Synthesis and Characterization of Rhenium 2,2'-pyridylNaphthyridine Metal Complexes

Benjamin F. Solomon

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Synthesis and Characterization of Rhenium 2,2′-pyridylnapthyridine Metal Complexes

by

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Honors Thesis

Submitted to:
Department of Chemistry
University of Richmond
Richmond, VA

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Abstract:

Rhenium (Re) is a group 7 heavy 5d transition metal in the same family as manganese (Mn) and technetium (Tc). Re-carbonyl complexes are known to be catalysts for many different kinds of reactions from C-C bond formation to reduction reactions like CO$_2$ reduction (CO$_2$RR)$^{1,2}$. With this in mind, we have prepared a set of six Re-carbonyl complexes of 2,2$'$-pyridyl-1,6-naphthyridine (1,6-pynap) and 2,2$'$-pyridyl-1,8-naphthyridine (1,8-pynap), a redox non-innocent ligand containing a bpy moiety as well as an additional aryl nitrogen binding location at which another metal-ligand bond could form. We have synthesized these complexes as precursors to multi-metallic molecular catalysts and have studied their properties through UV-Vis and NMR spectroscopies.
Background:

Naphthyridines are a class of 10-member heterobicyclic ring systems consisting of two fused pyridine rings. The name naphthyridine comes from the similar benzene-benzene fused-ring compound, naphthalene, and the six-member aromatic nitrogen containing ring, pyridine. The combination of the words naphthalene and pyridine yields the common name naphthyridine, coined in 1893 by German chemist Arnold Reissert who synthesized the first naphthyridine derivative in the same year. There are six structural isomers of naphthyridine shown in Figure 1. By using different isomers of naphthyridine, the distance between nitrogen functionalities of the compound can be altered predictably, meaning that the molecule is able to be finely tuned to improve its function for a particular purpose.

![Figure 1. Isomers of naphthyridine](image)

Structurally, naphthyridines are interesting for pharmaceutical purposes for a number of reasons. Reviews of biological activity of naphthyridines cite myriad possible applications from antimicrobial to anti-allergic to anti-Alzheimer's. The structural rigidity of the ring system allows for predictable distances between functionalities. Additionally, the flat characteristic of naphthyridines means that synthesis is not complicated by chirality. The aromaticity of the compound allows it to participate in aromatic stacking interactions with the ring nitrogens able to participate in hydrogen bonding interactions with polar sidechains. The structure is also relatively simple to synthesize in high yield by Friedländer synthesis and by this method is highly functionalizable. The simplicity of the naphthyridine structure and the ease of synthesis of functionalized naphthyridines gives it a large capacity for the development of pharmaceuticals and for other biological purposes. One such example of a naphthyridine-containing pharmaceutical is Gemifloxacin, an antibiotic used to treat pneumonia and bronchitis.

Naphthyridines are interesting in coordination chemistry because they bear aromatic nitrogens which form stable metal-ligand bonds by the donation of the nitrogen lone pair. Because naphthyridines have two aromatic nitrogens, either or both may participate in metal-ligand bonding. If the naphthyridine acts as a bridging ligand, where each aromatic nitrogen is bonded to a different metal center, the distances between the two bonding metal centers can be tuned depending on which isomer of naphthyridine is used as the bridging ligand. This is important for bimetallic catalysis where tuning the interactions between multiple metal centers changes the reactivity.

Bimetallic catalysis is a version of catalysis that utilizes multinuclear complexes and clusters to do reactions. The benefit of using these kinds of molecules and clusters is that they can be used to perform complicated multi-step reactions. Examples of the uses for bimetallic catalysis include CO₂...
Bimetallic catalysis comes with two problems: the generation of the catalysts themselves and the creation of complex structural and electronic effects. These complex effects arise from combination of two heavy metals attached to a single ligand. When metal-metal bonds are formed, the metals can be described as ligands of each other, complicating the assignment of electronic donation between substituents further. Given the fact that the complexes generated in this study are intended merely as precursors to bimetallic catalysis, the concept itself is mostly a goal for future research. The importance of the design of these ligands to that end is very important since the ligands’ ability to bear multiple metals is necessary for it to become a candidate for the synthesis of a bimetallic complex. To investigate whether a second metal could be attached to the distant nitrogen site, a protonation study was conducted to determine the ability of the nitrogens to donate their lone pairs.

Figure 2. Reaction of Re(CO)₅Cl with bpy (2,2'-bipyridine) analog 2,2'-pyridyl-1,6-naphthyridine. The reaction displaces two carbonyl ligands and attached the pyridynaphthyridine ligand at the bidentate α,α'-diimine binding pocket.

Bipyridines, specifically bpy (2,2'-bipyridine), are ligands that are well-known for their redox activity and have become nearly ubiquitous in CO₂ reduction reaction (CO₂RR) catalysis research. Typically, bipyridines are bidentate ligands that attach to metals via their α,α'-diimine binding pocket shown in Figure 2. Ruthenium bipyridine complexes are used extensively as chromophores attached to TiO₂ in dye sensitized solar cells. They work so well for this purpose because their π* energy levels are low enough that photoexcitation can cause transfer of electrons from the chelated metal’s d-orbitals to the ligand’s associated π* orbitals. Ligands that participate in electronic transfer in this and other similar ways are referred to as redox non-innocent since they participate in the electrochemical reaction for some process. This well-studied excitation creates spectroscopically what is referred to as the metal-to-ligand charge transfer band (MLCT). Because the molecule absorbs a particular wavelength of light to activate this pathway, UV-Vis experiments can be used to determine the wavelength, or band of wavelengths, which cause this interaction to take place. The longer the wavelength of light for the MLCT λₘₐₓ, the lower the energy of light that is absorbed to cause this charge transfer. Because bipyridines have these low-lying π* energy levels while still being higher in energy than metal d-orbitals, the λₘₐₓ of MLCT is typically between 350-550nm. Molar absorptivity coefficients for bipyridine-bearing complexes typically range between 2,000 - 30,000 M⁻¹ cm⁻¹ depending on what other ligands the complex bears. For example, Ru(bpy)³⁺ has λₘₐₓ, MLCT = 452nm and ε = 14,600 M⁻¹ cm⁻¹ and Re(bpy)(CO)Cl has λₘₐₓ, MLCT = 370nm and ε = 3,754 M⁻¹ cm⁻¹.
Re carbonyl complexes in the context of catalysis are dominated by the 0 and +1 oxidation states. This means that Re is able to undergo simple single-electron transfer mechanisms. However, important reduction reactions such as CO2RR and other catalytic processes such as those for organic reactions often require multi-electron transfer. For these reactions, electrocatalytic non-innocent bpy ligands are coordinated to the Re(CO) which allows the complex to perform multi-electron transfers. Because bipyridines serve this function, the creation of Re(bpy) complexes is common in order to justify them as molecular catalysts. Within the context of bimetallic catalysis, the use of the naphthyridine ligand in place of bpy adds a distant aryl nitrogen center some distance away from the metal center. The distant aryl nitrogen center is believed to be able to act as a ligand for a second metallic bonding site forming the bridging ligand in Figure 3.
Experimental:

\[
\text{Pyridin-2-yl)pivalamide.} \quad \text{2-aminopyridine (30.00 g, 319 mmol, 1 eq) was dissolved under N}_2 \text{ atmosphere in CH}_2\text{Cl}_2 (250 mL). To this solution triethylamine (49 mL, 351 mmol, 1.1 eq) was added and the solution was cooled to 0°C. When the solution was cooled, pivaloyl chloride (44 mL, 351 mmol, 1.1 eq) was added dropwise such that the temperature of solution did not rise above 10°C. The mixture was allowed to warm to room temperature and was stirred for 2 hours. The mixture was then washed with H}_2\text{O (3 × 50 mL) and saturated NaHCO}_3 \text{ solution (50 mL). The CH}_2\text{Cl}_2 \text{ solution was dried over MgSO}_4 \text{ and concentrated in vacuo and recrystallized in a minimal amount of CH}_2\text{Cl}_2 \text{ to give a white crystalline solid Yield: 47.36 g (266 mmol, 83.4%).}
\]

Mass spec (m/z): 178 (M+, 54.61%), 135 (15.22%), 122 (26.18%), 94 (100%), 57 (73.47%)
$^1$H NMR (300 MHz, CDCl$_3$) δ 9.32 (s, 1H), 8.48 (dt, 1H), 8.24 (ddd, 1H), 7.90 (td, 1H), 7.17 (ddd, 1H), 1.38 (s, 9H)
**N-(3-Formylpyridin-2-yl)-2,2-dimethylpropanamide.** N-(Pyridin-2-yl)pivalamide (8.515 g, 47.8 mmol, 1 eq) which was pre-dried for 24 hours under vacuum was dissolved under N₂ atmosphere in THF (85 mL) and the solution was cooled to −78°C. 2.5M nBuLi (47.8 mL, 120 mmol, 2.5 eq) was added dropwise to the solution. After addition of nBuLi, the solution was allowed to warm to 0°C and was stirred for 2 hours. The solution was cooled back to −78°C and DMF (mL, mmol, 3 eq) was added dropwise to the solution. The solution was then allowed to warm overnight to room temperature. The solution was then added to a 6M HCl/ice mixture. The organic layer turned a bright yellow color. The aqueous layer was basified with K₂CO₃ and extracted 3 times with EtOAc. The combined organic layers of this extraction were then washed with H₂O (20 mL) and saturated NaCl solution (20 mL). The organic layer was then dried over MgSO₄ and concentrated in vacuo. The product was collected as a brown oil. Yield (crude oil): 7.75 g (37.6 mmol, 78%).

**GC-MS (m/z):** 206 (M⁺, 1.29%), 149 (9.84%), 94 (66.77%), 57 (100%), 41 (39.92).
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 10.93 (s, 1H), 9.95 (s, 1H), 8.70 (dd, 1H), 8.07 (dd, 1H), 7.22 (dd, 1H), 1.39 (s, 9H)
2-Amino-3-pyridinecarboxaldehyde. The crude N-(3-Formylpyridin-2-yl)-2,2-dimethylpropanamide reaction product (a brown oil) was dissolved in 3M HCl and stirred at reflux for 4 hours. The resulting solution was washed with EtOAc (2 × 50 mL). The solution was then basified with K₂CO₃ and extracted 4 times with EtOAc. The combined organic layers were dried over MgSO₄, concentrated in vacuo, and the resulting solid was purified by sublimation onto a water coldfinger. The product was obtained as a yellow crystalline solid. Yield 3.10 g (25.4 mmol, 67%)

GC-MS (m/z): 122 (M⁺, 52.43%), 94 (100%), 67 (57.59%), 39 (51.01%)
$^1$HNMR (500 MHz, CDCl$_3$) $\delta$ 9.91 (s, 1H), 8.25 (dd, 1H), 7.94 (dd, 1H), 7.14 (s, 1H), 6.83 (dd, 1H), 6.09 (s, 1H)
2,2′-pyridyl-1,8-naphthyridine. 2-aminonicotinaldehyde (0.50 g, 4.1 mmol, 1.67 eq) was dissolved in EtOH (15 mL). To this solution 2-acetylpyridine (0.30 mL, 2.67 mmol, 1 eq) was added with 1 drop of saturated NaOH solution in MeOH and the mixture was stirred overnight at reflux conditions. If the reaction was not complete after 12 hours, additional NaOH solution was added and the solution was allowed to stir at reflux for additional time. The solution, which became a bright orange color, was allowed to cool to room temperature. Volatiles were removed in vacuo and the product was purified by sublimation* at 80°C. The product was obtained as an off-white crystalline solid. Yield 0.538 g (2.61 mmol, 97.1%).

*Product may need to be purified by recrystallization before sublimation.

GC-MS (m/z): 207 (M⁺, 100%), 179 (22.07%), 76 (9.55%), 51 (9.56%).
2,2-Pyridyl-1,8 Naphthyridine Assignment

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np = non-protonated

**HSQC:**
9.33 to 155.74, 9.22 to 154.13, 9.03 to 127.02, 9.06 to 142.82, 8.43 to 140.56, 7.97 to 125.61, 8.97 to 121.64, 8.43 to 140.56, 8.77 to 138.86, 7.87 to 129.18.

**HMBC:**
8.97 to 124.18, 7.97 to 124.18, 9.06 to 159.88, 9.03 to 159.88, 9.06 to 153.26, 8.77 to 153.26, 8.97 to 156.58, 8.43 to 156.58.

**NOESy:**
8.97 to 9.06, 9.06 to 8.77.

**COSy:**
9.33 to 7.97 and 8.77, 9.06 to 8.97, 9.03 to 8.43, 7.85, and 9.22.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.21 (dd, $J = 4.3$, 2.0 Hz, 1H), 8.93 (dd, $J = 8.0$, 1.1 Hz, 1H), 8.84 (d, $J = 8.5$ Hz, 1H), 8.78 (dd, $J = 4.8$, 1.8, 0.9 Hz, 1H), 8.39 (d, $J = 8.5$ Hz, 1H), 8.33 (dd, $J = 8.1$, 2.0 Hz, 1H), 7.96 (d, $J = 8.1$, 4.3 Hz, 1H), 7.46 (ddd, $J = 7.6$, 4.9, 1.2 Hz, 1H).
$^{13}$C NMR (126 MHz, CDCl$_3$) δ 159.28, 155.11, 154.92, 153.35, 148.81, 137.99, 137.74, 137.58, 124.97, 123.09, 122.97, 122.27, 120.45.
COSy
NOESy
Re(1,8-pynap)(CO)$_3$Cl. 2,2$'$-pyridyl-1,8-naphthyridine (0.290 g, 1.40 mmol, 1 eq) and Re(CO)$_5$Cl (0.500 g, 1.38 mmol, 1 eq) were added to a 50 mL round bottom flask with a stir bar and condensor. 14 mL of absolute EtOH was added to the flask and the mixture was refluxed overnight. The resulting cherry red solid precipitate was filtered and vacuum dried. Yield: 0.629 g (1.23 mmol, 87.6%).

$^1$H NMR (500 MHz, DMSO) δ 9.33 (dd, $J = 4.2$, 1.9 Hz, 1H), 9.22 (dd, $J = 5.5$, 1.5 Hz, 1H), 9.06 (d, $J = 8.6$ Hz, 1H), 9.03 (d, $J = 8.2$ Hz, 1H), 8.98 (d, $J = 8.7$ Hz, 1H), 8.77 (dd, $J = 8.1$, 1.9 Hz, 1H), 8.44 (td, $J = 7.9$, 1.5 Hz, 1H), 7.97 (dd, $J = 8.1$, 4.2 Hz, 1H), 7.87 (ddd, $J = 7.6$, 5.4, 1.2 Hz, 1H).
Re(1,8-pynap)(CO)₃ACN. Re(1,8-pynap)(CO)₃Cl (0.2 g, 0.39 mmol, 1 eq) was added to a 25 mL round bottom flask with stir bar and condenser. AgPF₆ (0.094 g, 0.37 mmol, 1 eq) was added quickly to the flask and the mixture was dissolved in 10 mL of acetonitrile. The solution was refluxed overnight. Filtered the solution through a fine fritted funnel to remove the AgCl precipitate. Product concentrated in vacuo. Yield (crude): 0.247 g (0.372 mmol, 95.4%).

¹H NMR (500 MHz, CD₃CN) δ 9.47 (ddd, J = 5.5, 1.5, 0.8 Hz, 1H), 9.43 (dd, J = 4.2, 1.9 Hz, 1H), 8.89 (d, J = 8.6 Hz, 1H), 8.69 (dd, J = 8.2, 1.9 Hz, 1H), 8.62 (dt, J = 8.2, 1.1 Hz, 1H), 8.54 (d, J = 8.7 Hz, 1H), 8.37 (td, J = 8.0, 1.6 Hz, 1H), 7.83 (dt, J = 5.1, 1.5 Hz, 2H), 8.00 (dd, J = 8.2, 4.2 Hz, 1H), 7.93 (ddd, J = 7.7, 5.4, 1.2 Hz, 1H), 7.78 (tt, J = 7.7, 1.6 Hz, 1H), 7.23 – 7.15 (m, 2H).
Re(1,8-pynap)(CO)_3Py. Re(1,8-pynap)(CO)_3Cl (0.2 g, 0.39 mmol, 1 eq) was added to a 100 mL round bottom flask with stir bar and condenser. AgPF_6 (0.098 g 0.39 mmol, 1 eq) was added quickly to the flask and the mixture was dissolved in 16 mL of acetonitrile. Pyridine (0.16 mL, 1.95 mmol, 5 eq) was added to the solution via syringe. The solution was refluxed overnight. Filtered the solution through a fine fritted funnel to remove the AgCl precipitate. Product was concentrated in vacuo. Yield: 0.137 g (0.195 mmol, 50%).

^1^H NMR (500 MHz, CD_3CN) δ 9.49 – 9.41 (m, 2H), 8.89 (d, J = 8.6 Hz, 1H), 8.69 (dd, J = 8.2, 1.9 Hz, 1H), 8.62 (d, J = 8.2 Hz, 1H), 8.54 (d, J = 8.7 Hz, 1H), 8.37 (td, J = 7.9, 1.6 Hz, 1H), 8.23 (dt, J = 5.0, 1.6 Hz, 2H), 8.00 (dd, J = 8.2, 4.2 Hz, 1H), 7.93 (ddd, J = 7.8, 5.4, 1.3 Hz, 1H), 7.78 (ddd, J = 9.3, 7.7, 1.6 Hz, 1H), 7.23 – 7.16 (m, 2H).
N-(Pyridin-4-yl)pivalamide. 4-aminopyridine (10.065 g, 107 mmol, 1 eq) was dissolved under N₂ atmosphere in CH₂Cl₂ (125 mL). To this solution triethylamine (16.3 mL, 117 mmol, 1.1 eq) was added and the solution was cooled to 0°C. When the solution was cooled, pivaloyl chloride (14.4 mL, 117 mmol, 1.1 eq) was added dropwise such that the temperature of solution did not rise above 10°C. The mixture was allowed to warm to room temperature and was stirred for 2 hours. The mixture was then washed with H₂O (3 × 50 mL) and saturated NaHCO₃ solution (50 mL). The CH₂Cl₂ solution was dried over MgSO₄ and concentrated in vacuo and recrystallized in a mixture of CH₂Cl₂ and Hexanes to give a white crystalline solid. Yield: 12.634 g (70.9 mmol, 66%).

GC-MS (m/z): 178 (M⁺, 40.13%), 135 (8.22%), 122 (16.83%), 94 (100%), 57 (75.76%)
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.43 (dd, 2H), 8.12 (s, 1H), 7.56 (dd, 2H), 1.30 (s, 9H).
N-(3-Formylpyridin-4-yl)-2,2-dimethylpropanamide. N-(Pyridin-4-yl)pivalamide (2.044 g, 11.5 mmol, 1 eq) which was pre-dried for 24 hours under vacuum was dissolved under N₂ atmosphere in THF (30 mL) and the solution was cooled to −78°C. 2.5M nBuLi (11.48 mL, 23.0 mmol, 2.5 eq) was added dropwise to the solution. After addition of nBuLi, the solution was allowed to warm to 0°C and was stirred for 2 hours. The solution was cooled back to −78°C and DMF (2.65 mL, 34.5 mmol, 3 eq) was added dropwise to the solution. The solution was then allowed to warm overnight to room temperature. The solution was then added to a 6M HCl/ice mixture. The organic layer turned a bright yellow color. The aqueous layer was basified with K₂CO₃ and extracted 3x with EtOAc. The combined organic layers of this extraction were then washed with H₂O and saturated NaCl solution. The organic layer was then dried over MgSO₄ and concentrated in vacuo. The product was collected as a brown oil. Yield (crude oil): 2.008 g (9.75 mmol, 84.9%).

GC-MS (m/z): 206 (M⁺, 0.79%), 150 (27.07%), 94 (20.27%), 57 (100%), 41 (32.60%).
$^1$H NMR (300 MHz, CDCl$_3$) δ 11.48 (s, 1H), 10.04 (s, 1H), 8.85 (s, 1H), 8.66 (s, 2H), 1.37 (s, 9H).
4-Amino-3-pyridinecarboxaldehyde. The crude N-(3-Formylpyridin-4-yl)-2,2-dimethylpropanamide reaction product (a brown oil) was dissolved in 3M HCl and stirred at reflux for 4 hours. The resulting solution was washed with EtOAc (2 × 50 mL). The solution was then basified with K₂CO₃ and extracted 4x with EtOAc. The combined organic layers were dried over MgSO₄, concentrated in vacuo, and the resulting solid was purified by sublimation onto a water coldfinger. The product was obtained as a yellow crystal. Yield: 0.62 g (5.08 mmol, 51.9%).

GC-MS (m/z): 122 (M⁺, 100%), 94 (96.16%), 77 (10.19%), 67 (98.56%), 39 (61.44%).
$^1$H NMR (300 MHz, CDCl₃) δ 9.82 (s, 1H), 9.21 (s, 1H), 8.75 (s, 1H), 8.66 (s, 1H), 7.90 (d, 1H), 7.01 (d, 1H).
PROTON_UR_NOPRINT CDC3 /opt/topspin rdominey 2
2,2′-pyridyl-1,6-naphthyridine. 4-aminonicotinaldehyde (0.6175 g, 5.06 mmol, 1.0 eq) was dissolved in EtOH (10 mL). To this solution 2-acetylpyridine (0.85 mL, 7.58 mmol, 1.5 eq) was added with 10 drops of saturated NaOH solution in MeOH and the mixture was stirred overnight at reflux conditions. If the reaction was not complete after 12 hours, additional NaOH solution was added and the solution was allowed to stir at reflux for additional time. The solution, which became a dark yellow-brown color overnight, was allowed to cool to room temperature. Volatiles were removed in vacuo and the product was purified by sublimation onto a water coldfinger. The product was obtained as an off-white crystalline solid. Yield: 0.832 g (4.01 mmol, 79.3%).

2,2-Pyridyl-1,6 Naphthyridine Assignment

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np = non-protonated
− Being the only singlet, s, 9.36 and C 152.19 are assigned H/C 13.
− s, 9.36 and d, 8.46 couple through space (NOESY), assigned H/C 15.
− d, 8.46 and d, 8.78 couple strongly in COSY, assigned H/C 16.
− The triplets each couple to a doublet by NOESY and COSY: t, 7.46- d, 8.80 and t, 7.94- d, 8.72. The triplets also couple to each other by NOESY and COSY. This proves ordering of d, 8.72- t, 7.94- t, 7.46- d, 8.80 from either Cs and Hs 3-6 or backwards from 6-3.
− For 3-6 spin system, 149.42 was assigned as C 6 because this is a shift that would be expected for C alpha to N. That makes the order of 3-6 this: 3(8.72/122.49), 4(7.94/137.19), 5(7.46/125.04), and 6(8.80/149.42) (HMBC).
− C 14 is assigned 123.58 as it is the only non-protonated carbon (np) not shielded by the electron density of a neighboring nitrogen. This shifts the peak up-field.
− H 13 J4-couples to C 146.12, assigned H/C 11 (HMBC).
− H/C 11 couple in COSY to H/C (8.04/122.76), assigned H/C 10.
− H 15 couples to both C 150.41 and C 160.72. By process of elimination, C (np) 155.13 must be C 2 (HMBC). For confirmation, H 4 (7.94) J4-couples to C 155.13 (HMBC).
− H 11 J4-couples to C 9, assigned H/C 9 and H/C 7 (HMBC).

GC-MS (m/z): 207 (M+, 100%), 206 (57.25%), 180 (15.12%), 179 (21.08%), 129 (16.62%), 78 (23.17%), 51 (30.30%)
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.40 (s, 1H), 8.87 (d, $J = 8.5$ Hz, 1H), 8.84 – 8.77 (m, 2H), 8.74 (dt, $J = 8.0$, 1.2 Hz, 1H), 8.50 (d, $J = 8.6$, 1.0 Hz, 1H), 8.12 (d, $J = 6.1$, 1.0 Hz, 1H), 7.95 (td, $J = 7.8$, 1.9 Hz, 1H), 7.46 (dd, $J = 7.5$, 4.7, 1.3 Hz, 1H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 160.69, 155.17, 152.24, 150.41, 149.44, 146.24, 137.20, 136.56, 125.03, 123.58, 122.72, 122.49, 120.83.
COSy
HSQC
HMBC

\[ \delta_{H} \text{ (ppm)} \]

\[ \psi_{C} \text{ (ppm)} \]
Re(1,6-pynap)(CO)\textsubscript{3}Cl. 2,2’-pyridyl-1,6-naphthyridine (0.312 g, 1.51 mmol, 1 eq) and Re(CO)\textsubscript{5}Cl (0.514 g, 1.42 mmol, 1 eq) were added to a 50 mL round bottom flask with a stirbar and condensor. 14 mL of absolute EtOH was added to the flask and the mixture was refluxed overnight. The resulting orange solid precipitate was filtered and vacuum dried. Yield: 0.683 g (1.33 mmol, 93.7%).

\textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}CN) δ 9.51 (d, \(J = 0.9\) Hz, 1H), 9.25 (ddd, \(J = 5.4, 1.7, 0.8\) Hz, 1H), 9.01 (d, \(J = 6.3\) Hz, 1H), 8.93 (dd, \(J = 8.7, 0.9\) Hz, 1H), 8.71 – 8.68 (m, 1H), 8.67 (d, \(J = 8.7\) Hz, 1H), 8.63 (dt, \(J = 6.3, 0.9\) Hz, 1H), 8.34 (td, \(J = 7.9, 1.6\) Hz, 1H), 7.78 (ddd, \(J = 7.7, 5.4, 1.2\) Hz, 1H).
Re(1,6-pynap)(CO)\textsubscript{3}ACN. Re(1,6-pynap)(CO)\textsubscript{3}Cl (0.2 g, 0.39 mmol, 1 eq) was added to a 25 mL round bottom flask with stirbar and condenser. AgPF\textsubscript{6} (0.094 g 0.37 mmol, 1 eq) was added quickly to the flask and the mixture was dissolved in 10 mL of acetonitrile. The solution was refluxed overnight. Filtered the solution through a fine fritted funnel to remove the AgCl precipitate. Product concentrated in vacuo. Yield: crude.

\textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}CN) \delta 9.58 (d, J = 0.8 Hz, 1H), 9.26 (ddd, J = 5.5, 1.6, 0.8 Hz, 1H), 9.07 (d, J = 6.4 Hz, 1H), 9.03 (dd, J = 8.7, 0.9 Hz, 1H), 8.75 (dt, J = 8.2, 1.0 Hz, 1H), 8.72 (d, J = 8.8 Hz, 1H), 8.58 (dt, J = 6.4, 0.9 Hz, 1H), 8.43 (td, J = 8.0, 1.6 Hz, 1H), 7.89 (ddd, J = 7.8, 5.5, 1.2 Hz, 1H).
Re(1,6-pynap)(CO)₃Py. Re(1,6-pynap)(CO)₃Cl (0.2 g, 0.39 mmol, 1 eq) was added to a 100 mL round bottom flask with stirbar and condenser. AgPF₆ (0.10 g 0.39 mmol, 1 eq) was added quickly to the flask and the mixture was dissolved in 15 mL of acetonitrile. Pyridine (0.16 mL, 1.95 mmol, 5 eq) was added to the solution via syringe. The solution was refluxed overnight. Filtered the solution through a fine fritted funnel to remove the AgCl precipitate. Product was concentrated in vacuo. Yield (crude): 0.280 g (0.40 mmol, 103%).

¹H NMR (500 MHz, CD₃CN) δ 9.61 (d, J = 0.8 Hz, 1H), 9.44 (dddd, J = 5.5, 1.5, 0.8 Hz, 1H), 9.14 (d, J = 6.3 Hz, 1H), 8.97 (ddd, J = 8.6, 0.9 Hz, 1H), 8.72 (dt, J = 6.3, 0.9 Hz, 1H), 8.62 – 8.54 (m, 2H), 8.51 (d, J = 8.7 Hz, 1H), 8.37 (dd, J = 8.0, 1.6 Hz, 1H), 7.95 (dddd, J = 7.7, 5.5, 1.2 Hz, 1H), 7.86 – 7.77 (m, 3H), 7.38 (ddd, J = 7.7, 5.6 Hz, 1H), 7.19 – 7.14 (m, 2H).
Results and Discussion:

Figure 4. Retrosynthesis of the pyridylnaphthyridine ligand

The general synthetic scheme for pyridyl-substituted naphthyridines uses a Friedländer synthesis of an ortho aromatic amine aldehyde isomer and 2-acetylpyridine. The two synthetic targets in this study were 2,2'-pyridyl-1,6-naphthyridine (1,6-pynap) and 2,2'-pyridyl-1,8-naphthyridine (1,8-pynap). The synthesis of each pyridyl naphthyridine ligand was carried out in four synthetic steps. The synthesis of 1,6-pynap uses 4-aminopyridine as starting material and the synthesis of 1,8-pynap uses 2-aminopyridine starting material. The first step in their synthesis is a pivaloyl protection of the reactive amine functional group. This step is carried out in methylene chloride at 0°C using triethylamine as a base. Slight excess of the base and the protecting group are used to ensure complete protection before continuing to the next step. One downside to this protecting group is that in some cases, the amine is double protected by the pivaloyl group, albeit in small quantities.

Reaction 1. N-(Pyridinyl)pivalamide

The protection of the amine functionality is necessary because the second step, shown in Reaction 2, utilizes the strong base nBuLi to deprotonate one of the aryl hydrogens and o-formylate at the deprotonation site with DMF. THF is a preferred solvent for nBuLi reactions as it minimizes the likelihood of side-reactions with the solvent. The dried crude product of this reaction is then refluxed in 3M HCL to remove the pivaloyl protecting group. The product, a yellow solid is purified by sublimation at 80-100°C to give ortho amine-aldehyde-substituted pyridine in Reaction 3 with a total two-step yield of 60%.

Reaction 2. N-(3-Formylpyridinyl)-2,2-dimethylpropanamide.
Reaction 3. Amino-3-pyridinecarboxaldehyde.

The product 4-aminonicotinaldehyde then undergoes the Friedländer condensation reaction, shown in Reaction 4, with 2-acetylpyridine to ring close and form the pyridyl naphthyridine structure. This is done by refluxing 4-aminonicotinaldehyde with 2-acetylpyridine in EtOH under nitrogen atmosphere. The reaction is catalyzed by a drop of saturated NaOH in MeOH. The product of this reaction can be purified from the reaction mixture by sublimation onto a coldfinger at 100°C at full vacuum.

Reaction 4. 2,2'-pyridynaphthyridine

Because the pyridynaphthyridine ligand bears an α,α'-diimine chelation site, it reacts easily with Re(CO)$_5$Cl, displacing two carbonyl ligands according to literature procedure$^{18}$. We adapted this literature procedure and used EtOH instead of hexanes or toluene and found that the product still precipitates out of solution despite the change in solvent. Our adapted reaction scheme is shown in Reaction 5.

Reaction 5. Re(pynap)(CO)$_3$Cl

According to the literature, the expected product of this reaction is the facial isomer$^2$. The Re(1,6-pynap)(CO)$_3$Cl complex was found to be extremely insoluble in many solvents. In particular, there is a lack of solubility in deuterated solvents for NMR spectroscopy (CDCl$_3$, ACN-d$_3$, DMSO-d$_8$). One potential means of increasing the solubility is to replace the chloride ligand with an L-type ligand which donates 2 electrons instead of the X-type chloride which only donates one electron. This replacement causes the compound to become cationic and, in our synthesis, the counterion used was hexafluorophosphate (PF$_6$).
Chloride ligands on α,α′-diimine-substituted Re are known to be replaceable by N-donor ligands such as pyridine and acetonitrile.\textsuperscript{15,18,19} The acetonitrile replacement reaction is shown in Reaction 6. It is conducted by reflux of Re(pynap)(CO)\textsubscript{3}Cl in acetonitrile along with AgPF\textsubscript{6}. The PF\textsubscript{6} will act as a counterion for the resulting cationic complex and the Ag will precipitate out of solution with chloride ion. The pyridine replacement reaction is shown in Reaction 7. The reaction is done under similar conditions to the acetonitrile reaction except 5 equivalents of pyridine are added. This molar excess is enough to do the replacement of the chloride ligand instead of the acetonitrile solvent.

![Reaction 6. Re(pynap)(CO)\textsubscript{3}ACN](image1)

![Reaction 7. Re(pynap)(CO)\textsubscript{3}Py](image2)

The characterization of each of the pyridynaphthyridine ligands was done by 2D NMR spectroscopy. NOESy, COSy, HSQC, and HMBC experiments were run on a 500 MHz NMR. For 1,6-pynap, the presence of the hydrogen in the five-position of the ligand was a hook which allowed for the characterization of most of the rest of the hydrogens on the ligand. This hydrogen is not located next to any protonated carbons and therefore is not split by indirect coupling through bonds in the \textsuperscript{1}H NMR. Characterization of the pyridyl spin system was able to be confirmed by the chemical shift of the nitrogen on the pyridine ring, which shifted one of the doublet proton peaks to higher frequency due to its electron withdrawing character.
Figure 5. Aromatic region zooms of $^1$H NMR for Re complexes. Trace 1- 2,2'-pyridyl-1,6-naphthyridine (1,6-pynap), Trace 2- Re(1,6-pynap)(CO)$_3$Cl, Trace 3- Re(1,6-pynap)(CO)$_3$ACN, Trace 4- Re(1,6-pynap)(CO)$_3$Py (Py = pyridine)

The attachment of the ligand to the metal, and the subsequent replacement of the chloride ligand with acetonitrile and pyridine causes the ligand to exist in slightly different chemical environments. The peak shifts of the ligand signals are shown in Figure 5. Judging based on the peak shape, the movement of many peaks show a trend of increasing or decreasing chemical shift depending on the field strength of the ligand substituted for chloride. For example, 7.53 (t, 1H) which is assigned as the triplet closest to the nitrogen in the pyridyl ring of the ligand, demonstrates shifting to higher frequency upon the addition of ligands of higher field strength.

Since one of the major purposes of this research is to investigate the ability of pyridylnaphthyridine ligands to form metal-ligand bonds with multiple metals, it is necessary to determine whether these complexes are actually capable of forming these bonds. This can be investigated by studying their ability to be protonated in solution by UV-Vis absorption spectroscopy. The titrations of Re(1,6-pynap)(CO)$_3$Cl and Re(1,8-pynap)(CO)$_3$Cl were studied in this manner. The data in Figures 6 and 7 show that for Re(1,6-pynap)(CO)$_3$Cl, upon addition of amounts of 0.1M HCl, there is a noticeable red-shifting of the MLCT peak which appears between 350-700 nm. This red-shifting of the MLCT peak is a result of a protonation occurring at the non-linking aryl nitrogen in the six-position of the naphthyridine. Because of this, it is believed that the Re(1,6-pynap)(CO)$_3$Cl complex is capable of acting as a linker for another metal.
Conversely, the UV-Vis titration spectrum of Re(1,8-pynap)(CO)₃Cl, shown in Figure 7, demonstrated no noticeable shifting of the MLCT. This suggests that the non-linking aryl nitrogen in the eight-position of the naphthyridine will not act as a linker for a new metal-ligand bond. It is not known why the 1,6-pynap complex is protonatable and the 1,8-pynap complex is not. It is speculated that the steric impact from the Re(CO)₃ metal center could play a role. Analysis of the NMR spectra of the 1,6-pynap ligand shows that the electron density on the eight-position does not experience any notable withdrawing effect which shouldn’t disqualify it from forming a metal-ligand bond. This gives credence to the steric impact theory.
Figure 8. Diagram of the photoisomerization of octahedral Ru(tpy)(1,8-pynap)OH$_2^{2+}$ (tpy = 2,2';6,2' -terpyridine)$^{21,22}$.

The exposure of substituted naphthyridine ligand-bearing Re, Cr, or Mn complexes to visible light has been found to cause photoisomerization of the complexes bearing photodissociable ligands such as aquos or carbonyls $^{23,24,21,22}$. In octahedral complexes of 1,8-pynap, photoexcitation of the complex can lead to the dissociation of a ligand $^{21}$. The resulting 5-coordinate complex can then undergo isomerization. This isomerization could be accomplished for example through either a turnstile or Berry pseudo-rotation mechanism. These processes can cause a photoisomerization of the complex changing between distal and proximal isomers created by the asymmetry of the pyridyl naphthyridine ligand (Figure 2). The distal and proximal isomers in these kinds of systems is defined by the proximity of the naphthyridine moiety to the photodissociable ligand. In Figure 2, the isomer where the naphthyridine is close to the photodissociable ligand is the proximal isomer and its geometric isomer is the distal isomer. The complexes investigated in this report do not display this kind of asymmetry, but further displacement of carbonyl ligands in these complexes could lead to these effects.

Conclusion:

We have synthesized six Re complexes of 2,2'-pyridyl naphthyridines. The ligands were first synthesized using a Friedländer synthesis of 2-acetylpypyridine and either 4-Amino-3-pyridinecarboxaldehyde or 2-Amino-3-pyridinecarboxaldehyde. The ligands were attached to Re by simple reflux in EtOH. Due to the solubility properties of the Re(pynap)(CO)$_3$Cl complexes, ligands replacements of the chloride ligand were done with acetonitrile and pyridine. To investigate the coordination properties of the complexes, UV-Vis spectra were recorded of titrations of the Re(pynap)(CO)$_3$Cl complexes in acetonitrile. These studies determined that the 1,6-pynap isomer is readily protonated in HCl while the 1,8-pynap isomer is not protonated under the same conditions. Continuing studies of these complexes including X-ray crystallography and catalytic studies are in progress.
References:


