = Me, $X_2$ = H, $L_1 = CH_3CN$, $L_2 = CF_3SO_3^-$, n = 1
**10** $X_1$ = Me, $X_2 = CF_3$, $L_1 = CH_3CN$, $L_2 = CF_3SO_3^-$, n = 1
**11** $X_1$ = OH, $X_2$ = H, $L_1 = CH_3CN$, $L_2 = CF_3SO_3^-$, n = 1

**2**

**3**

**4** X = H
**5** X = $CF_3$
**6** X = $NMe_2$

**7** X = H
**8** X = $CF_3$

**12**

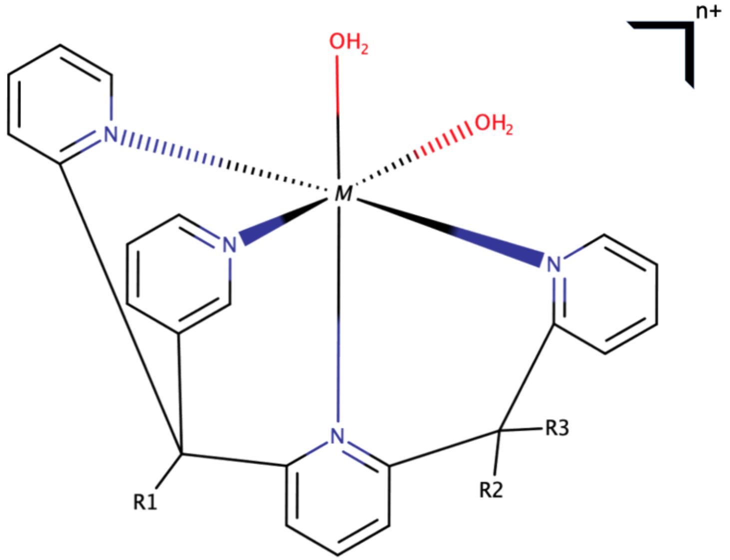
**13** X = Me
**14** X = H

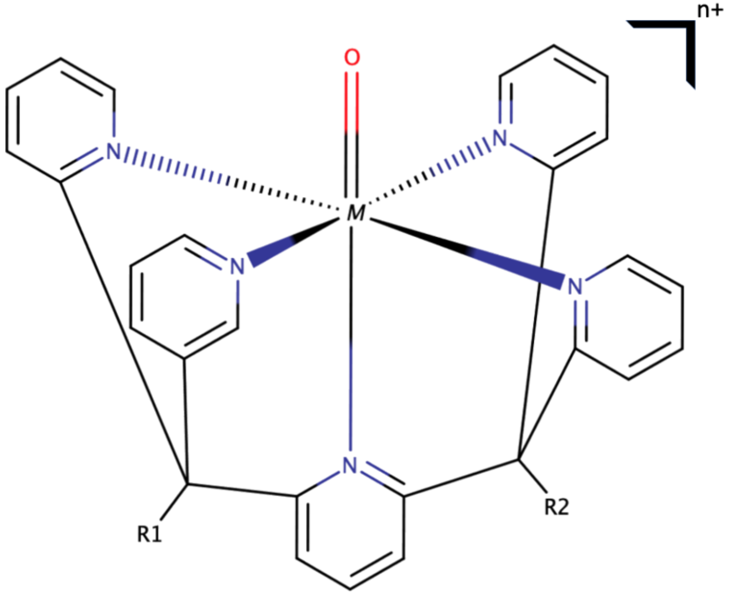
**15** n = 0
**16** n = 3

*J. Am. Chem. Soc.* **1997**, *119* (36), 8566–8567 *Nature Chemistry* **2010**, *2* (5), 362–368 *Acc. Chem. Res.* **2015**, *48* (7), 2027–2036

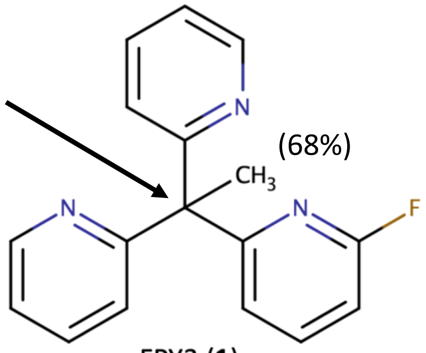
# Motivations for using polypyridine ligands to make OP decomposition catalysts

- Neutral ligands + metal cation → cationic complex → water solubility (?)
- Seem to support high-oxidation state transition metal oxo complexes
- Octahedral complex containing PY4 ligand can have two more open coordination sites *cis* to each other that can be occupied by water/hydroxide ligands. Therefore, $[(PY4)M(H_2O)_2]^{n+}$ complex is ideal candidate for catalyst that can catalyze OP decomposition via hydrolysis
- Octahedral complex containing PY5 ligand will have one more open coordination site that can be occupied by oxo ligand. Therefore, $[(PY5)M(=O)]^{n+}$ complex is ideal candidate for catalyst that can catalyze OP decomposition via oxidation





# Synthesis of PY4Me$_2$H

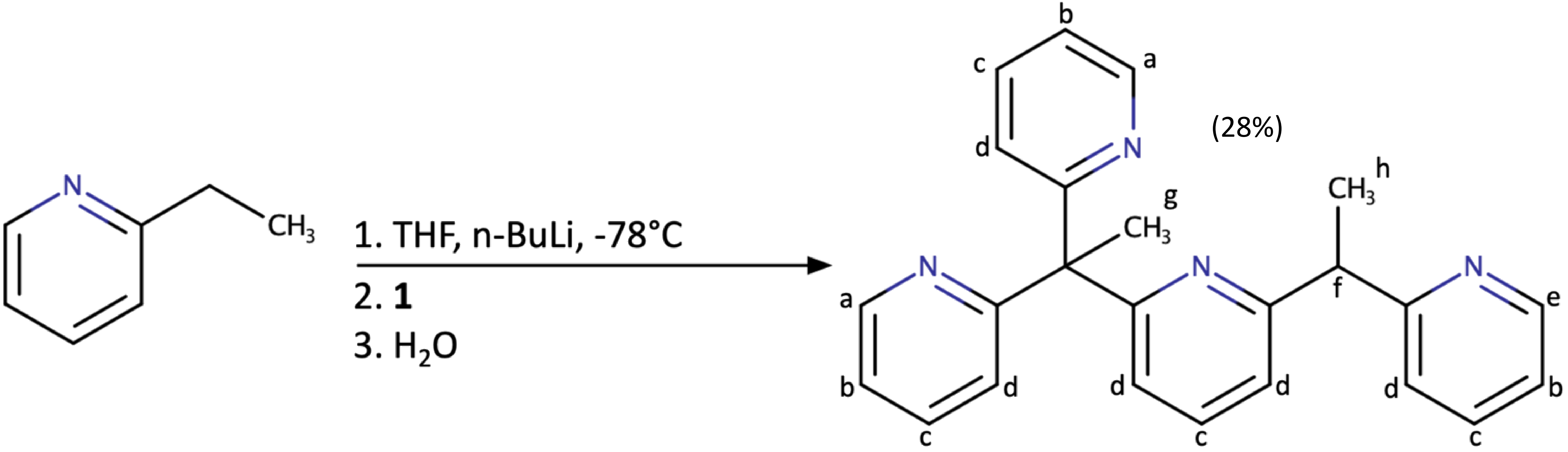


Precursor synthesized following procedure by Grohmann

(68%)

FPY3 (**1**)

- Procedure from Castellano
- 2-ethylpyridine deprotonated at benzylic position
- Carbanion couples with precursor **1** via S$_N$Ar mechanism to form PY4Me$_2$H

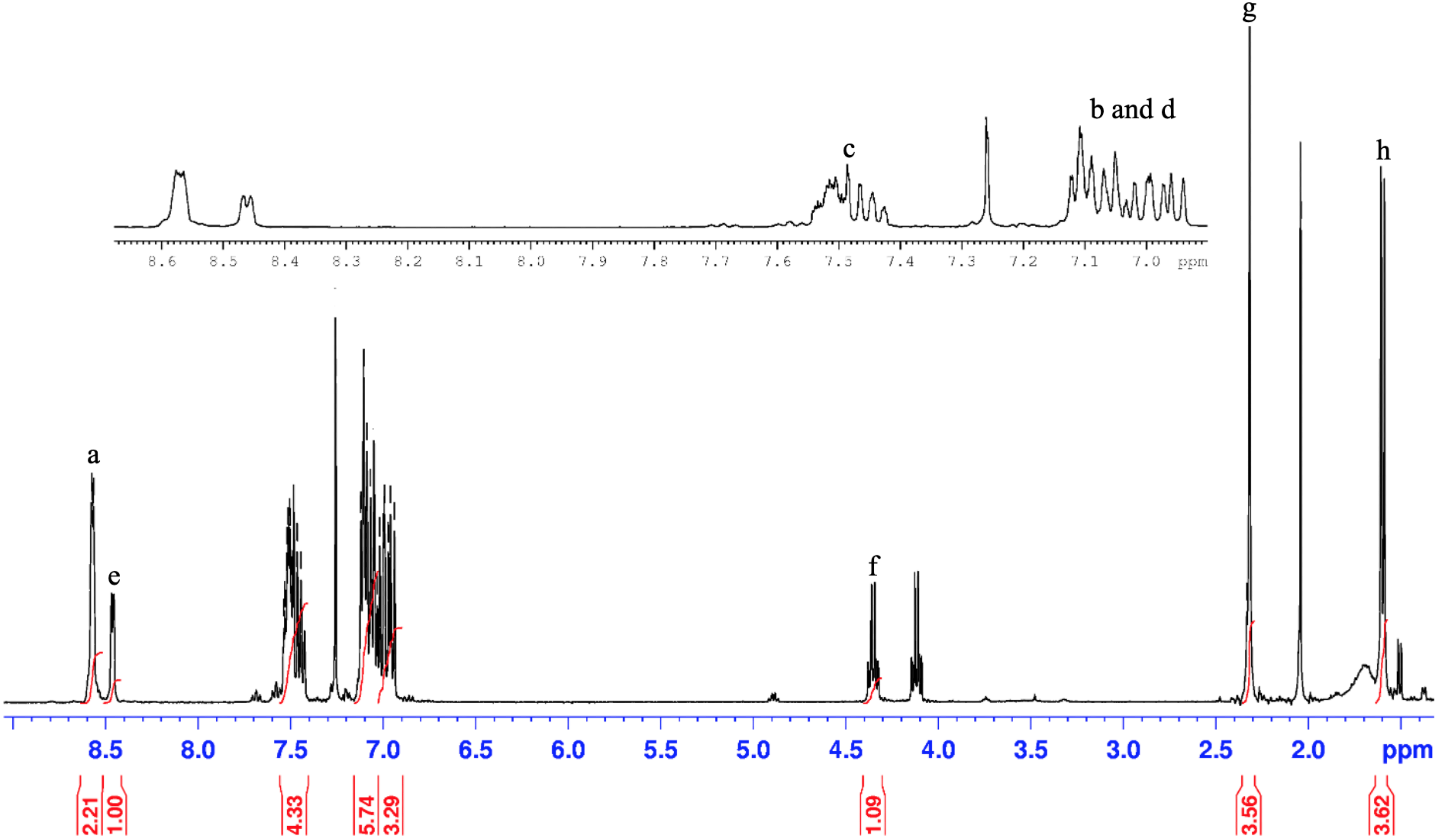


**2**

*Tetrahedron Letters* **2012**, *53* (1), 54–55

*Energy Environ. Sci.* **2014**, *7* (4), 1477–1488

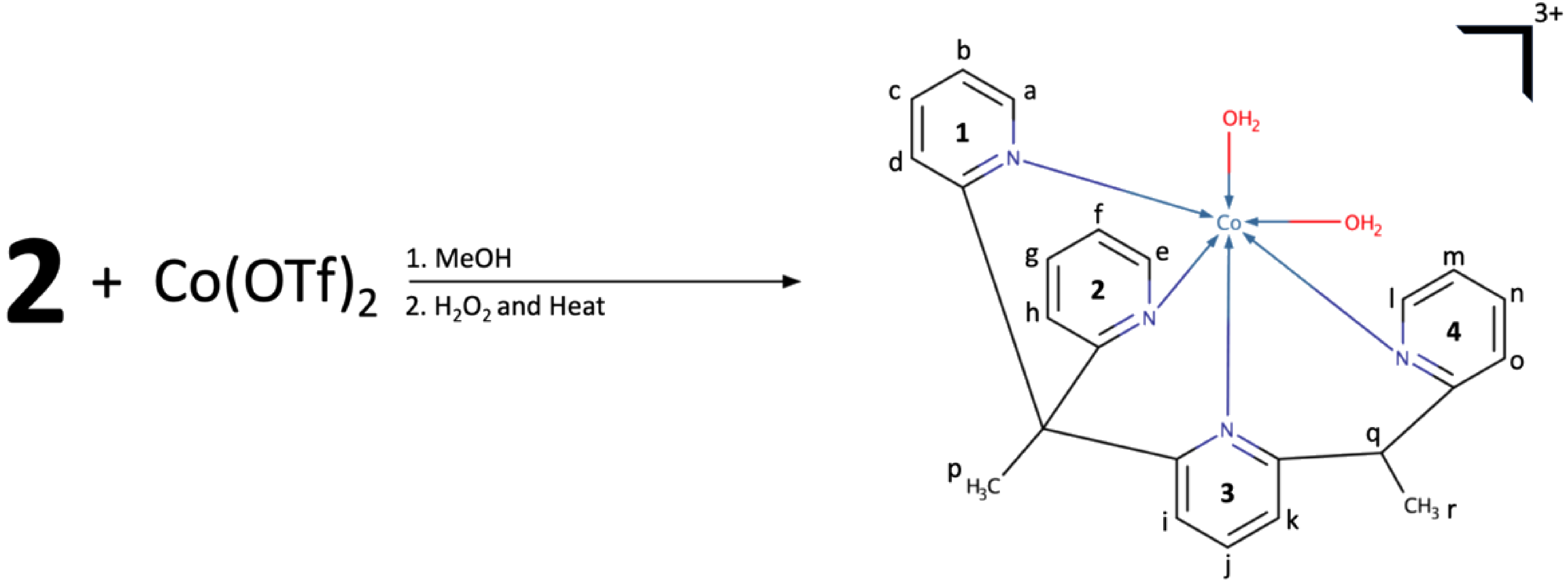
# $^1$H NMR of PY4Me$_2$H



- $^1$H NMR interpretable b/c two of the monosubstituted rings are chemically equivalent
- Still complex spectrum, though

# Synthesis of diaqua(PY4Me$_2$H)cobalt(III)

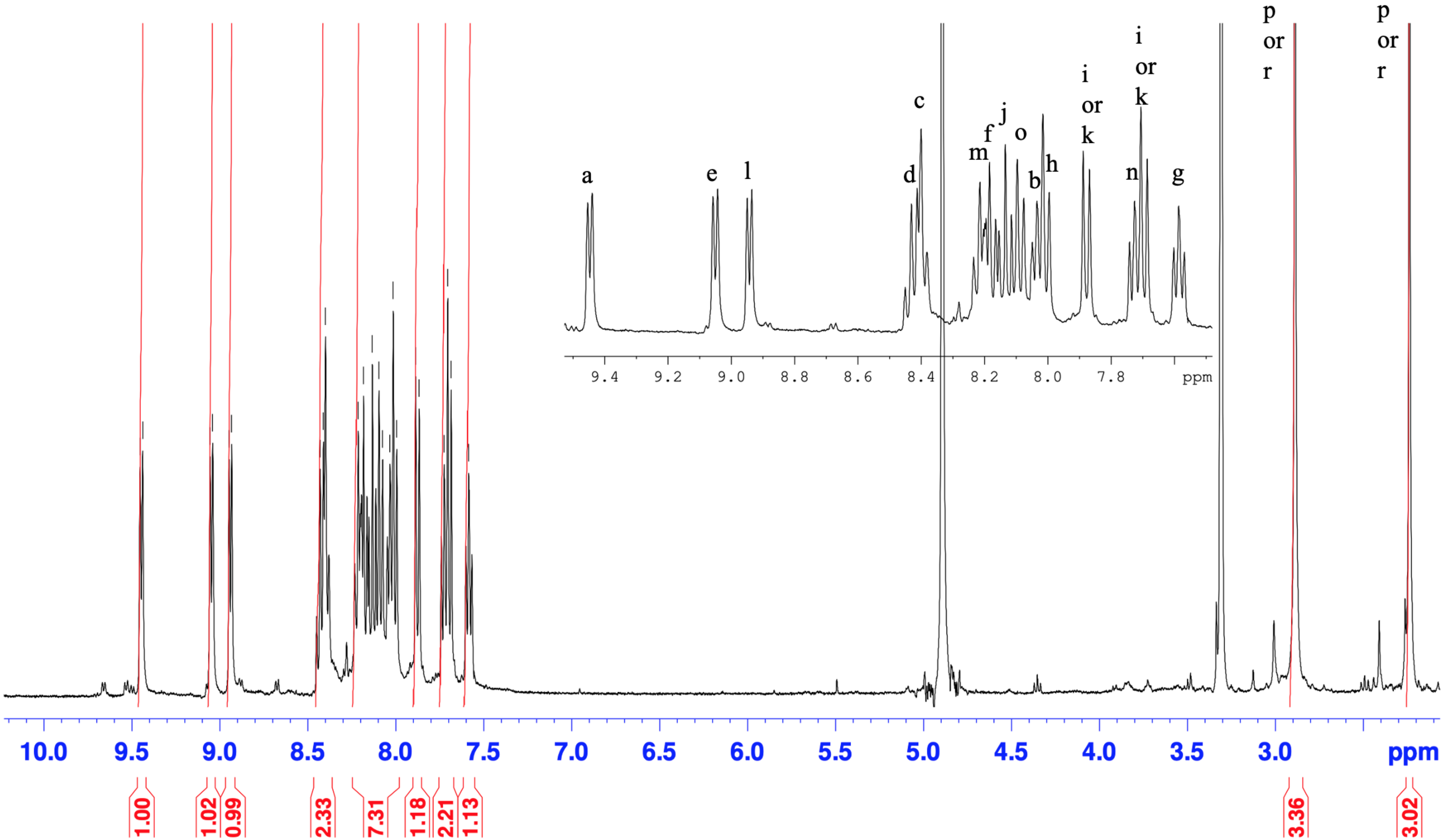
- diaqua(PY4Me$_2$H)cobalt(III) synthesized from cobalt (II) triflate via ligand substitution reaction and subsequent oxidation with $H_2O_2$
- Identity of counterion unknown
- Each ring now chemically inequivalent due to geometry around metal center



$$\mathbf{2} + Co(OTf)_2 \xrightarrow[\text{2. } H_2O_2 \text{ and Heat}]{\text{1. MeOH}}$$

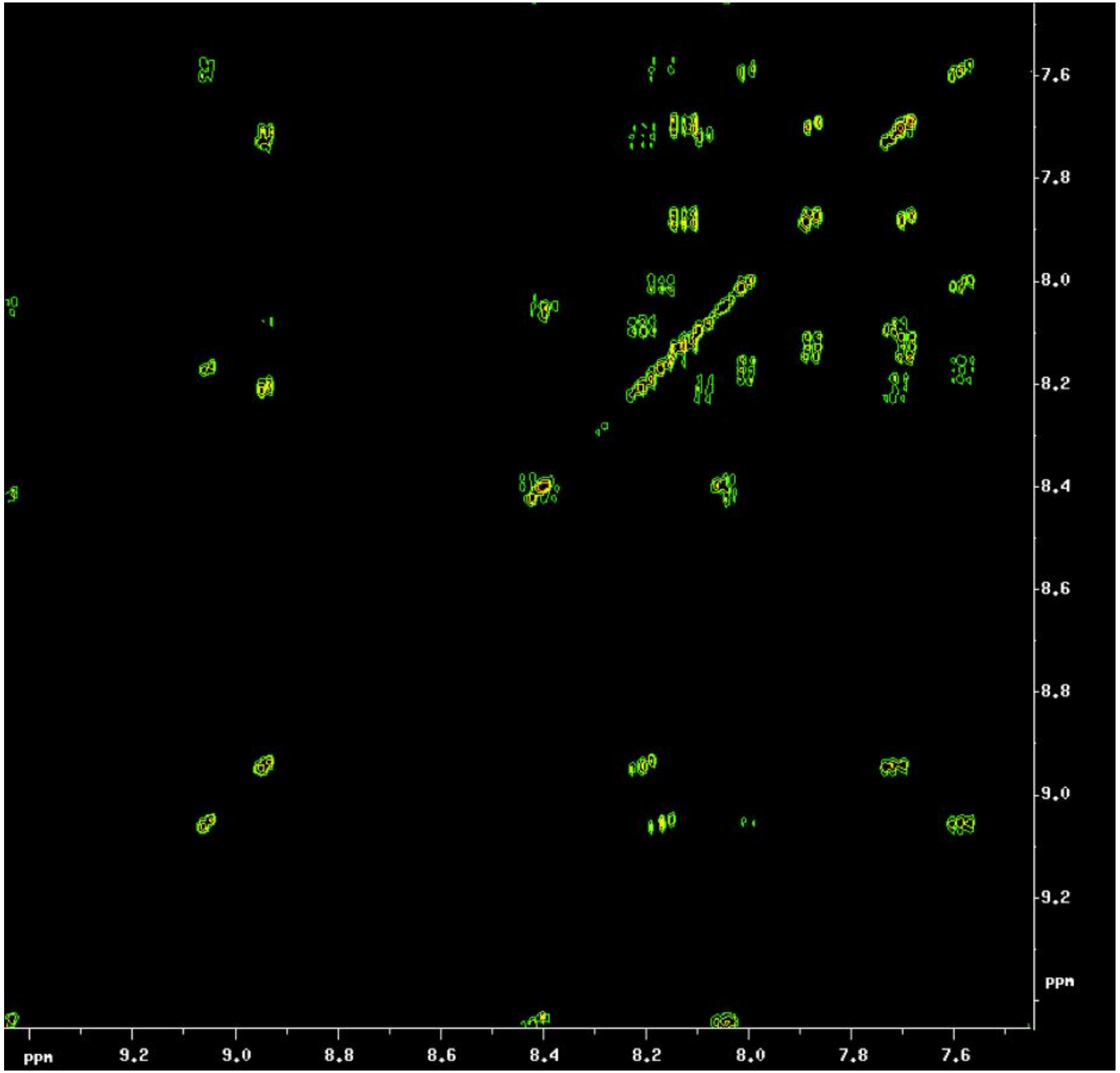
**3**

# $^1$H NMR of diaqua(PY4Me$_2$H)cobalt(III)



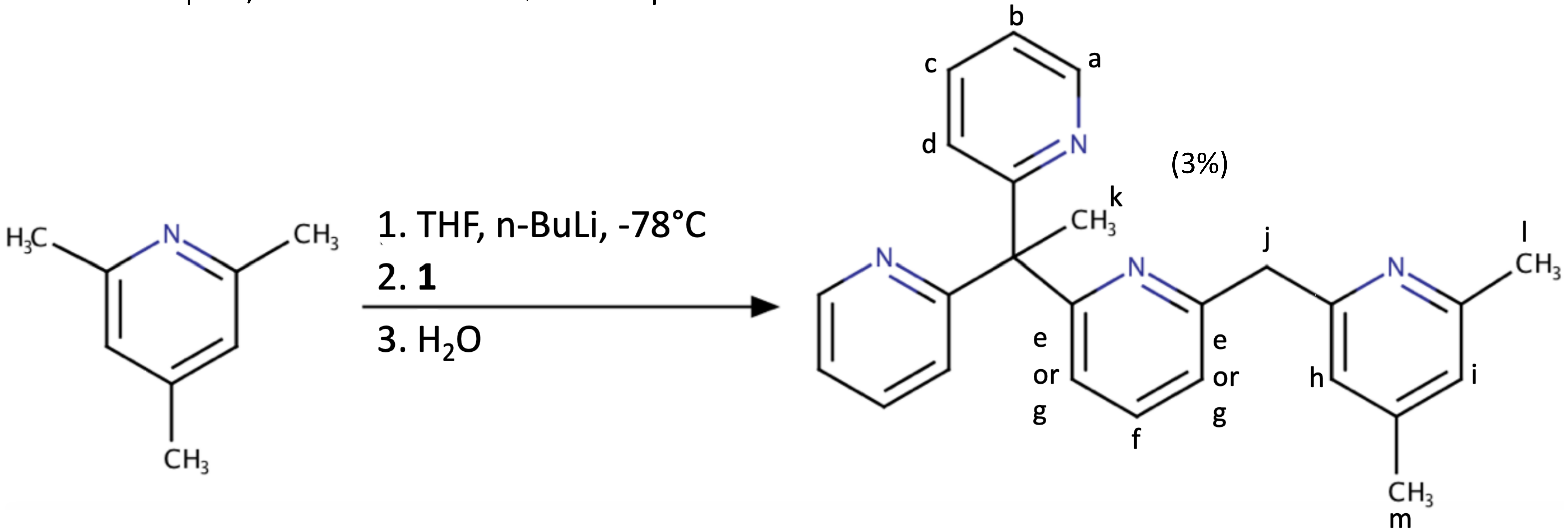
- Too complex to characterize with $^1$H NMR alone b/c now four chemically inequivalent rings
- Need $^1$H-$^1$H COSY (next slide) to confirm generation of complex
- Still cannot conclude which ring is which set of signals
- (Where is "q?")

# $^1$H-$^1$H COSY of diaqua(PY4Me$_2$H)cobalt(III)

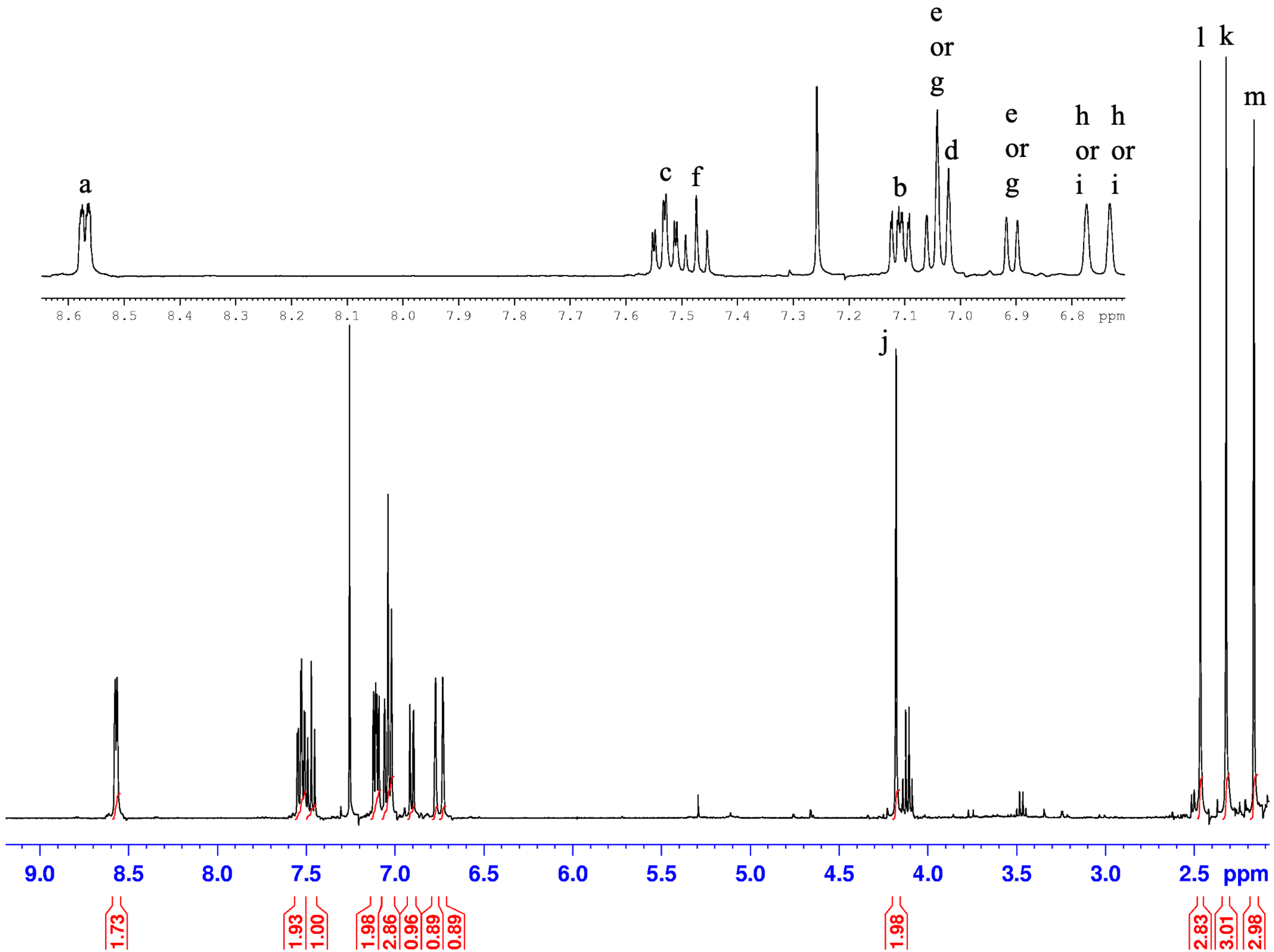


# Synthesis of PY4-Collidine

- Motivation: want more interpretable $^1$H NMR of ligand and ligand-containing complex
- 2,4,6-Collidine deprotonated at benzylic position
- Carbanion couples with precursor **1** via $S_NAr$ mechanism to form PY4-Collidine
- Desired *ortho*- coupling product seems to be favored
- Yield is poor/isolation is difficult → needs optimization

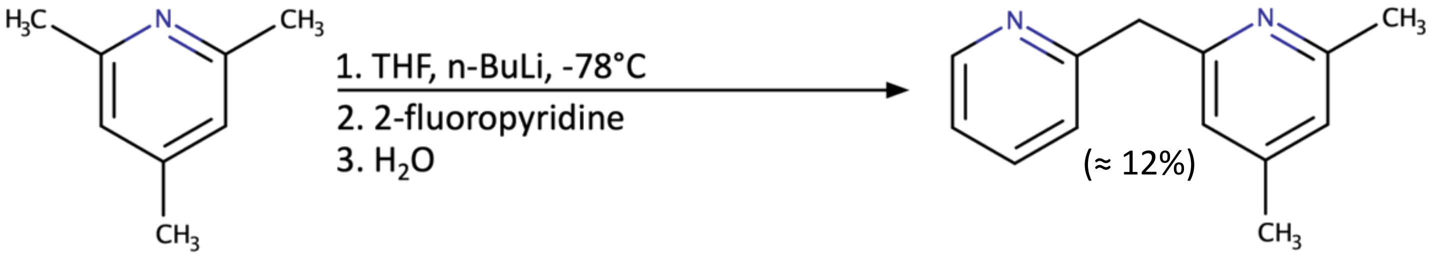


# $^1$H NMR of PY4-Collidine



- $^1$H NMR fully interpretable
- Will $^1$H NMR of complex containing PY4-Collidine be fully interpretable?

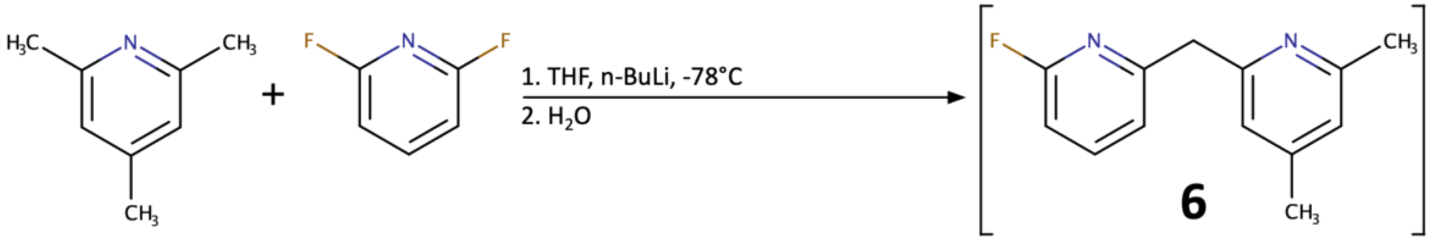
# Attempts towards PY4-Collidine optimization/purification



1. THF, n-BuLi, -78°C
2. 2-fluoropyridine
3. $H_2O$

(≈ 12%)

- Was able to increase yield of analog by adjusting reaction conditions
- Complete purification still an issue
- Attempts to synthesize **4** using optimization conditions failed

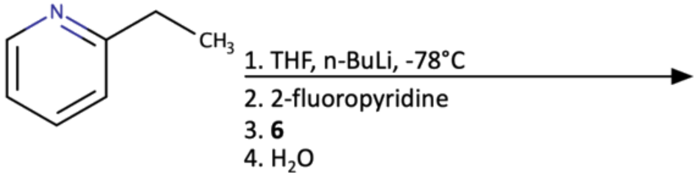


1. THF, n-BuLi, -78°C
2. $H_2O$

**6**

(Isolated intermediate)

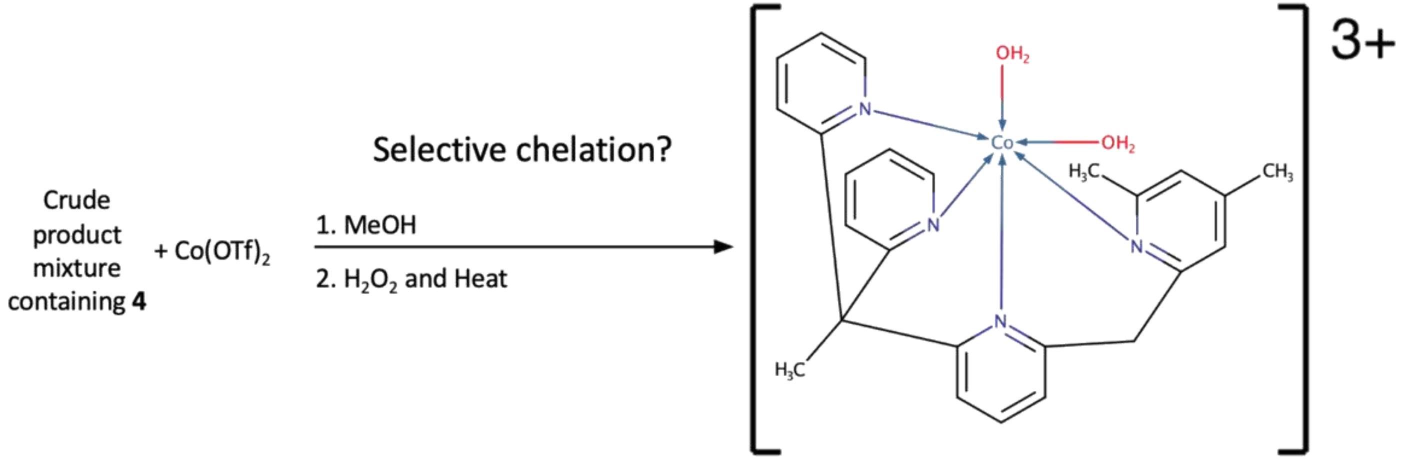
Different order of reagent addition unsuccessful



1. THF, n-BuLi, -78°C
2. 2-fluoropyridine
3. **6**
4. $H_2O$

**4** (Desired product not isolated)

Attempt to synthesize desired diaqua(**4**)cobalt(III) complex via selective chelation gave mixture of products



Crude product mixture containing **4**

+ $Co(OTf)_2$

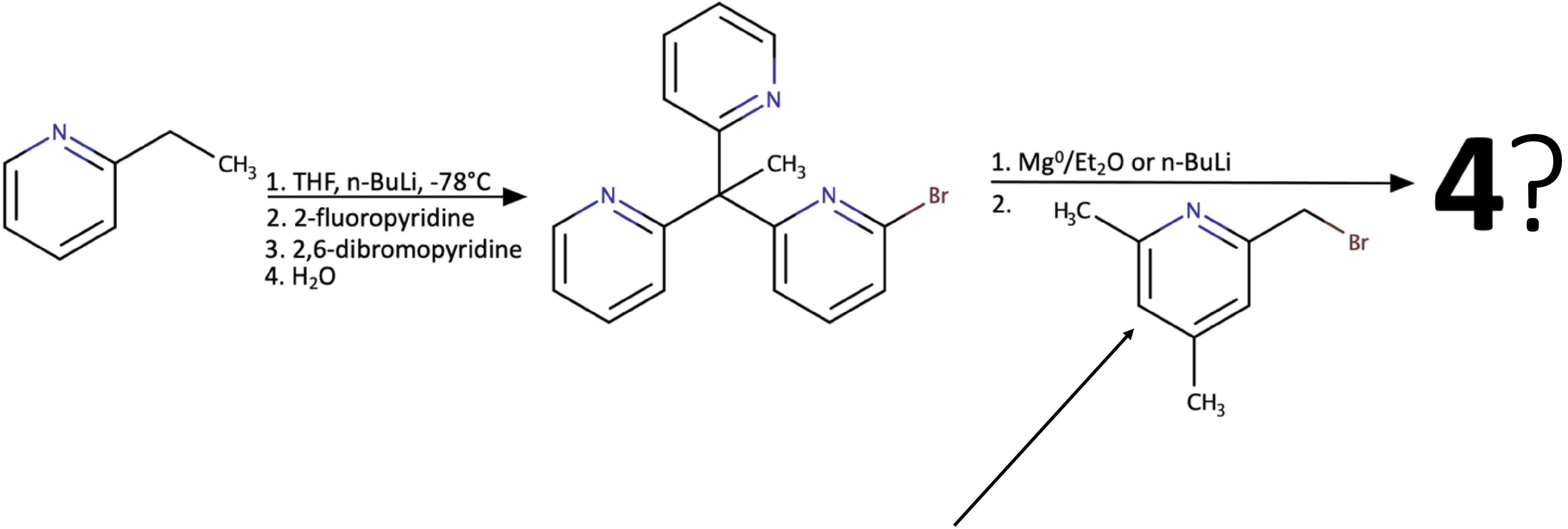
Selective chelation?

1. MeOH
2. $H_2O_2$ and Heat

(Not isolated)

# Current steps towards PY4-Collidine

- New synthetic route involving polarity inversion of the reactants
- FPY3 did not seem to undergo nucleophilic attack by 2,4,6-collidine anion easily (lots of FPY3 recovered after reaction)
- Will making PY3 species the nucleophile and collidine species the electrophile increase reaction favorability?



2-(bromomethyl)-4,6-dimethylpyridine just synthesized by Emmie Starchvick following procedure by Bandyopadhyay

*Org. Biomol. Chem.*, 2014, **12**, 1072

# Acknowledgements

- Thank you to:
  - Dr. George Greco for being an excellent research advisor/mentor and inorganic chemistry professor
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