INVESTIGATION INTO THE SCOPE, LIMITATIONS, AND MECHANISTIC ASPECTS OF A REGIOSELECTIVE ACYLATION OF CYCLOPLATINATED COMPLEXES

by

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June, 2015

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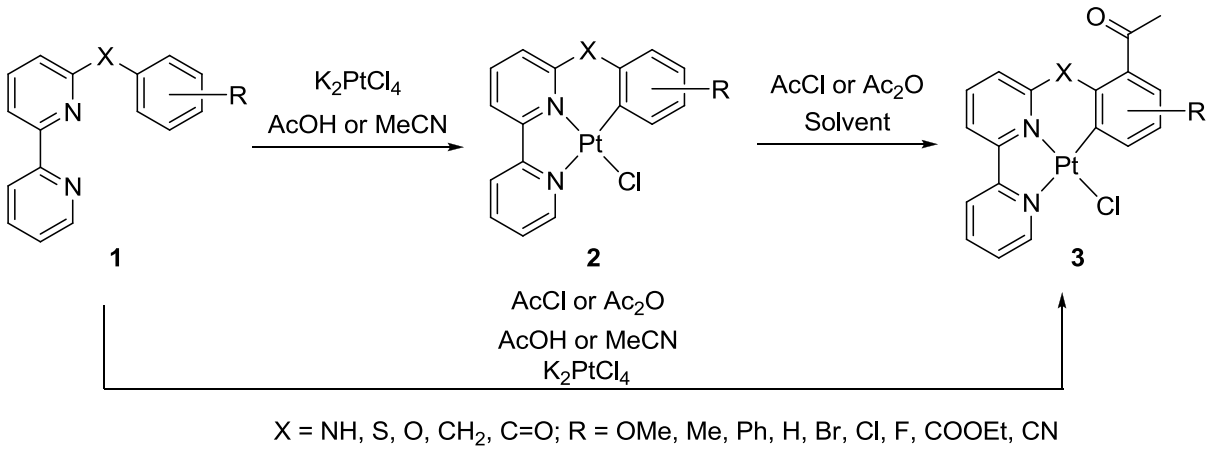
In the reaction of *N*-isopropyl-*N*-phenyl-2,2'-bipyridin-6-amine with potassium tetrachloroplatinate, the selective C–H bond activation was complicated by the low selectivity of $sp^2$ C–H bond activation in acetonitrile and low yield of $sp^3$ C–H activation in acetic acid. The product resulting from the highly selective $sp^3$ activation was collected in low yield due to competing side reactions. Following $C^{iPr}$–N bond dissociation, the platinum complex (**2a**, X = NH, R = H) was regioselectively acylated. It was later discovered that **2a** could be regioselectively acylated by reacting with acetic anhydride in acetic acid. Furthermore, the acylated platinum complex (**3a**, X = NH, R = H) was also prepared in a cascade intramolecular cycloplatination-acylation reaction by reacting the organic ligand (**1a**, X = NH, R = H) with potassium tetrachloroplatinate in a mixture of acetic acid and acetic anhydride. A series of ligands with structural modifications have been designed, synthesized, cycloplatinated, and acylated to investigate the scope of this reaction, and to shed light on the mechanism of the acylation. The reaction showed great tolerance to various linker groups (X), as well as many electron donating/withdrawing groups (R) on the phenyl ring. Reaction conditions were optimized and a variety of solvents were useful in this reaction, including acetonitrile, benzonitrile, and 1,2-dichloroethane. Alternate electrophiles such as benzoyl chloride were also useful in the acylation reaction. Experimental results of the acylation reaction of a library of

substrates (**2**) will be reported, and the mechanistic implications of these results will be discussed.



# INVESTIGATION INTO THE SCOPE, LIMITATIONS, AND MECHANISTIC ASPECTS OF A REGIOSELECTIVE ACYLATION OF CYCLOPLATINATED COMPLEXES

A Thesis

Presented To

The Faculty of the Department of Chemistry

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by

Jeffrey Samuel Carroll

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| δ | Chemical shift |
| K | Kelvin |
| $^{o}C$ | Degrees centigrade |
| AcOH | acetic acid |
| MeCN | acetonitrile |
| THF | tetrahydrofuran |
| $Ac_2O$ | acetic anhydride |
| AcCl | acetyl chloride |
| EtOH | ethanol |
| $Et_2O$ | diethyl ether |
| PhCHO | benzaldehyde |
| BzCl | benzoyl chloride |
| PCC | pyridinium chlorochromate |
| $MgSO_4$ | magnesium sulfate |
| $H_2SO_4$ | sulfuric acid |
| DME | 1,2-dimethoxyethane |
| $K_2PtCl_4$ | potassium tetrachloroplatinate |
| CuI | copper(I) iodide |
| $CH_2Cl_2$ | dichloromethane |
| n-BuLi | *n*-butyl lithium |
| $NaO^{t}Bu$ | sodium tert-butoxide |
| $ZnCl_2$ | zinc (II) chloride |
| $CDCl_3$ | deuterated chloroform |
| $CD_2Cl_2$ | deuterated dichloromethane |

| | |
|---|---|
| DMSO-d6 | deuterated dimethylsulfoxide |
| HCl | hydrogen chloride |
| r.t. | room temperature |
| TLC | Thin layer chromatography |
| pm | picometers |
| mmol | millimoles |
| $Pd(dba)_2$ | bis(dibenzylideneacetone)palladium(0) |
| $Pd(OAc)_2$ | palladuim(II) acetate |
| $PPh_3$ | triphenylphosphine |
| $Pd(PPh_3)_4$ | tetrakis(triphenylphosphine)palladium(0) |
| $K_2CO_3$ | potassium carbonate |
| h | hours |
| $Na_2CO_3$ | sodium carbonate |
| NaOH | sodium hydroxide |
| DPPF | 1,1’-bis(diphenylphosphino)ferrocene |

# CHAPTER 1: INTRODUCTION AND BACKGROUND

## 1.1 Importance and Applications of Cyclometalated Complexes

Cyclometalated complexes have been studied in detail over the past four decades and have found numerous applications in areas such as synthesis,[1-3] catalysis,[4-8] photochemistry,[9-11] and biology.[13-15] A significant amount of research in the development of anti-cancer drugs is directed at cyclometalated complexes.[14,16] Applications in chemical sensing[17,18] and nanotechnology[19] have also been found. Cyclometalated complexes have been shown to catalyze the coveted C–H bond activation of alkanes,[7,8] which can have an impact on the utilization of natural gas as a chemical feedstock.[20]

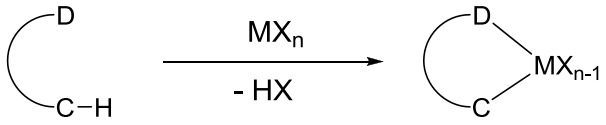
## 1.2 Importance and Applications of Cycloplatinated Complexes

Cyclometalated platinum complexes in particular have proven to be very useful in a variety of fields. They have found applications in biological labeling,[21,22] chemical sensing,[23-26] as well as photocatalysis.[27] Our group has recently developed highly luminescent platinum(II) complexes[28-30] that have potential applications as phosphorescent emitters in OLED devices.[30] The spin-orbit coupling of the platinum atom promotes an efficient emission from the triplet state due to adequate intersystem crossing ability from singlet to triplet states.[31] Platinum complexes are used in cancer treatments,[32] and research has been conducted to employ cyclometalated platinum complexes as emissive DNA probes.[33]

## 1.3 Cyclometalation as a Tool for Studying C–H Bond Activation

Cyclometalation is an important tool for studying the processes of C–H activation by transition metals. Cyclometalation is the intramolecular version of C–H bond activation, shown in **Scheme 1**.

**Scheme 1**. Schematic representation of intramolecular C–H activation



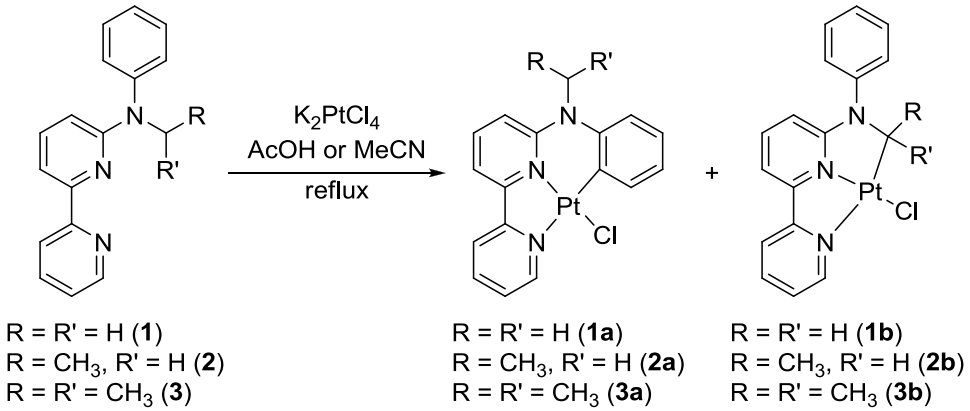

D = donor atom such as N, O, S, and P

The cyclometalated products formed in these reactions can often be isolated and characterized, giving insight to the C–H activation process. For example, agostic interaction is conceived to be an important process in intermolecular C–H bond activation but could not be fully characterized. With chelation stabilization, complexes displaying agostic interaction have been isolated and fully characterized.[34,35] Elucidation and exploitation of C–H bond activation and functionalization by transition metals has long been considered one of the "holy grails" of synthetic chemistry.[36]

Selectivity of C–H activation is a difficult issue and can be studied with cyclometalation reactions of carefully designed ligands. The selectivity of a reaction refers to the ability of the reaction to form one compound out of two or more possibilities. Recently, a solvent-controlled switch of selectivity was reported in the reaction of N-alkyl-N-phenyl-2,2'-bipyridin-6-amine (**1**-**3**) with $K_2PtCl_4$. When acetic acid was used as the reaction solvent, $sp^3$ C–H bond activation was preferred, while in acetonitrile, $sp^2$ C–H bond activation was preferred (**Table 1**).[37] Ligand **1** was refluxed in acetic acid to form, almost exclusively, the $sp^3$ C–H activation product **1b**. When acetonitrile was used, cyclometalation occurred through the $sp^2$ C–H bond activation pathway,

forming **1a**. Cyclometalated products from both reactions were isolated in good yields. Similar control over the selectivity of C–H bond activations was observed when the methyl group was replaced with an ethyl group. Ligand **2** formed **2b** and **2a** when acetic acid and acetonitrile were used as the reaction solvent, respectively.

**Table 1**. The reactions of **1**-**3** with $K_2PtCl_4$ in different solvents.




| Product | In AcOH | | | In MeCN | | |
|---|---|---|---|---|---|---|
| | t (h) | Ratio[a] | Yield[b] | t (h) | Ratio[a] | Yield[b] |
| **1a** :**1b** | 24 | 4:96 | 73% | 72 | 100:0 | 73% |
| **2a** : **2b** | 48 | 3:97 | 63% | 48 | 93:7 | 70% |
| **3a** : **3b** | 48 | 0:100 | 38% | 72 | 70:30 | 36% |

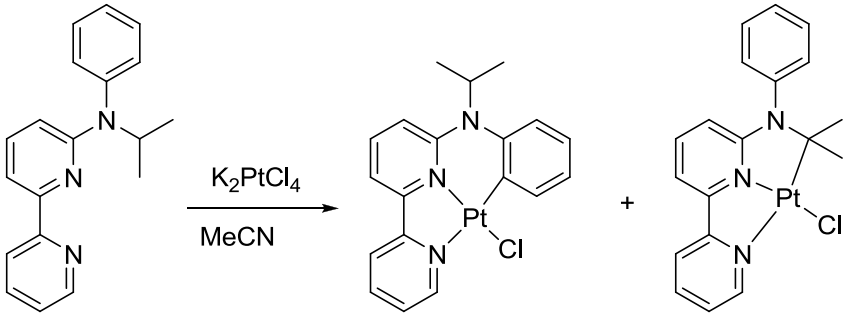
[a] Isomeric ratio determined by proton NMR spectra of the crude products; [b] Isolated yield of the pure major isomer.

The solvent controlled switch of selectivity was not perfect, however. Ligand **3**, with the isopropyl group, had undesirable results when reacted with $K_2PtCl_4$ in solvent. The reaction of **3** in acetic acid selectively formed **3b**, but in poor yield. In acetonitrile, the reaction experienced low selectivity, a 70:30 mixture of **3a**:**3b**, as well as a poor yield. These two issues were closely examined[38] and remedied to improve the control of selectivity of different C–H activations.

The low selectivity of the reaction of **3** in acetonitrile may have several contributing factors. The bond strength is known to generally decrease from methyl, to primary, to secondary, to tertiary C–H bonds. This could indicate that the secondary C–H bond in **3** is more reactive than the primary and methyl C–H bonds in **2** and **1**, respectively. This could make $sp^3$ C–H bond

activation on the isopropyl moiety more competitive than in the ethyl or methyl analogs, resulting in a mixture of **3a** and **3b**. Another factor to consider when confronting the selectivity issue in this reaction is the possibility of isomerization of the kinetic product, **3a**, forming the thermodynamic product, **3b**. The isomerization is likely to occur by protonolysis of the $sp^2$ C–Pt bond in **3a** by HCl generated in the cyclometalation. An appropriate scavenger for the HCl may be able to neutralize the HCl and discourage the isomerization, thus improving the selectivity. A few bases were used in the reaction and remarkable improvements in selectivity, up to 99%, were observed (**Table 2**).

**Table 2**. The effect of bases on the selectivity of reaction of **3** with $K_2PtCl_4$ in acetonitrile.[a]



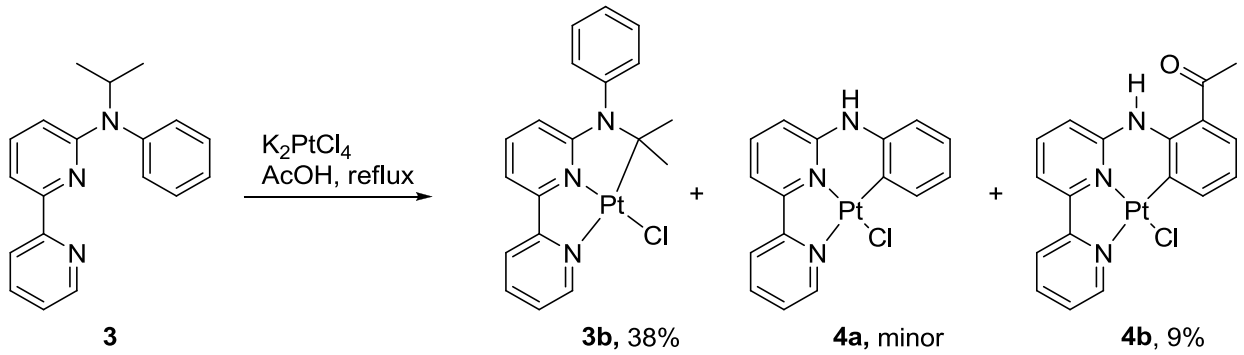

**3** **3a** **3b**

| Base | equivalents | Time (days) | Yield (%)[b] | selectivity (**3a**:**3b**) |
|---|---|---|---|---|
| None | | 3 | 36[c] | 70:30 |
| sodium acetate | 1 | 10 | 64 | 99:1 |
| triethylamine | 1 | 5 | 52 | 98:1 |
| triethylamine | 1 | 10 | 91 | 94:6 |
| DABCO[e] | 1 | 10 | 58 | 98:2 |
| TMP[d] | 1 | 2 | 41 | 97:3 |
| TMP | 2 | 3 | 34 | 90:10 |
| $Na_2CO_3$ | 1 | 5 | trace | - |
| NaOH | 1 | 5 | trace | - |
| **3** | 1 | 1 | 83 | 100:0 |

[a]Reactions were run with equimolar amount of the ligand **3** and $K_2PtCl_4$ in acetonitrile at reflux. [b]Isolated yield. [c]Isolated yield of pure **3a**. [d]2,2'-6,6'-tetramethylpiperidine. [e]1,4-diazabicyclo[2.2.2]octane.

The low yield of **3b** in acetic acid can be attributed to side reactions involved in the reaction. Isolation and characterization of the side products indicated that the isopropyl group was lost, and the phenyl ring was regioselectively acylated (**Scheme 2**).

**Scheme 2**. Reaction of **3** with $K_2PtCl_4$ in acetic acid




**3** **3b,** 38% **4a,** minor **4b**, 9%

Experiments suggested that the $C^{iPr}$–N bond was cleaved by heterolytic dissociation of the C–N bond. Although C–N bond dissociation is typically considered an unfavorable process, it is plausible considering ability of the bipyridine-Pt motif to stabilize the amide anion and the relative stability of the resulting isopropyl cation, compared with the stabilities of ethyl or methyl cations. Since the C–N bond dissociation may be facilitated by HCl formed in the cyclometalation, a base was employed in an attempt to suppress the side reaction. It was found that adding 1 equivalent of NaOAc to the reaction of **3** with $K_2PtCl_4$ in acetic acid suppressed the C–N dissociation, but not completely, increasing the yield to 50%. Using additional equivalents of base led to decomposition of the complex, likely by reduction of the Pt(II) to Pt(0), as a black precipitate was observed

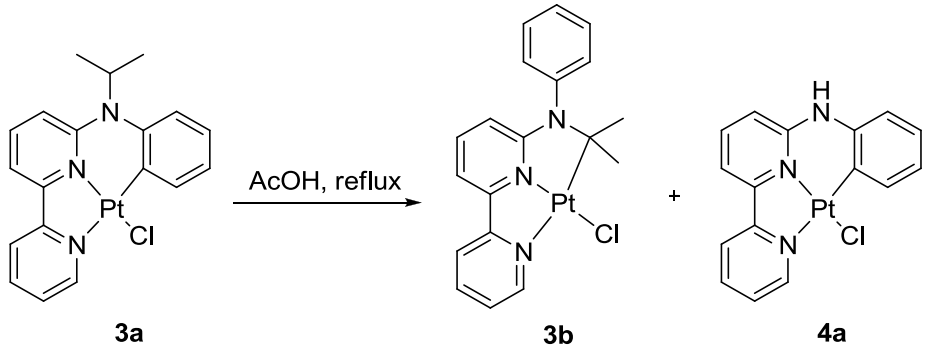
### 1.4 Selective Acylation of N^N*C Coordinated Platinum Complexes

The formation of the acylated cyclometalated platinum complex **4b** was remarkable. It is a regioselective functionalization of a cyclometalated platinum complex, which is not common in the literature. Functionalization of cyclometalated complexes is a useful tool for synthetic chemists. The metal center may provide the possibility of a regioselective functionalization of the organometallic ligand that was not possible with the free ligand.[39] Despite this, the vast

majority of structural modifications to cyclometalated complexes in the literature are made to the ligand before it is cyclometalated.

Further experiments were carried out to explore this interesting reaction. Complex **3a** was refluxed in acetic acid, forming **3b** and **4a**, but no **4b** was formed (**Scheme 3**). This suggests that the formation of **4b** is dependent on the presence of HCl, since the HCl is generated from the cycloplatination with $K_2PtCl_4$ (**Scheme 2**). This is consistent with the observation that there was no formation of **4b** when NaOAc was used to neutralize the HCl in the reaction of **3** with $K_2PtCl_4$ in acetic acid.

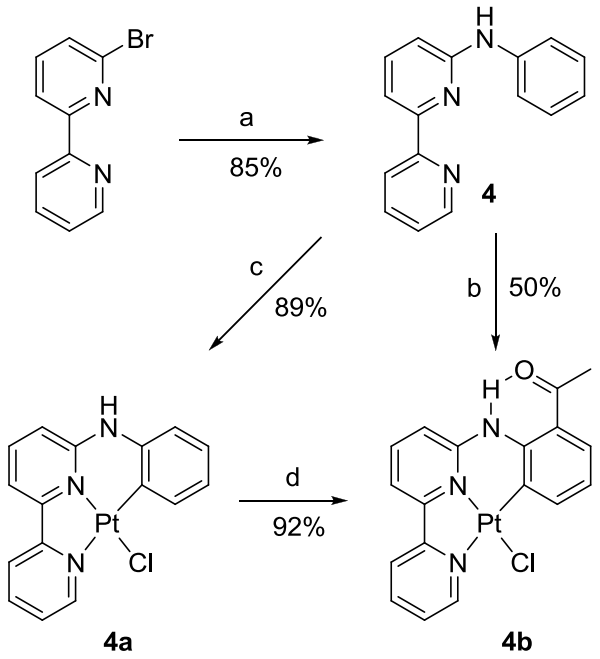
**Scheme 3.** Isomerization of **3a** in acetic acid, forming **3b**, along with formation of **4a**.




In order to further explore the acylation reaction, ligand **4** was synthesized by palladium-catalyzed cross-coupling of 6-bromo-2,2'-bipyridine and aniline (**Scheme 4**). The ligand was refluxed in acetic acid with $K_2PtCl_4$ to form **4a** cleanly. No **4b** was formed in this complexation, possibly due to the precipitation and poor solubility of **4a** upon formation. The complex was then refluxed in a 1:1 v/v mixture of acetic acid/ acetic anhydride to form the acylated complex **4b** in a high yield. The acylated complex **4b** was also directly prepared in a cascade cyclometalation-

acylation reaction by refluxing the ligand **4** and one equivalent of $K_2PtCl_4$ in a 1:1 acetic acid/ acetic anhydride mixture in a fair yield.

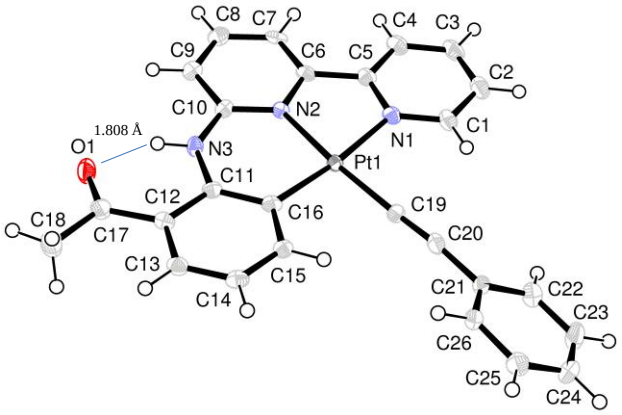
**Scheme 4**. Cycloplatination of **4** and related reactions[a]




[a]Reagents and conditions: (a) Aniline (2 eq.), $Pd(dba)_2$ (2%), DPPF (2%), $NaO^tBu$ (1.2 eq.), toluene, reflux. (b) $K_2PtCl_4$ (1 eq.), AcOH-$Ac_2O$ (1:1), reflux. (c) $K_2PtCl_4$ (1 eq.), AcOH, reflux. (d) AcOH-$Ac_2O$ (1:1), reflux.

Attempts to grow a crystal of **4b** for crystal structure analysis were unsuccessful on account of poor solubility. To increase the solubility, the chloride ligand of **4b** was replaced with a phenylacetylide ligand, forming **4c**. The crystal structure of **4c** (**Figure 1**) indicated a strong hydrogen bonding interaction between the carbonyl oxygen and the hydrogen bonded to the amine. This hydrogen bonding may stabilize the acylated complex and may be worthy of mechanistic consideration (Chapter 5.2)

**Figure 1**. Perspective drawing of the molecular structure of **4c**.



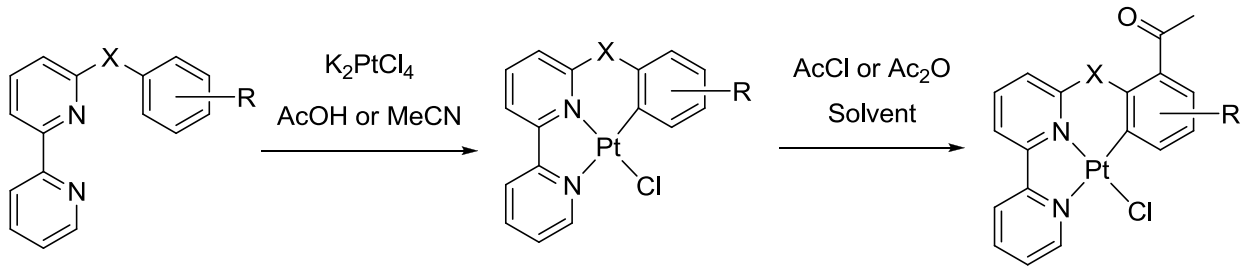

Clarification of this C–C bond forming acylation reaction would be of great value. As with any new reaction, it is important to delineate the scope and mechanism of the reaction, so that the reaction may be applied to a variety of substrates. The growing importance and variety of applications of cyclometalated complexes foreshadows the inevitable need for a broader arsenal of synthetic tools involving these compounds. Regioselective acylation may be used as a way to functionalize cyclometalated complexes. Since regioselectivity is a fundamental problem that synthetic chemists face, a new regioselective functionalization reaction could be a very useful tool in synthesis. Mechanistic understanding of the observed case may lead to more informed exploitation of the reaction in analogous syntheses.

# CHAPTER 2: RESEARCH OBJECTIVES

This research was carried out to accomplish three general goals in regards to the acylation of cycloplatinated complexes: optimization of reaction conditions, delineation of the scope and limitations of the reaction, and clarification of the mechanism of the reaction. Optimization of the reaction conditions allows for the most efficient applications of the reaction. A variety of solvents have been explored so as to broaden the scope of the reaction, including the use of various electrophiles.

A series of ligands were designed with structural variations to investigate the acylation reaction. Synthesis of the ligands, followed by complexation, afforded a variety of cycloplatinated complexes that were then subjected to the acylation reaction conditions (see general scheme, **Scheme 5**). Structural modifications to the N^N*C complexes include replacement of the linker group (NH, $CH_2$, O, S, C=O) and introduction of substituents on different positions of the phenyl ring. The results of the acylation reactions are reported in Chapter 4.

**Scheme 5**. General Scheme including complexation of the ligands, followed by acylation.




X = NH, S, O, $CH_2$, C=O; R = OMe, Me, Ph, H, Br, Cl, F, COOEt, CN

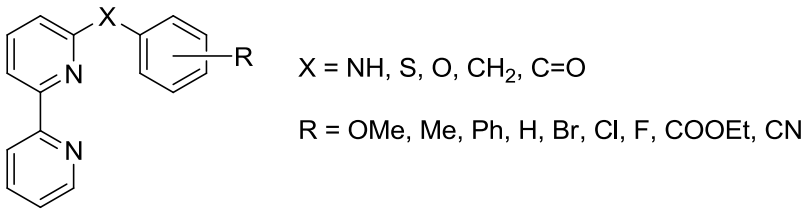
Experimental results from the acylation of N^N*C platinum complexes were used to derive insights on the mechanism of the reaction. The site of acylation was determined. The role of hydrogen bonding in the reaction was clarified. Electronic effects of linker groups and substituents on the phenyl ring were examined. The possible reaction mechanisms are discussed in Chapter 5.

# CHAPTER 3: LIGAND DESIGN, SYNTHESIS, AND COMPLEXATION

## 3.1 Ligand Design

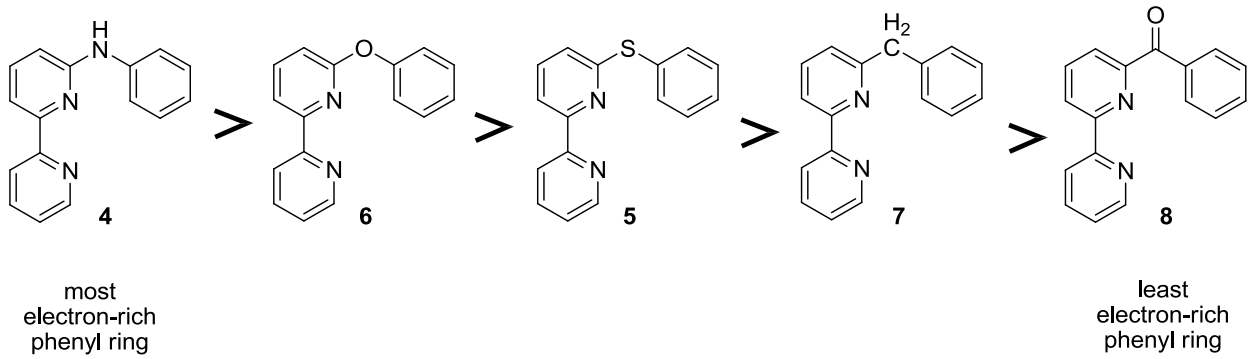
A series of ligands were designed with structural variations and substituents that would shed light on the scope, limitations, and mechanism of the acylation reaction described in this research. The ligands synthesized have the bipyridine moiety, with various linker atoms or groups and substituents located at each position on the phenyl ring (**Figure 2**). Synthesis of the ligands (Section 3.2) and their respective cyclometalated complexes (Section 3.3) are described in this chapter, along with the experimental details and characterization data (Section 3.4).

**Figure 2**. General structure of ligands with various linker atoms or groups and substituents on the phenyl ring.



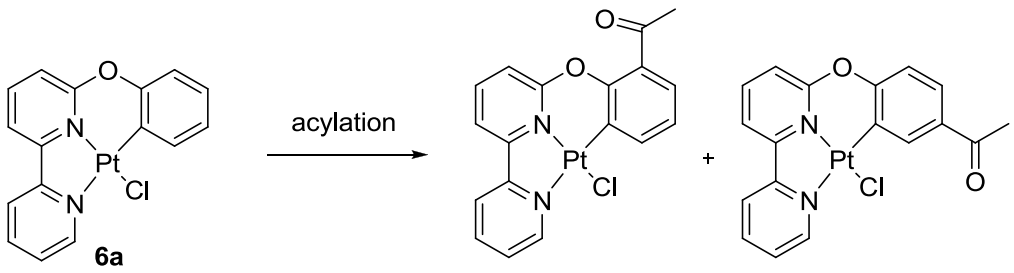

The linker atoms or groups used in this study include amino (**4**), sulfur (**5**), oxygen (**6**), methylene (**7**), and carbonyl (**8**). Ligands with these linker atoms or groups offer a range of electron-donating to electron-withdrawing abilities (**Figure 3**). The electron-richness of the phenyl ring may have an effect on the acylation of the complexes, depending on the mechanism. If the phenyl ring of a complex is less electron-rich, it will be less susceptible to electrophilic attack, which is likely involved in the mechanism of the acylation.

**Figure 3**. Ranking of ligands **4-8** in descending order of electron-richness of the phenyl ring.



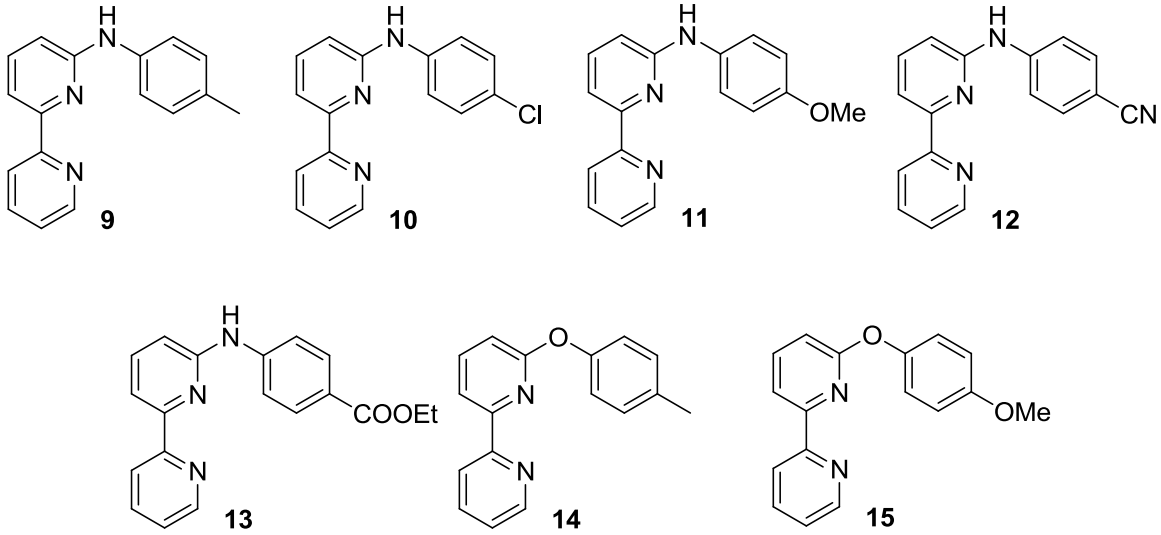

In addition to differences in electron donating abilities, ligands **5-8** can also offer insight into the role of hydrogen bonding in the reaction. As mentioned in Section 1.4, acylated cycloplatinated complex **4c** exhibited hydrogen bonding between the carbonyl oxygen and the amino hydrogen, as evidenced by the X-ray crystal structure (**Figure 1**). Ligands **5-8** eliminate the possibility of hydrogen bonding, which could have mechanistic implications. Although hydrogen bonding of the incoming acyl cation is unlikely, hydrogen bonding may drive the reaction by stabilizing the product. If the acylation of **4a** was directed to the position *ortho* to the amino linker group by hydrogen bonding, acylation of **6a** may occur, at least to some degree, at the position *para* to the oxygen linker atom (**Scheme 6**). Additionally, ligand **8**, featuring a *meta* directing carbonyl linker group, provides a means to test if the acylation can take place at the position *meta* to the linker group, or if the acylation would occur at all with an electron-withdrawing linker group.

**Scheme 6**. Possible outcomes of acylation of **6a**.



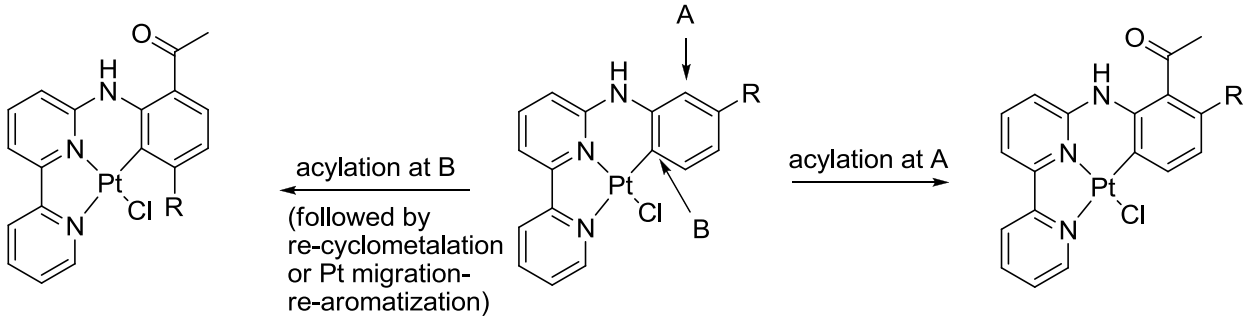

Ligands with substituents at each position on the phenyl ring have been designed. The substituents selected represent a range of electron-donating and electron-withdrawing groups, which may provide insights on the acylation in regards to the electron-richness of the phenyl ring, as previously mentioned. Ligands with substituents in the position *para* to the linker atom or group are particularly useful in this regard, since steric hindrance of the acylation by the substituent is unlikely from this position on the phenyl ring. The structures of these ligands are shown in **Figure 4**.

**Figure 4**. Structures of ligands designed with substituents *para* to the linker group or atom.



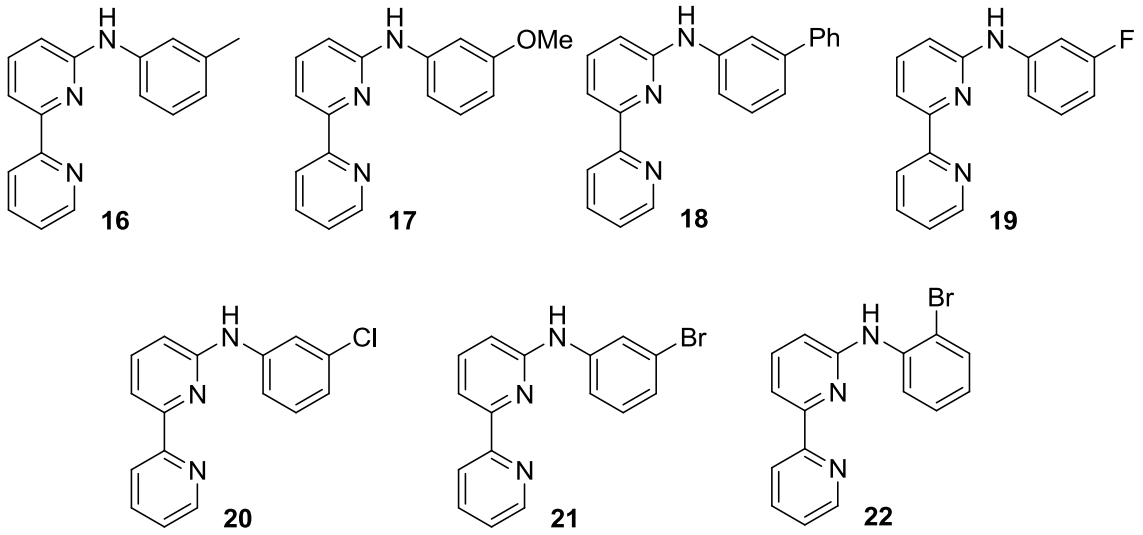
As was mentioned in Chapter 1, the acylation of **4a** was regioselective, occurring *ortho* to the amino linker group. It is unclear, however, which of the two *ortho* carbons of the phenyl ring is acylated (**Scheme 7**, R = H). It is impossible to distinguish the acylated complex formed by acylation at the unmetalated carbon (site A) from the complex formed by acylation at the metalated carbon (site B) because the phenyl ring of **4a** is symmetrical. By introducing a substituent to the position *meta* to the amino linker group, the phenyl ring becomes unsymmetrical. The acylated complex can then be characterized by NMR experiments, allowing for identification of the site of acylation.

**Scheme 7**. Possible outcomes of acylation of complexes with a substituent at the position *meta* to the amino linker group.




Substituents at this position on the phenyl ring are more likely to sterically hinder the acylation, so ligands were designed with bulky substituents (bromo, chloro, methyl) and less sterically demanding substituents (fluoro). It is worthwhile to test the acylation on a complex with a substituent *ortho* to the amino linker group as well. This could block the site of acylation and potentially force the acylation elsewhere, presumably *para* to the amino linker group on the phenyl ring. The structures of these ligands are shown in **Figure 5**.

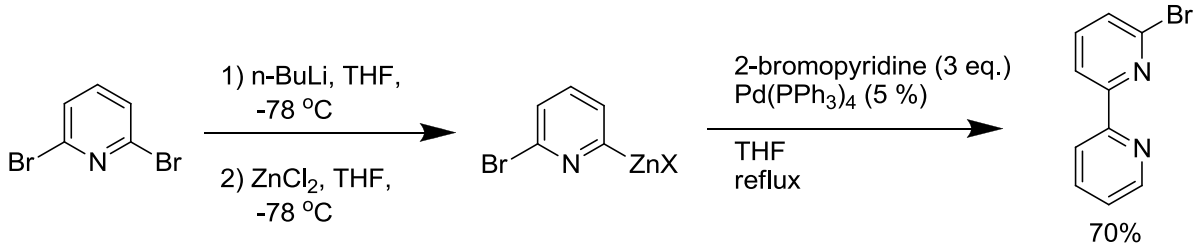
**Figure 5**. Structures of ligands designed with substituents *meta* and *ortho* to amino linker group.




### 3.2 Synthesis of Ligands

The starting material for the majority of the ligands synthesized in this research, 6-bromo-2,2'-bipyridine, was synthesized in good yields using a Negishi cross-coupling of 2,6-dibromopyridine and 2-bromopyridine, as per literature procedure[40] (**Scheme 8**).

**Scheme 8**. Synthesis of 6-bromo-2,2'-bipyridine.




Several ligands were synthesized by Buchwald-Hartwig cross-coupling of 6-bromo-2,2'-bipyridine with 1-4 equivalents of aniline or an aniline derivative with a substituent on the phenyl ring. This palladium-catalyzed cross-coupling reaction generally produced the desired

ligands in fair to high yields. The general scheme for these syntheses, along with their respective yields, is reported in **Table 3**.

All aniline derivatives were purchased from Sigma Aldrich with the exception of 3-aminobiphenyl and ethyl 4-aminobenzoate, the reagents used in the syntheses of **18** and **13**, respectively. A Suzuki cross-coupling of 3-bromoaniline and phenylboronic acid (**Scheme 9**) afforded the 3-aminobiphenyl in high yield. Following the literature procedure,[41] a Fischer Esterification was performed to convert 4-aminobenzoic acid to the desired compound, ethyl 4-aminobenzoate, which was then used in the synthesis of **13**.

**Scheme 9**. Syntheses of 3-aminobiphenyl and ethyl 4-aminobenzoate.

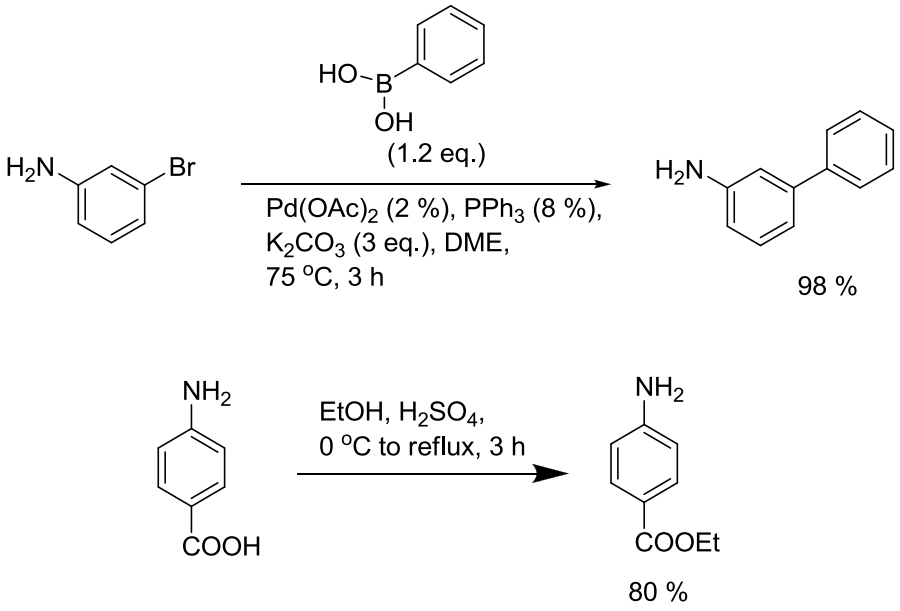
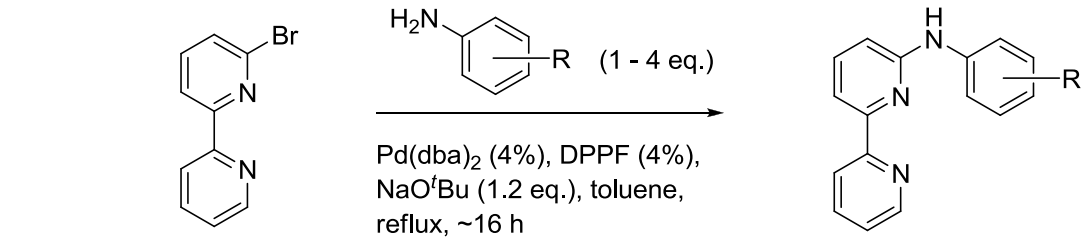
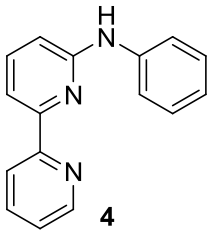
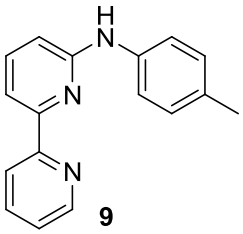
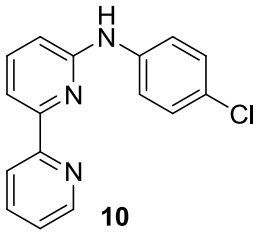
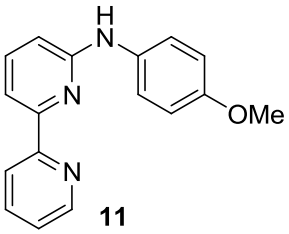
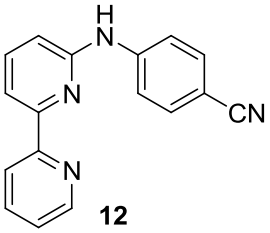
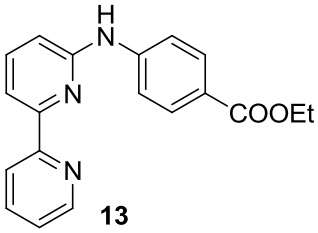
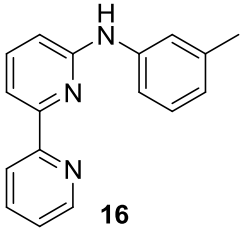
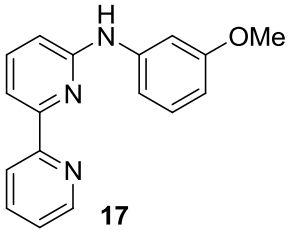
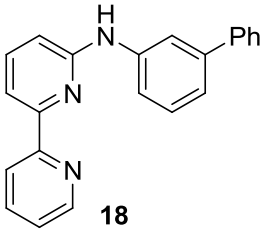
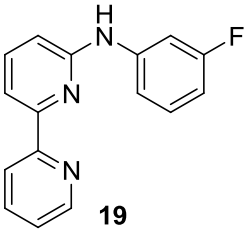
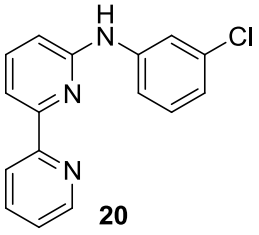
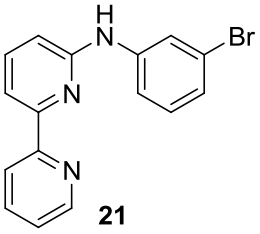
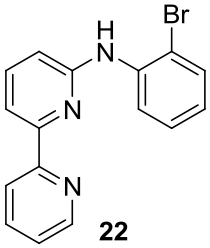


**Table 3.** Synthesis of ligands **4**, **9**-**13**, and **16**-**22**.



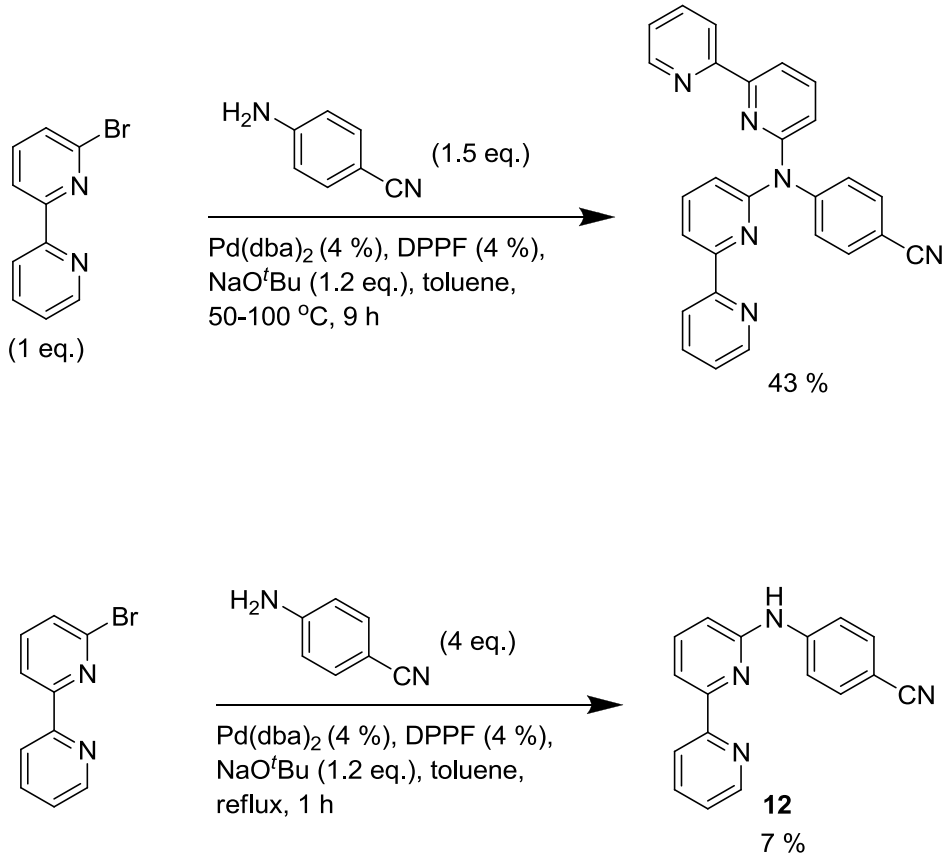

| | | | |
|---|---|---|---|
|  **4** 86% |  **9** 73% |  **10** 66% |  **11** 51% |
|  **12** 7% |  **13** 15% |  **16** 63% |  **17** 86% |
|  **18** 65% |  **19** 62% |  **20** 21% |  **21** 25% |
|  **22** 58% | | | |

Not all of these ligands were synthesized in satisfactory yields, namely compounds **20**, **21**, **12**, and **13**. Ligand **20** was isolated in a 21% yield, while ligand **21** had a yield of 25%. Ligands **20** and **21** have halides that are good electrophiles for cross-coupling reactions at the position

*meta* to the amino linker. This makes oligomerization and homocoupling possible in these cases, which may have contributed to the low yields. Ligand **19** has a fluoride in the *meta* position and was synthesized in a 62% yield. This makes sense because the fluoride is a poor electrophile compared with chloride or bromide, and oligomerization/homocoupling in the reaction is less likely.

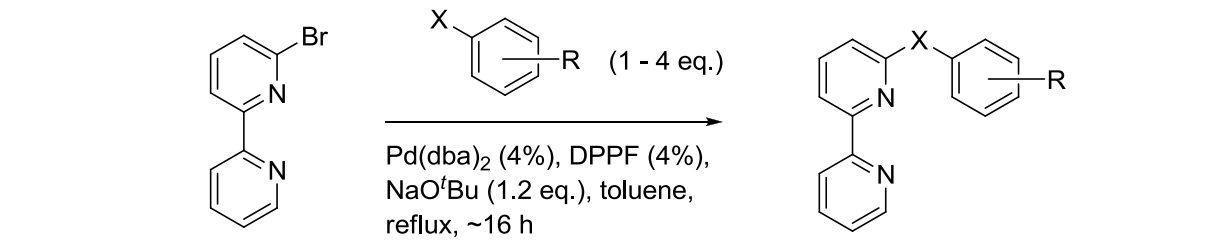
The synthesis of ligands **12** and **13** had very poor yields, 7% and 15% respectively. The major product from the cross-coupling reaction of bromobipyridine and 4-aminobenzonitrile was isolated and identified by $^{1}$H NMR as the tertiary amine shown in **Scheme 10**. The integrations of the signals corresponding to pyridyl hydrogens were double the integrations of the phenyl proton signals. This indicated that a second bipyridyl moiety was incorporated into the structure of the compound. The aniline derivatives used for the synthesis of these ligands have strong electron withdrawing groups in the *para* position. This electron withdrawing effect makes the amino proton in **12** more acidic, which encourages deprotonation of the secondary amine, followed by palladium-catalyzed cross-coupling with another bipyridine to form a tertiary amine. In order to discourage the formation of the tertiary amine, four equivalents of 4-aminobenzonitrile were used, and the reaction time was limited. Alternate bases, such as $K_3PO_4$ and $CsCO_3$, were tried in the reaction, but this afforded similar results to using $NaO^tBu$ as the base. The same challenge was faced in the synthesis of **13**. Despite the poor yields, a sufficient amount of the ligands were isolated for use in this study.

**Scheme 10**. Synthesis of **12** and undesired tertiary amine.




For ligands with oxygen and sulfur linker atoms, the same general scheme used in the synthesis of ligands **4**, **9**-**13**, and **16**-**22** was used. Instead of cross-coupling bromobipyridine with aniline or an aniline derivative, it was cross-coupled with phenol, thiophenol, or a phenol derivative. The general scheme, ligands, and respective yields are outlined in **Table 4**.

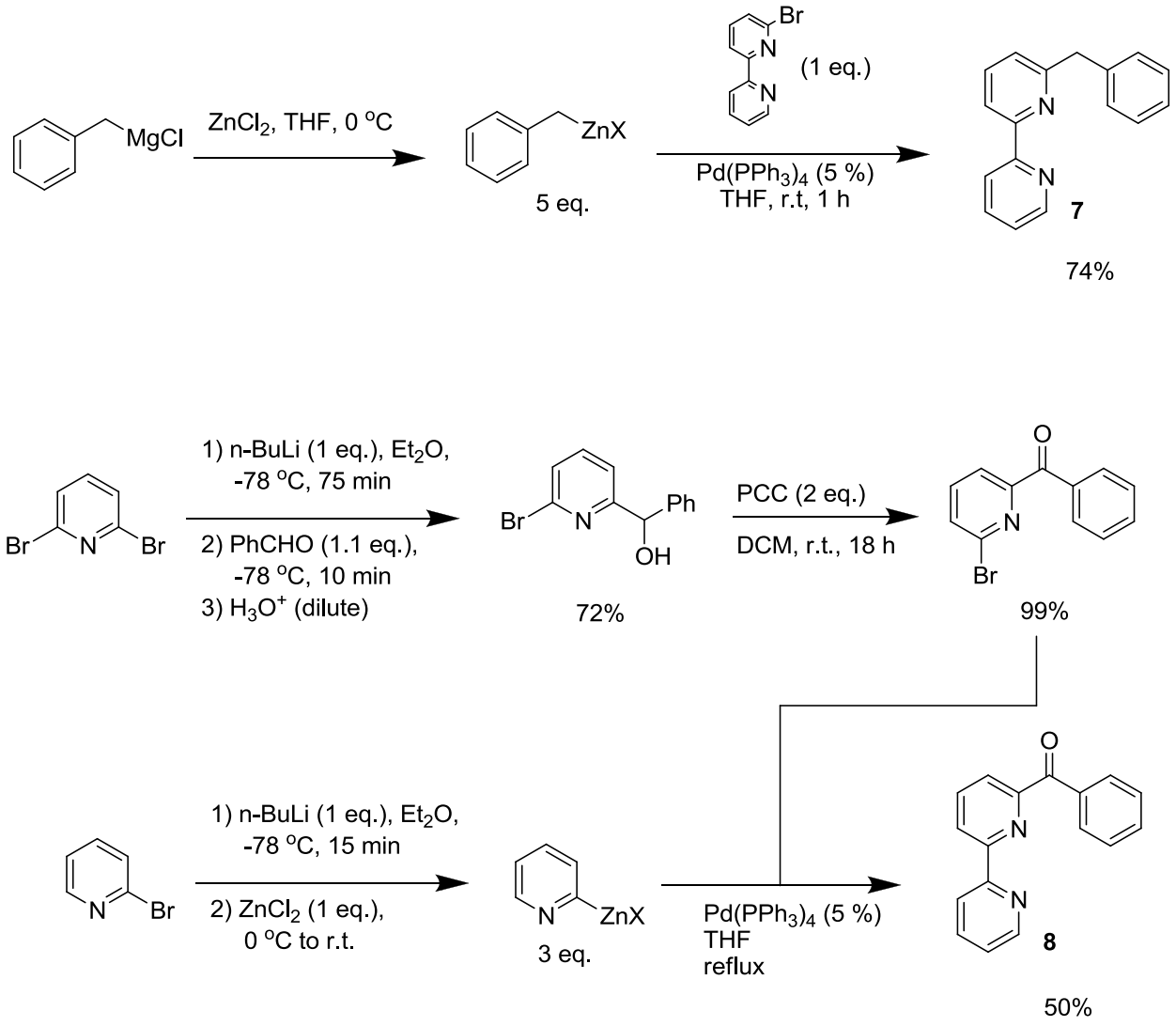
**Table 4.** Synthesis of ligands **5**, **6**, **14**, and **15**.




| | | | |
|---|---|---|---|
| **5** | **6** | **14** | **15** |
| 92% | 89% | 99% | 81% |

Synthesis of ligands with methylene (**7**) and carbonyl (**8**) linker groups called for a different synthetic strategy, since they involve C-C bond forming cross-coupling (**Scheme 11**) . Ligand **7** was synthesized by transmetalation of benzylmagnesium chloride to form the corresponding zinc reagent, followed by Negishi coupling to bromobipyridine to afford ligand **7** in a 74% yield. Ligand **8** was synthesized by first treating 2,6-dibromopyridine with *n*-BuLi. The resulting organolithium reagent was treated with benzaldehyde, followed by acidic workup to form the corresponding secondary alcohol in 72% yield. Pyridinium chlorochromate oxidation gave a 99% yield of the ketone with the desired pyridyl bromide moiety. This compound was cross-coupled *via* Negishi reaction with 2-pyridylzinc to form ligand **8** in 50% yield.

**Scheme 11**. Synthesis of ligands **7** and **8**.

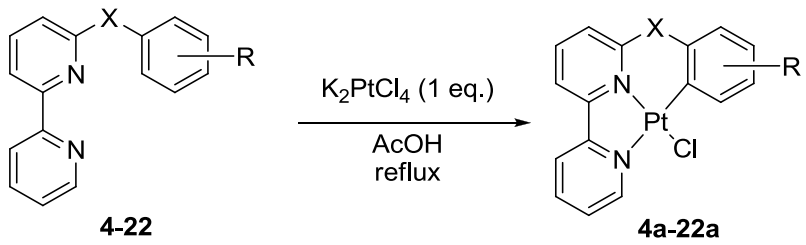



### 3.3 Synthesis of Complexes

All complexes were synthesized by refluxing one equivalent of the ligand and one equivalent of $K_2PtCl_4$ in acetic acid. The complexes formed cleanly with little to no reduction of the Pt(II) to platinum metal. The complexes precipitated out of the reaction mixture and were filtered. Some were filtered through a bed of silica to get satisfactorily pure complexes in good to excellent yields. Cyclometalation occurred at the *ortho* position to the linker group, with the

substituents *meta* or *para* to the metalated carbon, as was expected considering sterics. The percent yields of the complexation reactions are outlined in **Table 5**. The reaction of **12** with $K_2PtCl_4$ in AcOH resulted in a dark reaction mixture with black precipitates. Some of the ligand was consumed/decomposed, and there was no sign of cyclometalation (formation of **12a**) on TLC.

**Table 5**. Synthesis of cyclometalated platinum complexes **4a**-**22a**.




**4-22** **4a-22a**

| Complex | Yield (%) | Complex | Yield (%) |
|---|---|---|---|
| **4a** | 89 | **14a** | 67 |
| **5a** | 93 | **15a** | 74 |
| **6a** | 52 | **16a** | 89 |
| **7a** | 87 | **17a** | 99 |
| **8a** | 63 | **18a** | 92 |
| **9a** | 91 | **19a** | 89 |
| **10a** | 82 | **20a** | 97 |
| **11a** | 76 | **21a** | 99 |
| **12a** | - | **22a** | 79 |
| **13a** | 89 | | |

### 3.4 Experimental Procedures

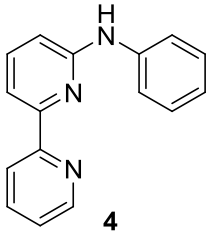
*General:*

All manipulations were conducted under a dry argon atmosphere and anhydrous conditions unless stated otherwise. Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All other anhydrous solvents used were purchased from Sigma-Aldrich with Sure Seal. All

catalysts and reagents were purchased from Sigma-Aldrich, with the exception of $K_2PtCl_4$ which was purchased from Strem Chemicals. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. Preparative chromatography was performed on silica gel 60 (0.063-0.200 mm) purchased from EMD chemicals. Thin layer chromatography was performed with silica gel 60 $F_{254}$ plates, purchased from EMD chemicals. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker 400 MHz spectrometer at 298K. Chemical shifts were reported relative to TMS (0.0 ppm for $^{1}H$), dichloromethane-d2 (53.8 ppm for $^{13}C$), chloroform-d (77.0 ppm for 13C), DMSO-d6 (39.5 ppm for $^{13}C$) and coupling constants are in Hertz. Elemental analyses were performed in Atlantic Microlab, Norcross, GA.

## Synthesis of Ligands

*N-phenyl-2,2'-bipyridin-6-amine (**4**)*

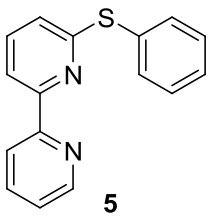



**4**

**General Procedure A**: To a 50 mL, dry, argon flushed, three-necked round-bottom flask were charged 6-bromo-2,2'-bipyridine (0.94 g, 4 mmol), aniline (0.73 mL, 8 mmol), $NaO^tBu$ (0.46 g, 2.8 mmol), $Pd(dba)_2$ (92 mg, 0.16 mmol), DPPF (89 mg, 0.16 mmol), and toluene (15 mL). The mixture was stirred and heated at reflux for 19 h. After cooling the reaction mixture to room temperature, it was diluted with 10 mL of ethyl acetate and filtered through a disc of Celite. The filtrate was extracted with ethyl acetate, and the organic phase was washed with brine and dried over $MgSO_4$. After filtration, the organic solvents were removed by rotary evaporator

and the crude product was purified by column chromatography on silica gel first with dichloromethane and hexanes (v/v 5/1) then with hexanes and ethyl acetate (v/v 3/1): off-white crystalline solid, 0.83 g, 85 %. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, J = 4.8 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 7.77 (d, J = 7.5 Hz, 1H), 7.74 (td, J= 7.7, 1.8 Hz, 1H), 7.57 (t, J= 8.0 Hz, 1H), 7.37 (d, J= 8.5 Hz, 2H), 7.29 (t, J = 7.4 Hz, 2H), 7.22 (t, J = 6.2, 1H), 6.99 (t, J= 7.3 Hz, 1H), 6.81 (d, J= 8.2 Hz, 1H), 6.59 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.4, 154.7, 149.1, 140.6, 138.6, 136.9, 129.2 (2C), 123.5, 122.6, 121.0, 120.1 (2C), 112.6, 108.9. Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.47; H, 5.31; N, 16.86.

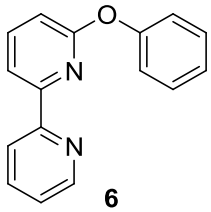
*6-(phenylthio)-2,2'-bipyridine (**5**)*




**5**

This compound was prepared according to **General Procedure A** using 1.5 equivalents of thiophenol. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 100/1, 50/1): brown/black solid, 92 %. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 4.8 Hz, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.12 (d, J = 7.7 Hz, 1H), 7.75 (td, J = 7.8, 1.8 Hz, 1H), 7.68-7.64 (m, 2H), 7.60 (t, J = 7.9 Hz, 1H), 7.47-7.41 (m, 3H), 7.28 (td, J = 6.1, 1.2 Hz, 1H), 6.93 (d, J = 8.0 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 160.4, 155.7, 155.3, 148.8, 137.4, 136.7, 135.0 (2C), 130.8, 129.3 (2C), 128.9, 123.7, 121.1, 121.0, 116.9.

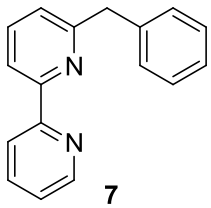
*6-phenoxy-2,2'-bipyridine (**6**)*




**6**

This compound was prepared according to **General Procedure A** using 1.5 equivalents of phenol. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 100/1): brown oil, 89 %. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.63 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 7.6 Hz, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.71 (td, J = 7.8, 1.8 Hz, 1H), 7.45-7.39 (m, 2H), 7.28-7.20 (m, 4H), 6.88 (d, J = 8.2 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl3) δ 163.1, 155.4, 154.4, 154.3, 149.0, 140.3, 136.9, 129.5 (2C), 124.5, 123.8, 121.2 (2C), 121.2, 115.5, 111.2.

*6-benzyl-2,2'-bipyridine (**7**)*

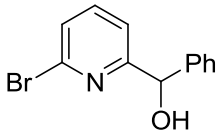



**7**

To a 25 mL 3-necked round-bottom flask under argon were charged THF (2.5 mL) and benzylmagnesium chloride (2M solution in THF, 2.5 mL, 5 mmol). This solution was cooled to 0$^{o}$C and stirred. $ZnCl_2$ (1.0 M in diethyl ether, 5 mL, 5 mmol) was added dropwise forming a white precipitate, and this mixture was warmed to room temperature. In a separate 25 mL 3-necked round-bottom flask under argon, 6-bromo-2,2'-bipyridine (235.1 mg, 1 mmol), $Pd(PPh_3)_4$

(57.8 mg, 0.05 mmol), and THF (4 mL) were stirred at room temperature, resulting in an orange homogeneous solution. This orange solution was added dropwise to the flask with the organo-zinc reagent, resulting in a brown mixture. The reaction mixture was stirred at room temperature for 1h. The reaction mixture was quenched with water (10 mL), EDTA (2.92 g, 10 mmol), and $Na_2CO_3$ (4.24 g, 40 mmol) and extracted with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the crude product was purified by column chromatography on silica gel with hexane and ethyl acetate (v/v 4/1): brown solid, 0.18 g, 74 %. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.7 Hz, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.21 (d, J = 7.9 Hz, 1H), 7.81 (td, J = 7.7, 1.7 Hz, 1H), 7.69 (t, J = 7.8 Hz, 1H), 7.39-7.27 (m, 5H), 7.25-7.20 (m, 1H), 7.10 (d, J = 7.7 Hz, 1H), 4.24 (s, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 160.3, 156.3, 155.4, 148.9, 139.5, 137.2, 136.7, 129.1 (2C), 128.4 (2C), 126.2, 123.4, 122.9, 121.2, 118.4, 44.7.

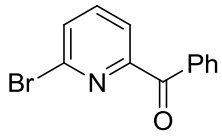
*(6-bromopyridin-2-yl)(phenyl)methanol*




To a 250 mL 3-necked round-bottom flask under argon were charged 2,6-dibromopyridine (4.74 g, 20 mmol) an anhydrous diethyl ether (100 mL). This solution was cooled to -78$^o$C and stirred for 15 min. *n*-BuLi (1.6 M in hexanes, 12.5 mL, 20 mmol) was added dropwise over 12 min. The resulting brown mixture was stirred at -78$^o$C for 75 min, then benzaldehyde (2.22 mL, 22 mmol) was added dropwise. The teal reaction mixture was quenched with 10 mL 3M HCl and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the crude product was purified by column

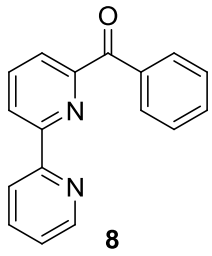
chromatography on silica gel with hexane and ethyl acetate (v/v 10/1): yellow oil, 3.81 g, 72 % $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.45 (t, J = 7.8 Hz, 1H), 7.40-7.24 (m, 6H), 7.13 (d, J = 7.5 Hz, 1H), 5.73 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.0, 142.1, 140.7, 139.1, 128.6 (2C), 128.0, 126.9 (2C), 126.7, 120.0, 75.0.

*(6-bromopyridin-2-yl)(phenyl)methanone*




To a 50 mL 1-necked round-bottom flask open to atmosphere were added (6-bromopyridin-2-yl)(phenyl)methanol (1.32 g, 5 mmol), pyridinium chlorochromate (PCC) (2.16 g, 10 mmol), and dichloromethane (21 mL). the black mixture was stirred at room temperature for 18 h. The solvent was removed and the crude product was purified by column chromatography on silica gel with hexane and ethyl acetate (v/v 4/1): off-white solid, 1.30 g, 99 %. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 7.53 Hz, 1H), 7.74 (t, J = 7.8 Hz, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.9 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 191.6, 155.7, 140.7, 139.2, 135.5, 133.2, 131.1 (2C), 130.8, 128.2 (2C), 123.4.

*2,2'-bipyridin-6-yl(phenyl)methanone (**8**)*

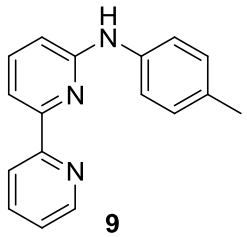



**8**

A 50 mL 3-necked round-bottom flask under argon was cooled to -78°C and charged with *n*-BuLi (1.6 M in hexanes, 4 mL, 6.4 mmol). A solution of 2-bromopyridine (572 µL, 6 mmol) and diethyl ether (5 mL) was made in a separate 25 mL teardrop flask under argon, and this solution was added dropwise to the *n*-BuLi flask. The resulting dark orange solution was stirred for 15 min at -78°C then warmed to 0°C. $ZnCl_2$ (1.0 M in diethyl ether, 6 mL, 6 mmol) was added dropwise and the resulting milky-pink mixture was warmed to room temperature. A solution of (6-bromopyridin-2-yl)(phenyl)methanone (524 mg, 2 mmol), $Pd(PPh_3)_4$ (116 mg, 0.1 mmol) and THF (10 mL) was made in a separate 25 mL teardrop flask under argon, and this orange solution was added dropwise to the flask with the organozinc reagent. The reaction mixture was heated at reflux for 16 h then cooled to room temperature. The reaction mixture was quenched with water (10 mL) and EDTA (8.0 g, 27.4 mmol), and then extracted with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the crude product was purified by column chromatography on silica gel with hexane and ethyl acetate (v/v 5/1): off-white solid, 228 mg, 44%. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.70 (d, J = 4.8 Hz, 1H), 8.65 (dd, J = 7.8, 1.3 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.22-8.17 (m, 2H), 8.09 (d, J = 7.7 Hz, 1H), 8.03 (t, J = 7.7 Hz, 1H), 7.79 (td, J = 7.7, 1.7 Hz, 1H), 7.63 (t, J = 7.3 Hz, 1H), 7.52

(t, J = 7.8 Hz, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 193.3, 155.2, 154.7, 154.1, 149.0, 137.9, 136.9, 136.3, 132.6, 131.1 (2C), 127.9 (2C), 124.3, 124.0, 123.2, 121.1.

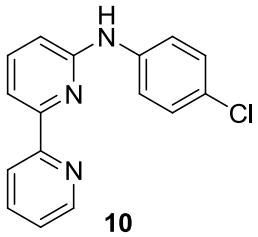
*N-p-tolyl-2,2'-bipyridin-6-amine (**9**)*




**9**

This compound was prepared according to **General Procedure A** with 1.3 equivalents of *p*-toluidine. The crude product was purified by column chromatography on silica gel first with dichloromethane and ethyl acetate (v/v 15/1) then increasing the polarity to (v/v 5/1): brown solid, 7 %. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.8 Hz, 1H), 8.32 (d, J = 8.0 Hz, 1H), 7.83-7.77 (m, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.34-7.27 (m, 3H), 7.17 (d, J = 8.3 Hz, 2H), 6.83 (d, J = 8.1 Hz, 1H), 6.53 (s, 1H), 2.35 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.4, 155.8, 154.6, 149.1, 138.5, 137.9, 136.7, 132.4, 129.7 (2C), 123.4, 121.0, 120.8 (2C), 112.1, 108.4, 20.8.

*N-(4-chlorophenyl)-2,2'-bipyridin-6-amine (**10**)*

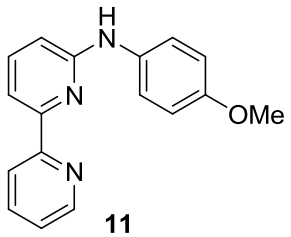



**10**

This compound was prepared according to **General Procedure A** with 1.3 equivalents of 4-chloroaniline. The crude product was purified by column chromatography on silica gel first with

dichloromethane and ethyl acetate (v/v 15/1) then increasing the polarity to (v/v 5/1): brown solid, 66%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.66 (d, J = 4.8 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.78 (t, J = 7.7 Hz, 1H), 7.60 (t, J = 7.8 Hz, 1H), 7.45-7.34 (m, 2H), 7.31-7.19 (m, 3H), 6.79 (s, 1H), 6.75 (d, J = 8.4 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.1, 154.8, 154.5, 149.0, 139.3, 138.5, 136.8, 129.0 (2C), 126.9, 123.5, 120.9, 120.7 (2C), 112.7, 109.4.

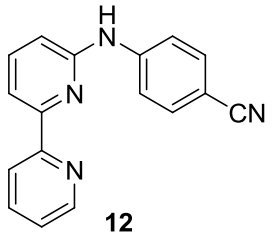
*N-(4-methoxyphenyl)-2,2'-bipyridin-6-amine (**11**)*




**11**

This compound was prepared according to **General Procedure A** with 1.5 equivalents of *p*-anisidine. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 10/1): brown oil, 51%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.4 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.77 (d, J = 7.6 Hz, 1H), 7.59 (t, J = 7.9 Hz, 1H), 7.37-7.27 (m, 2H), 6.92 (d, J = 8.9 Hz, 2H), 6.71 (d, J = 8.2 Hz, 1H), 6.46 (s, 1H), 3.83 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.6, 156.4, 156.1, 154.7, 149.1, 138.5, 136.8, 133.4, 123.7 (2C), 123.4, 121.0, 115.5 (2C), 111.9, 107.7, 55.5.

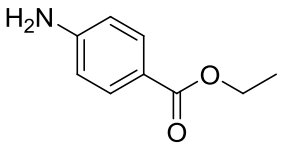
*N-(4-cyanophenyl)-2,2'-bipyridin-6-amine (**12**)*




**12**

This compound was prepared according to **General Procedure A** with 4 equivalents of 4-aminobenzonitrile. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 3/1): brown solid, 15%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.69 (d, J = 4.8 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 8.02 (d, J = 7.6 Hz, 1H), 7.85 (td, J = 7.8, 1.8 Hz, 1H), 7.74 (t, J = 7.7 Hz, 1H), 7.70-7.59 (m, 4H), 7.33 (t, J = 6.0 Hz, 1H), 6.88 (d, J = 8.2 Hz, 1H), 6.80 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 155.9, 154.9, 153.4, 149.3, 144.9, 139.0, 137.0, 133.5 (2C), 123.8, 121.0, 119.6, 117.7 (2C), 114.3, 111.1, 103.8.

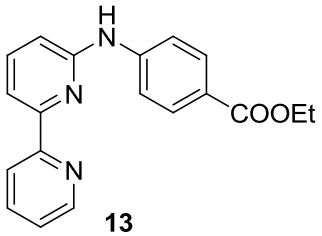
*ethyl 4-aminobenzoate (benzocaine)*




To a 100 mL 3-necked round-bottom flask under argon were added 4-aminobenzoic acid (4.0 g, 29 mmol) and absolute ethanol (50 mL). This solution was stirred and cooled to 0$^{o}$C, followed by dropwise addition of concentrated $H_2SO_4$ (2.5 mL) which resulted in a white precipitate. The reaction mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was neutralized with $NaHCO_3$, extracted with ethyl acetate, and dried over $MgSO_4$. The

solvent was removed and the crude product was washed with water then dried in air: off-white solid, 3.8 g, 80%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.7 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.15 (s, 2H), 1.35 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.7, 150.8, 131.4 (2C), 119.8, 113.7 (2C), 60.2, 14.3.

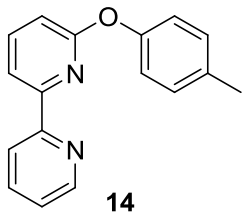
*ethyl 4-(2,2'-bipyridin-6-ylamino)benzoate (**13**)*




**13**

This compound was prepared according to **General Procedure A** with 4 equivalents of benzocaine. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 3/1): tan solid, 15%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 4.8 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.7 Hz, 2H), 7.97 (d, J = 7.6 Hz, 1H), 7.83 (td, J = 7.7, 1.8 Hz, 1H), 7.71 (t, J = 7.9 Hz, 1H), 7.58 (d, J = 8.8 Hz, 2H), 7.31 (t, J = 6.2 Hz, 1H), 6.91 (d, J = 8.1 Hz, 1H), 6.85 (s, 1H), 4.37 (q, J = 7.2 Hz, 2H), 1.40 (t, J = 7.1 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 166.4, 156.0, 154.7, 153.9, 149.2, 145.1, 138.8, 136.9, 131.1 (2C), 123.7, 123.2, 121.0, 117.2 (2C), 113.7, 110.6, 60.6, 17.4.

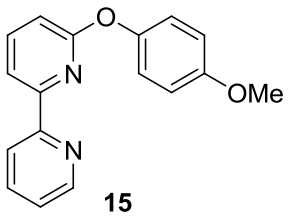
*6-(p-tolyloxy)-2,2'-bipyridine (**14**)*



**14**

This compound was prepared according to **General Procedure A** with 1.5 equivalents of *p*-cresol. The crude product was purified by column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 4/1): brown oil, 99%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 4.8 Hz, 1H), 8.18 (d, J = 8.0 Hz, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.78 (t, J = 7.8 Hz, 1H), 7.73 (td, J = 7.8 Hz, 1H), 7.26 (t, J = 6.1 Hz, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.11 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.1 Hz, 1H), 2.39 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.2, 155.3, 154.2, 151.8, 148.8, 140.1, 136.6, 133.8, 129.9 (2C), 123.5, 121.0, 120.8 (2C), 115.2, 110.8, 20.7.

*6-(4-methoxyphenoxy)-2,2'-bipyridine (**15**)*

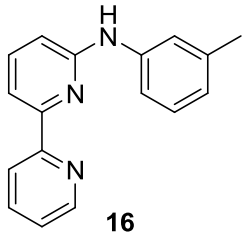


**15**

This compound was prepared according to **General Procedure A** with 1.3 equivalents of 4-methoxyphenol. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 20/1): brown oil,

81%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 8.1 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.76 (t, J = 7.8 Hz, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.23 (t, J = 6.0 Hz, 1H), 7.15 (d, J = 8.8 Hz, 2H), 6.94 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.2 Hz, 1H), 3.82 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 163.5, 156.4, 155.4, 154.1, 148.9, 147.5, 140.1, 136.8, 123.6, 122.3 (2C), 121.1, 115.1, 114.5 (2C), 110.6, 55.5.

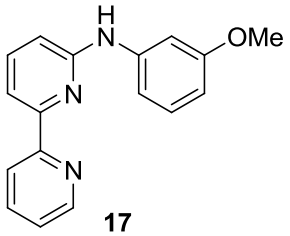
*N-m-tolyl-2,2'-bipyridin-6-amine (**16**)*




**16**

This compound was prepared according to **General Procedure A** with 1.5 equivalents of *m*-toluidine. The crude product was purified by column chromatography on silica gel with hexane and ethyl acetate (v/v 3/1): off-white solid, 63%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 4.8 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 7.80 (td, J = 7.7, 1.8 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.29 (td, J = 6.2, 1.1 Hz, 1H), 7.25-7.22 (m, 2H), 6.92-6.86 (m, 2H), 6.57 (s, 1H), 2.38 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.4, 154.7, 149.1, 140.5, 139.0, 138.5, 136.8, 129.0, 123.4, 123.4, 121.0, 120.8, 117.2, 112.4, 108.8, 21.5.

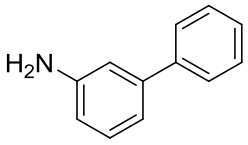
*N-(3-methoxyphenyl)-2,2'-bipyridin-6-amine (**17**)*




**17**

This compound was prepared according to **General Procedure A** with 1.5 equivalents of *m*-anisidine. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 10/1): brown solid, 86%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 4.2 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 7.53 (t, J = 7.6 Hz, 1H), 7.24-7.14 (m, 3H), 7.10 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.56 (d, J = 8.2 Hz, 1H), 3.74 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 160.1, 156.1, 155.0, 154.2, 148.8, 141.9, 138.3, 136.6, 129.6, 123.3, 120.8, 112.3, 111.7, 109.5, 107.5, 105.0, 55.0.

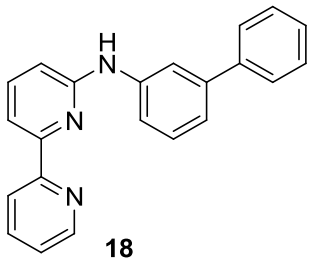
*3-aminobiphenyl*




A 100 mL 3-necked round-bottom flash under argon was charged with phenylboronic acid (1.5 g, 12 mmol), 3-bromoaniline (1.1 mL, 10 mmol), triphenylphosphine (210 mg, 0.8 mmol), aqueous $K_2CO_3$ (2M, 15 mL, 30 mmol), and 1,2-dimethoxyethane (15 mL). This mixture was purged for five minutes, then $Pd(OAc)_2$ (45 mg, 0.2 mmol) was added and the reaction mixture was heated at reflux for 3 h. After cooling to room temperature the reaction mixture was

quenched with water (20 mL) and extracted with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the crude product was purified by column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 4/1): yellow oil, 1.7 g, 98%. $^1$H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, J = 7.1 Hz, 2H), 7.41 (t, J = 7.4 Hz, 2H), 7.32 (t, J = 7.4 Hz, 1H), 7.22 (t, J = 7.8 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.90 (t, J = 2.0 Hz, 1H), 6.67 (dd, J = 8.0, 2.4 Hz, 1H), 3.72 (s, 2H).

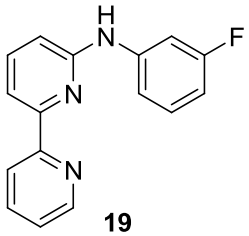
*N-(biphenyl-3-yl)-2,2'-bipyridin-6-amine (**18**)*




**18**

This compound was prepared according to **General Procedure A** with 1.2 equivalents of 3-aminobiphenyl. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): pale orange solid, 65%. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.72 (d, J = 4.7 Hz, 1H), 8.41 (d, J = 8.0 Hz, 1H), 7.95-7.85 (m, 2H), 7.81 (td, J = 8.0, 1.8 Hz, 1H), 7.72-7.64 (m, 3H), 7.53-7.23 (m, 7H), 6.92 (d, J = 8.3 Hz, 1H), 6.80 (s, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.3, 155.2, 154.6, 149.1, 142.3, 141.1, 141.1, 138.6, 136.7, 129.5, 128.7, 127.4, 127.1, 123.5, 121.2, 121.1, 118.5, 112.6, 109.2.

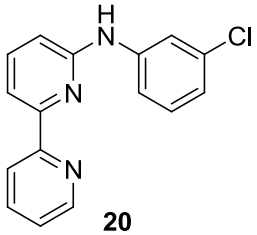
*N-(3-fluorophenyl)-2,2'-bipyridin-6-amine (**19**)*




**19**

This compound was prepared according to **General Procedure A** with 2 equivalents of 3-fluoroaniline. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 10/1): brown solid, 62%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.67 (d, J = 4.7 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 7.81 (t, J = 7.5 Hz, 1H), 7.64 (t, J = 7.7 Hz, 1H), 7.46 (d, J = 11.3 Hz, 1H), 7.32-7.20 (m, 2H), 7.09 (d, J = 8.0 Hz, 1H), 6.88-6.77 (m, 2H), 6.71 (t, J = 8.4 Hz, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 164.6, 162.2, 156.2, 154.7, 154.6, 149.1, 142.6, 142.5, 138.7, 137.0, 130.2, 130.1, 123.6, 121.1, 114.5, 114.5, 113.1, 109.9, 108.7, 108.5, 106.3, 106.0.

*N-(3-chlorophenyl)-2,2'-bipyridin-6-amine (**20**)*

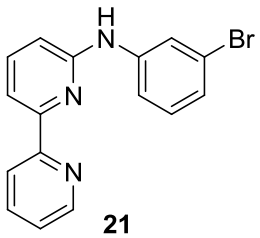



**20**

This compound was prepared according to **General Procedure A** with 1.5 equivalents of 3-chloroaniline. The crude product was purified by column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 3/1): off-white crystalline solid, 21%. $^{1}$H NMR (400

MHz, $CDCl_3$): δ 8.68 (d, J = 4.9 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.5 Hz, 1H), 7.82 (td, J = 7.8, 1.8 Hz, 1H), 7.69 (s, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.33-7.21 (m, 3H), 7.00 (dt, J = 6.7, 2.2 Hz, 1H), 6.84 (d, J = 8.1 Hz, 1H), 6.62 (s, 1H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 156.1, 154.7, 154.5, 149.1, 142.0, 138.7, 136.9, 134.7, 130.1, 123.6, 122.0, 121.0, 119.2, 117.2, 113.1, 109.7.

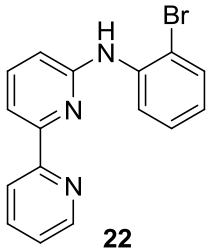
*N-(3-bromophenyl)-2,2'-bipyridin-6-amine **(21)***




**21**

This compound was prepared according to **General Procedure A** with 1 equivalent of 3-bromoaniline. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 5/1): tan crystalline solid, 25%. $^1H$ NMR (400 MHz, $CDCl_3$): δ 8.68 (d, J = 4.6 Hz, 1H), 8.34 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.88 (d, J = 3.7 Hz, 1H), 7.82 (td, J = 7.8, 1.8 Hz, 1H), 7.67 (t, J = 7.9 Hz, 1H), 7.34-7.27 (m, 2H), 7.19 (t, J = 7.8 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 6.64 (s, 1H). $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 156.1, 154.6, 154.4, 149.1, 142.1, 138.7, 136.9, 130.3, 124.8, 123.6, 122.8, 122.1, 121.1, 117.6, 113.1, 109.7.

*N-(2-bromophenyl)-2,2'-bipyridin-6-amine (**22**)*

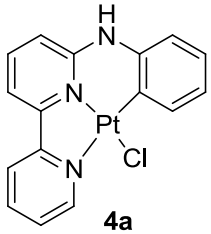



**22**

This compound was prepared according to **General Procedure A** with 1 equivalent of 2-bromoaniline. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): brown solid, 58%. $^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.62 (d, J = 4.8 Hz, 1H), 8.07 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.82-7.60 (m, 3H), 7.58-7.42 (m, 2H), 7.33-7.17 (m, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 156.1, 155.7, 154.0, 148.9, 143.3, 138.1, 136.8, 133.9, 132.4, 128.8, 128.5, 124.9, 123.5, 121.0, 115.6, 114.6.

## Synthesis of Complexes

*Complex **4a***

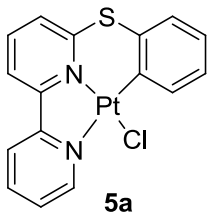



**4a**

**General Procedure B**: To a 50 mL, dry, three-necked round-bottom flask with condenser and drying tube were added ligand **4** (40 mg, 0.25 mmol), $K_2PtCl_4$ (66 mg, 0.25 mmol), and acetic acid (6 mL). The mixture was heated at reflux for 24 h. After the mixture was cooled to

room temperature, the precipitates were collected by filtration, washed with acetic acid, water, methanol, and ethyl acetate: yellow solid, 67 mg, 89%. $^{1}$H NMR (400 MHz, DMSO) δ 10.69 (s, 1H), 9.74 (d, J = 5.5 Hz, 1H), 8.64 (d, J = 8.3 Hz, 1H), 8.60 (d, J= 7.7 Hz, 1H), 8.32 (t, J= 7.3 Hz, 1H), 8.14 (t, J= 7.4 Hz, 1H), 8.05 (d, J = 7.4 Hz, 1H), 7.86 (t, J = 6.9 Hz, 1H), 7.49 (d, J= 8.5 Hz, 1H), 7.09 (t, J= 12.4 Hz, 1H), 6.78 (t, J= 7.2 Hz, 1H). $^{13}$C NMR (75 MHz, DMSO) δ 155.4, 152.5, 147.8, 144.7, 139.6, 139.2, 135.6, 134.9, 126.5, 124.5, 123.0, 120.3, 118.2, 115.2, 115.0, 113.6. Anal. Calcd for $C_{16}H_{12}ClN_3Pt$: C, 40.30; H, 2.54; N, 8.81. Found: C, 40.49; H, 2.52; N, 8.79.

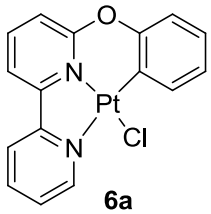
*Complex **5a***




**5a**

This compound was prepared according to **General Procedure B**: yellow solid, 93%. $^{1}$H NMR (400 MHz, DMSO) δ 9.57 (d, J = 5.6, 1H), 8.68 (d, J = 8.2 Hz, 1H), 8.52 (d, J = 7.9 Hz, 1H), 8.40 (td, J = 7.9, 1.6 Hz, 1H), 8.29 (t, J = 7.8 Hz, 1H), 8.13 (dd, J = 8.0, 1.2 Hz, 1H), 8.02 (dd, J = 7.8, 1.6 Hz, 1H), 7.94 (t, J = 6.5 Hz, 1H), 7.41 (dd, J = 7.5, 1.5 Hz, 1H), 7.00 (td, J = 7.4, 1.7 Hz, 1H), 6.94 (td, J = 7.3, 1.6 Hz, 1H).

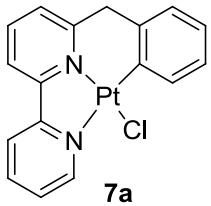
*Complex **6a***




**6a**

This compound was prepared according to **General Procedure B**: yellow solid, 52%. $^{1}$H NMR (400 MHz, DMSO) δ 9.61 (d, J = 5.5, 1H), 8.72 (d, J = 8.3 Hz, 1H), 8.57-8.32 (m, 4H), 7.93 (t, J = 6.6 Hz, 1H), 7.67 (dd, J = 6.5, 2.9 Hz, 1H), 7.22-7.07 (m, 2H), 6.97 (t, J = 7.4 Hz, 1H).

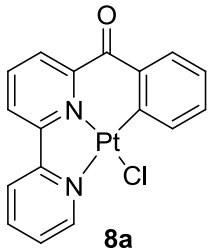
*Complex **7a***




**7a**

This compound was prepared according to **General Procedure B**: yellow-brown solid, 87%. $^{1}$H NMR (400 MHz, DMSO) δ 9.40 (d, J = 5.2, 1H), 8.62 (d, J = 8.1 Hz, 1H), 8.47 (d, J = 7.9 Hz, 1H), 8.37 (t, J = 8.2 Hz, 1H), 8.28 (t, J = 7.8 Hz, 1H), 8.02-7.64 (m, 3H), 7.06 (d, J = 6.8 Hz, 1H), 6.94-6.77 (m, 2H), 4.37 (s, 2H).

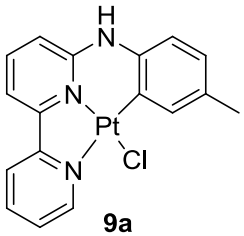
*Complex **8a***




**8a**

This compound was prepared according to **General Procedure B**. The solvent was evaporated and the crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 4/1): brown solid, 63%. $^{1}$H NMR (400 MHz, DMSO) δ 9.56 (d, J = 5.4 Hz, 1H), 8.82 (d, J = 8.0 Hz, $^{3}J_{Pt–H}$ = 88.2 Hz, 1H), 8.72 (d, J = 8.1 Hz, 1H), 8.58 (t, J = 7.9 Hz, 1H), 8.43 (t, J = 7.8 Hz, 2H), 8.31 (d, J = 8.0 Hz, $^{3}J_{Pt–H}$ = 46.0 Hz, 1H), 7.99 (t, J = 6.5 Hz, 1H), 7.84 (dd, J = 7.8, 1.6 Hz, 1H), 7.26 (t, J = 7.3 Hz, 1H), 7.18 (t, J = 7.4 Hz, 1H).

*Complex **9a***

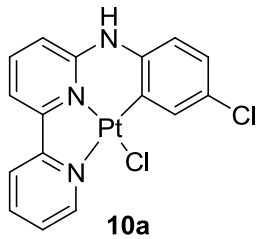



**9a**

This compound was prepared according to **General Procedure B**: bright orange solid, 91%. $^{1}$H NMR (400 MHz, DMSO) δ 10.62 (s, 1H), 9.75 (d, J = 5.4 Hz, 1H), 8.63 (d, J = 8.2 Hz, 1H), 8.41 (s, $^{3}J_{Pt–H}$ = 33.2 Hz, 1H), 8.31 (t, J = 7.7 Hz, 1H), 8.11 (t, J = 8.4 Hz, 1H), 8.02 (d, J = 7.0

Hz, 1H), 7.85 (t, J = 6.7 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 6.87 (dd, J = 8.0, 1.9 Hz, 1H), 2.21 (s, 3H).

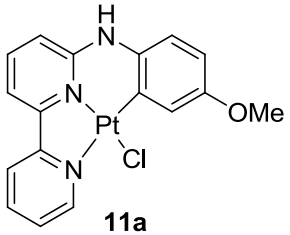
*Complex **10a***




**10a**

This compound was prepared according to **General Procedure B**: bright orange solid, 82%. $^{1}$H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 9.71 (d, J = 5.3 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H), 8.59 (s, $^{3}J_{Pt-H}$ = 44.0 Hz, 1H), 8.33 (t, J = 7.9 Hz, 1H), 8.16 (t, J = 8.3 Hz, 1H), 8.08 (d, J = 7.3 Hz, 1H), 7.87 (t, J = 6.5 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.18-7.04 (m, 2H).

*Complex **11a***

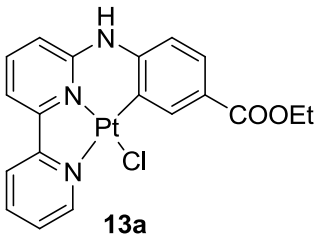



**11a**

This compound was prepared according to **General Procedure B**. The solvent was evaporated and the crude product suspended in dichloromethane, filtered, and washed with dichloromethane, methanol, and hexane: red solid, 76%. $^{1}$H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 9.73 (d, J = 5.2 Hz, 1H), 8.63 (d, J = 8.4 Hz, 1H), 8.31 (t, J = 7.7 Hz, 1H), 8.25 (s, $^{3}J_{Pt-H}$ =

36.2 Hz, 1H), 8.07 (t, J = 8.1 Hz, 1H), 7.99 (d, J = 7.1 Hz, 1H), 7.85 (t, J = 6.8 Hz, 1H), 7.51 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 8.5 Hz, 1H), 6.68 (dd, J = 8.7, 2.9 Hz, 1H), 3.70 (s, 3H).

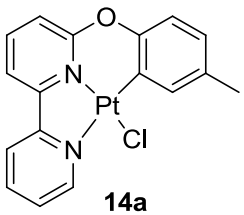
*Complex **13a***




**13a**

This compound was prepared according to **General Procedure B**: orange solid, 89%. $^{1}$H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 9.73 (d, J = 5.3 Hz, 1H), 9.28 (s, 1H), 8.65 (d, J = 8.2 Hz, 1H), 8.33 (t, J = 7.6 Hz, 1H), 8.20 (t, J = 8.1 Hz, 1H), 8.11 (d, J = 7.4 Hz, 1H), 7.88 (t, J = 6.7 Hz, 1H), 7.70 (dd, J = 8.4, 2.0 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.15 (d, J = 8.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.33 (t, J = 7.1 Hz, 3H).

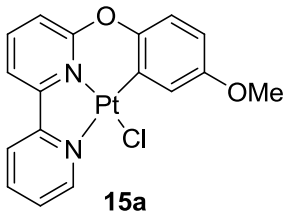
*Complex **14a***




**14a**

This compound was prepared according to **General Procedure B**: yellow-orange solid, 67%. $^{1}$H NMR (400 MHz, DMSO) δ 9.60 (d, J = 5.1 Hz, 1H), 8.89 (d, J = 8.1 Hz, 1H), 8.51-8.33 (m, 3H), 8.21 (s, $^{3}J_{Pt–H}$ = 54.6 Hz, 1H), 7.91 (t, J = 6.9 Hz, 1H), 7.61 (dd, J = 6.9, 2.8 Hz, 1H), 7.04 (d, J = 8.2 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 2.24 (s, 3H).

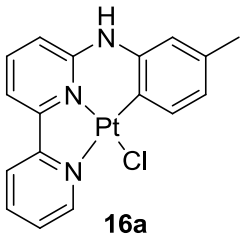
*Complex **15a***




**15a**

This compound was prepared according to **General Procedure B**: orange solid, 74%. $^{1}$H NMR (400 MHz, DMSO) δ 9.60 (d, J = 5.5 Hz, 1H), 8.70 (d, J = 8.1 Hz, 1H), 8.57-8.31 (m, 3H), 8.00 (d, J = 3.1 Hz, 1H), 7.92 (t, J = 6.9 Hz, 1H), 7.62 (t, J = 4.8 Hz, 1H), 7.12 (d, J = 8.8 Hz, 1H), 6.70 (dd, J = 8.9, 3.1 Hz, 1H), 3.72 (s, 3H).

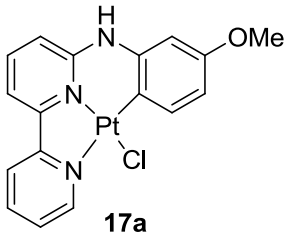
*Complex **16a***




**16a**

This compound was prepared according to **General Procedure B**: red solid, 89%. $^{1}$H NMR (400 MHz, DMSO) δ 10.62 (s, 1H), 9.74 (d, J = 5.8 Hz, 1H), 8.65 (d, J = 8.3 Hz, 1H), 8.45 (d, J = 8.1 Hz, 1H), 8.32 (t, J = 8.0 Hz, 1H), 8.14 (t, J = 8.4 Hz, 1H), 8.05 (d, J = 7.4 Hz, 1H), 7.86 (t, J = 6.6 Hz, 1H), 7.49 (d, J = 8.6 Hz, 1H), 6.94 (s, 1H), 6.62 (d, J = 8.2 Hz, 1H), 2.27 (s, 3H).

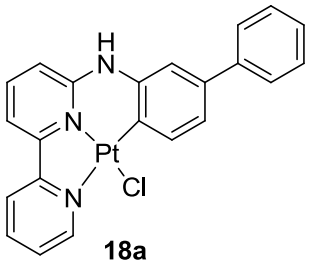
*Complex **17a***




**17a**

This compound was prepared according to **General Procedure B**: red solid, 99%. $^{1}$H NMR (400 MHz, DMSO) δ 10.69 (s, 1H), 9.75 (d, J = 5.8 Hz, 1H), 8.66 (d, J = 8.2 Hz, 1H), 8.46 (d, J = 8.8 Hz, 1H), 8.33 (t, J = 7.8 Hz, 1H), 8.16 (t, J = 8.4 Hz, 1H), 8.08 (d, J = 7.3 Hz, 1H), 7.86 (t, J = 6.6 Hz, 1H), 7.48 (d, J = 8.7 Hz, 1H), 6.74 (d, J = 2.7 Hz, 1H), 6.45 (dd, J = 9.0, 2.6 Hz, 1H), 3.76 (s, 3H).

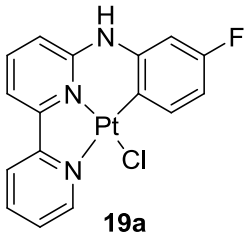
*Complex **18a***




**18a**

This compound was prepared according to **General Procedure B**: orange solid, 92%. $^{1}$H NMR (400 MHz, DMSO) δ 10.81 (s, 1H), 9.70 (d, J = 5.1 Hz, 1H), 8.63 (t, J = 8.6 Hz, 2H), 8.32 (t, J = 7.3 Hz, 1H), 8.16 (t, J = 8.0 Hz, 1H), 8.06 (d, J = 7.4 Hz, 1H), 7.86 (t, J = 6.6 Hz, 1H), 7.67 (d, J = 7.7 Hz, 2H), 7.48 (t, J = 7.6 Hz, 3H), 7.42-7.31 (m, 2H), 7.07 (d, J = 8.3 Hz, 1H).

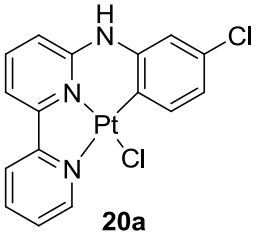
*Complex **19a***




**19a**

This compound was prepared according to **General Procedure B**: orange solid, 89%. $^{1}$H NMR (400 MHz, DMSO) δ 10.80 (s, 1H), 9.73 (d, J = 5.6 Hz, 1H), 8.66 (d, J = 8.3 Hz, 1H), 8.58 (t, J = 8.4 Hz, 1H), 8.34 (t, J = 7.9 Hz, 1H), 8.19 (t, J = 8.3 Hz, 1H), 8.11 (d, J = 7.2 Hz, 1H), 7.88 (t, J = 6.5 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 6.93 (dd, J = 11.4, 2.8 Hz, 1H), 6.63 (td, J = 8.8, 2.8 Hz, 1H).

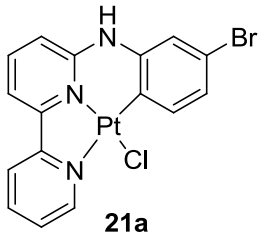
*Complex **20a***




**20a**

This compound was prepared according to **General Procedure B**: orange solid, 82%. $^{1}$H NMR (400 MHz, DMSO) δ 10.79 (s, 1H), 9.70 (d, J = 5.7 Hz, 1H), 8.65 (d, J = 8.2 Hz, 1H), 8.57 (d, J = 8.6 Hz, 1H), 8.33 (t, J = 7.8 Hz, 1H), 8.18 (t, J = 8.3 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 7.87 (t, J = 6.6 Hz, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.16 (d, J = 2.3 Hz, 1H), 6.79 (dd, J = 8.7, 2.4 Hz, 1H).

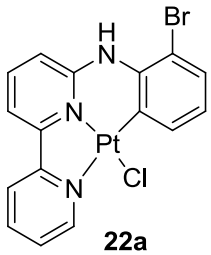
*Complex **21a***




**21a**

This compound was prepared according to **General Procedure B**: orange solid, 99%. $^{1}$H NMR (400 MHz, DMSO) δ 10.78 (s, 1H), 9.71 (d, J = 5.5 Hz, 1H), 8.66 (d, J = 8.3 Hz, 1H), 8.52 (d, J = 8.6 Hz, 1H), 8.33 (t, J = 7.5 Hz, 1H), 8.19 (t, J = 8.1 Hz, 1H), 8.10 (d, J = 7.2 Hz, 1H), 7.87 (t, J = 6.6 Hz, 1H), 7.45 (d, J = 8.5 Hz, 1H), 7.30 (d, J = 2.1 Hz, 1H), 6.91 (dd, J = 8.5, 2.1 Hz, 1H).

*Complex **22a***




**22a**

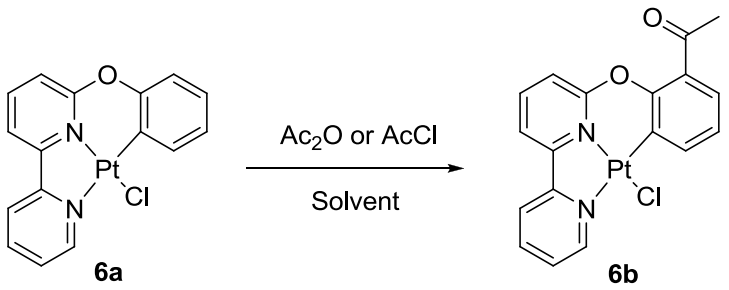
This compound was prepared according to **General Procedure B**: brown-orange solid, 79%. $^{1}$H NMR (400 MHz, DMSO) δ 9.36 (d, J = 5.7 Hz, 1H), 9.00 (d, J = 8.7 Hz, 1H), 8.78 (d, J = 7.8 Hz, 1H), 8.71 (t, J = 7.9 Hz, 1H), 8.54 (t, J = 8.3 Hz, 1H), 8.28-8.16 (m, 2H), 7.96 (d, J = 3.8 Hz, 1H), 7.91-7.79 (m, 1H), 7.05 (d, J = 9.0 Hz, 1H), 6.93-6.84 (m, 1H).

# CHAPTER 4: ACYLATION OF CYCLOPLATINATED COMPLEXES

## 4.1 Optimization of Reaction Conditions

The acylation of N^N*C cycloplatinated complexes was first observed as a side reaction in the reaction of **3** with $K_2PtCl_4$ in acetic acid. It was found that the cycloplatinated complex **3a** could be regioselectively acylated in high yield by refluxing it in a 1:1 mixture of acetic acid and acetic anhydride. Long reaction times were needed in order to get complete conversion of the starting complex to the acylated complex. Complexes generally tend to decompose if they are heated for prolonged periods of time, so these conditions are not ideal. Using acetic acid or acetic anhydride as the source of the acetyl group limited the reaction in the number of solvents that could be used. Acetyl chloride was found to be a more efficient alternative. A series of solvents were screened in the reaction of **6a** with acetyl chloride. Complex **6a** was selected for its good solubility in the solvents selected. The results from these reactions are detailed in **Table 6**.

**Table 6.** Acylation of **6a** using different solvents.



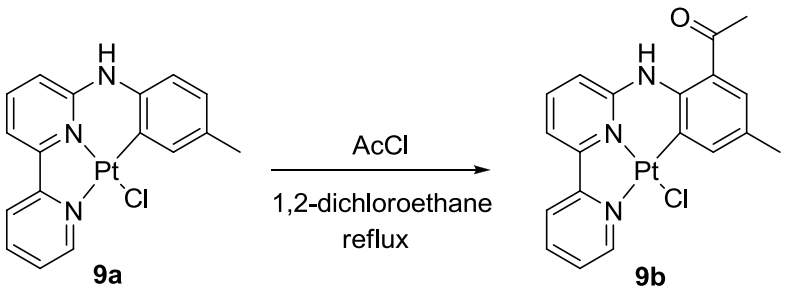

| Solvent | Electrophile Source | Temperature | Time | Yield (%) |
|---|---|---|---|---|
| AcOH | $Ac_2O$ | reflux | 3 d | 34 |
| AcOH | AcCl (excess) | reflux | 1 h | 84 |
| MeCN | AcCl (40 eq.) | reflux | 6 h | 35 |
| PhCN | AcCl (20 eq.) | 170 $^{o}$C | 3 h | 75 |
| 1,2-dichloroethane | AcCl (20 eq.) | reflux | 1 h | 75 |
| DMF | AcCl (20 eq.) | reflux | 1 h | no reaction |
| THF | AcCl (20 eq.) | reflux | 3 h | no reaction |

The reaction in acetonitrile was slow and black precipitates formed, likely platinum metal. The major product was more polar than **6a** and **6b** on TLC and was not characterized. Complex **6a** had poor solubility in THF, which may be a reason the reaction did not proceed. Most of the starting material from this reaction was recovered. The reaction in DMF did not proceed, and there was no decomposition of the starting material. This may be due to the reaction of the acetyl chloride with DMF forming dimethylacetamide and formyl chloride, as was demonstrated to occur at reflux by Knunyants and coworkers.[42]

The best results were achieved when acetic acid was used as the solvent with acetyl chloride. The reaction was complete after one hour, and the product was easily collected, as it precipitated out of solution. The reaction in benzonitrile proceeded cleanly and was complete in 3 hours. Adding hexane to the reaction mixture precipitated the acylated complex **6b**. Using 1,2-dichloroethane as the solvent afforded a 75% yield of the acylated complex **6b**.

Experiments were carried out to see how much of the acyl chloride was needed for the reaction to proceed in a high yield. Three reactions were run with complex **9a** and different equivalents of acetyl chloride in 1,2-dichloroethane (**Table 7**). It turned out that using 10 equivalents of acetyl chloride was enough to afford an 82% yield of the acylated complex **9b**. When 5 equivalents were used, the product was collected in a 49% yield. The product was accompanied by a black precipitate, indicating some decomposition of the starting material. The decomposition occurred to a higher degree when only two equivalents of acetyl chloride were used, and the amount of product was deemed too little to be collected.

**Table 7.** Acylation of **9a** using different equivalents of AcCl.

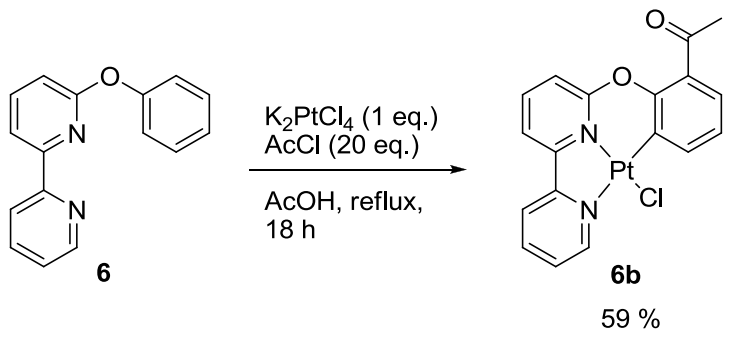



**9a** **9b**

| Equivalents of AcCl | Time | Yield (%) |
|---|---|---|
| 10 | 1 h | 82 |
| 5 | 3 h | 49 |
| 2 | 3 h | - |

As an alternative to the two step synthetic route of ligand complexation followed by acylation, the cycloplatinated acylated complexes can also be synthesized in a cascade cycloplatination-acylation reaction (**Scheme 12**). Ligand **6** was refluxed in acetic acid with one equivalent of $K_2PtCl_4$ and 20 equivalents of AcCl. After one hour, TLC analysis suggested that **6**, **6a**, and **6b** were all present in the reaction mixture. After 18 hours, there was only a small amount of the unacylated complex **6a** present, and the ligand **6** had been consumed. After suction filtration and filtration through a bed of silica, the acylated complex **6b** was collected in a 59% yield, which is comparable to the overall yield of the stepwise cycloplatination-acylation synthetic route.

**Scheme 12**. Cascade cycloplatination-acylation of **6**.




### 4.2 Modification to the Linker Group or Atom

The platinum complexes synthesized for investigation of the acylation reaction are summarized in **Figure 6**. Complexes with various linker atoms or groups, linking the bipyridyl moiety to the phenyl ring, were subjected to the acylation reaction (**Table 8**). The reactions of complexes with amino (**4a**), sulfur (**5a**), oxygen (**6a**), and methylene (**7a**) linker groups or atoms proceeded cleanly with the exception of **5a**. Despite the small reaction scale, **5b** was collected in a 40% yield. The starting material **5a** did not decompose and 12% of this was collected after column chromatography. The reaction of **5a** also proceeded, but not to completion, when it was refluxed in a 1:1 acetic acid/acetic anhydride mixture. Some of the starting material remained unreacted, even after two days of refluxing in the 1:1 acetic acid/ acetic anhydride mixture. Using these conditions, a 54% yield of **5b** was collected and 24% of the starting material **5a** were recovered after column chromatography. There was no reaction observed for complex **8a**. On TLC, there was a spot corresponding to the starting material and no new spots. Upon filtration, 93% of the starting material was recovered. It should be noted that this compound seemed to have poor solubility in the reaction solvent, even at reflux.

**Figure 6**. Structures of platinum complexes for acylation reaction investigation.

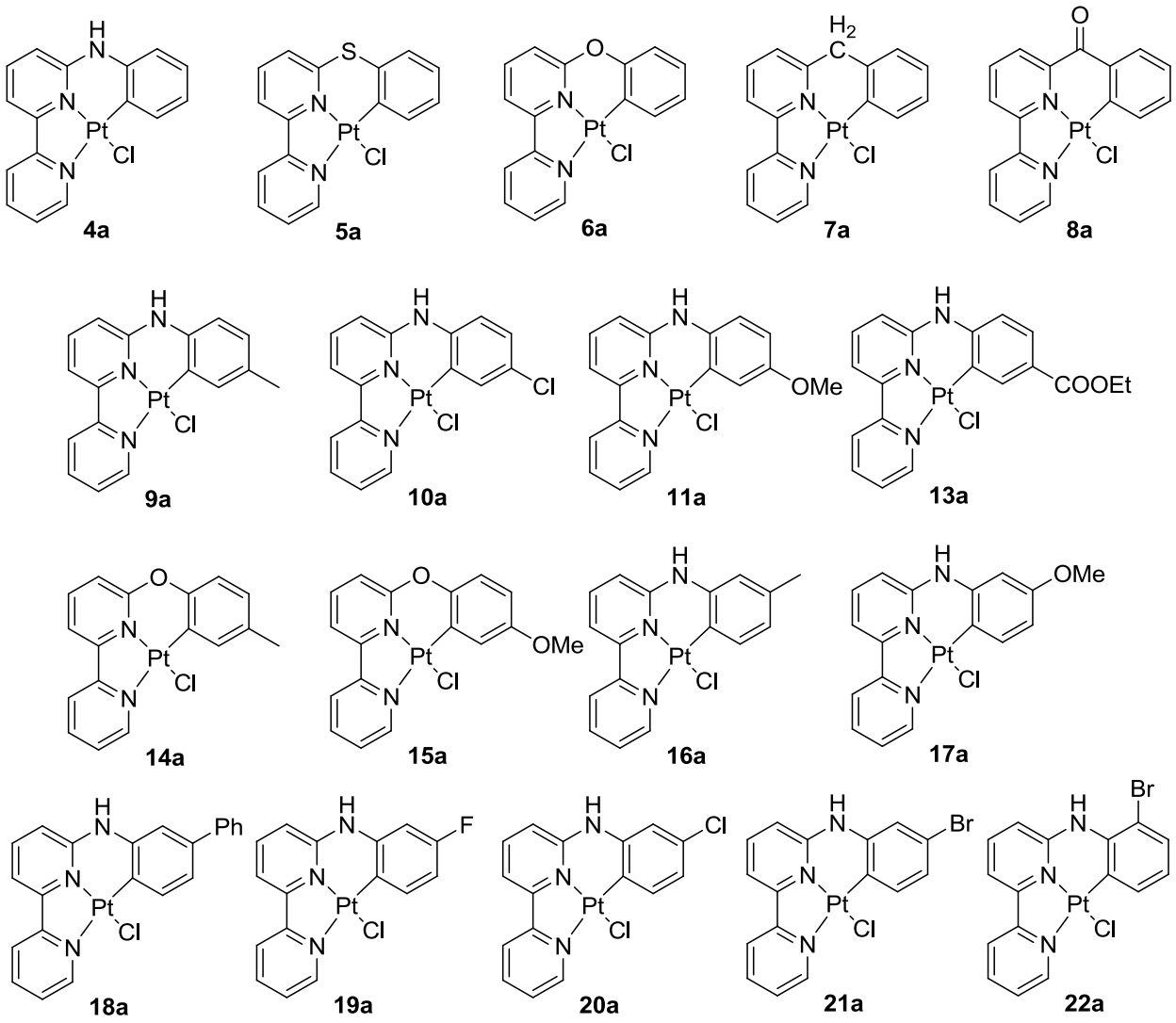
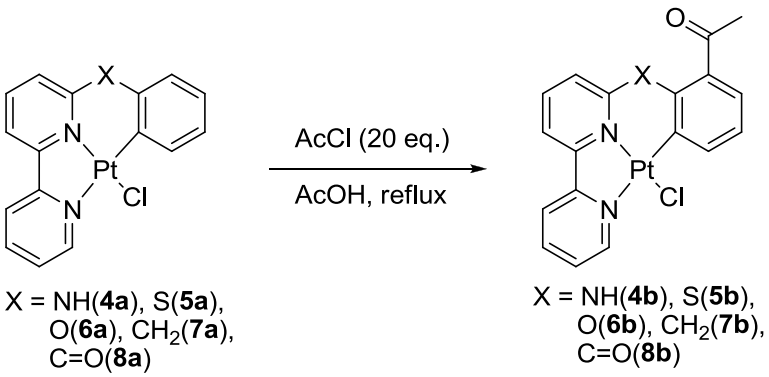


**Table 8.** Acylation of complexes with various linker groups.




X = NH(**4a**), S(**5a**), O(**6a**), $CH_2$(**7a**), C=O(**8a**)

X = NH(**4b**), S(**5b**), O(**6b**), $CH_2$(**7b**), C=O(**8b**)

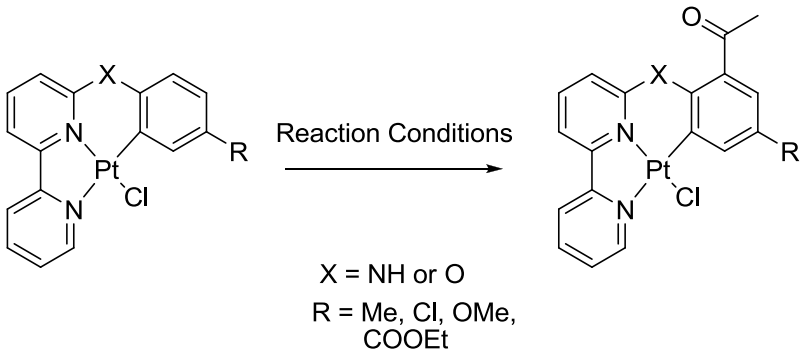
| Starting Material | Linker group (X) | Time (h) | Yield (%) |
|---|---|---|---|
| **4a** | NH | 1 | 86 |
| **5a** | S | 3 | 40 (12% SM) |
| **6a** | O | 3 | 77 |
| **7a** | $CH_2$ | 6 | 62 |
| **8a** | C=O | 2 | - |

### 4.3 Substituents on the Phenyl Ring

Complexes with substituents in the position *para* to the linker atom or group all proceeded to form the acylated complexes. The complexes were acylated cleanly and collected in good to

excellent yields. The acylation reaction was not significantly affected by the difference in electron-richness of the phenyl ring due to the electron withdrawing or electron donating effect of the substituents. The results of these reactions are reported in **Table 9**.

**Table 9.** Acylation of complexes with substituents *para* to the linker atom or group.




| Starting Material | Linker Group (X) | Substituent (R) | Reaction Conditions | Yield (%) |
|---|---|---|---|---|
| **9a** | NH | Me | AcCl (20 eq.), AcOH, reflux, 1 h | 91 |
| **10a** | NH | Cl | AcCl (20 eq.), AcOH, reflux, 1 h | 94 |
| **11a** | NH | OMe | AcCl (20 eq.), AcOH, reflux, 1 h | 69 |
| **13a** | NH | COOEt | 1:1 AcOH:$Ac_2O$, reflux, 21 h | 75 |
| **14a** | O | Me | AcCl (20 eq.), AcOH, reflux, 1 h | 90 |
| **15a** | O | OMe | AcCl (20 eq.), AcOH, reflux, 24 h | 61 (16% SM) |

Complexes with substituents *ortho* or *meta* to the amino linker group did not fare as well in the acylation reaction. No reaction was observed when complexes **16a**, **18a**, **20a**, **21a**, and **22a** were refluxed in acetic acid and 20 equivalents of acetyl chloride. There were no new spots

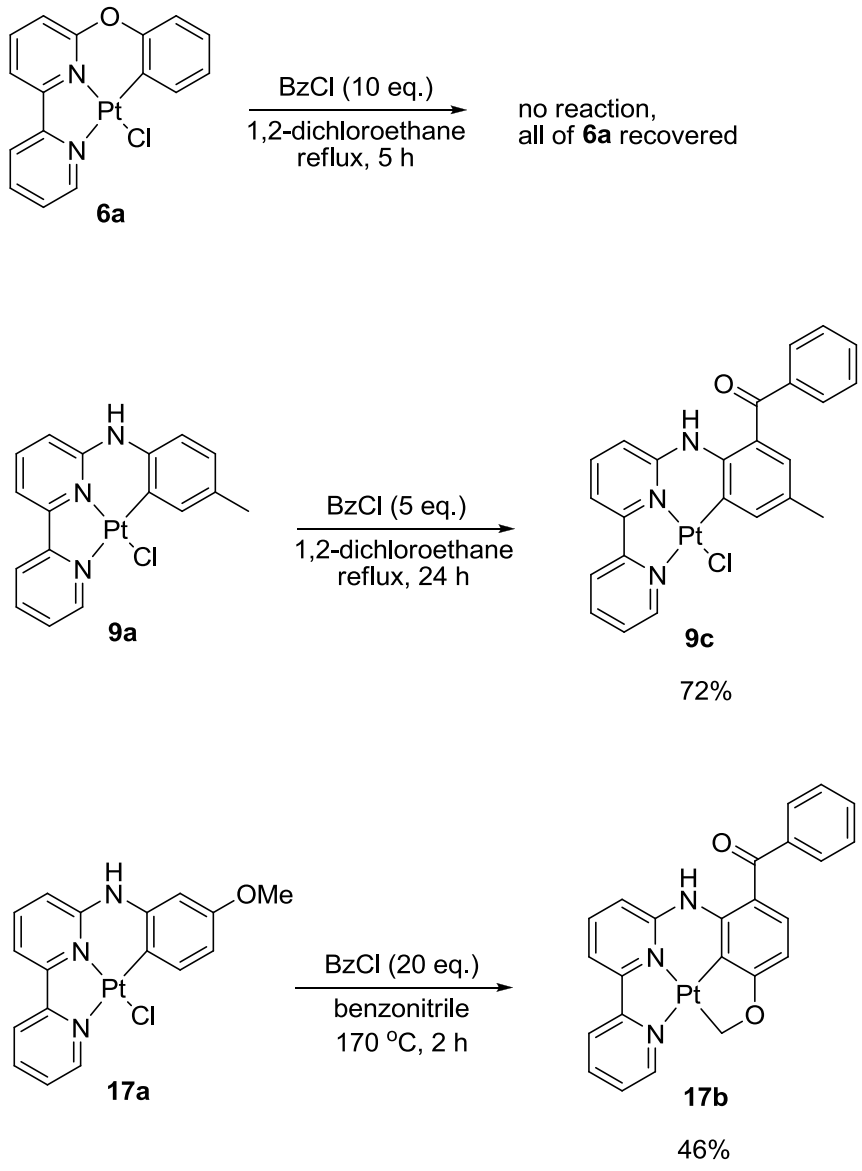
observed on TLC. The starting materials were collected in yields of 61%, 88%, 66%, 61%, and 79% respectively. Compounds **16a**, **20a**, and **21a** had low percent recoveries owing to the small scale of these reactions, and the inherent loss of material in the suction filtration workup. The starting materials were unreacted, although some decomposition and formation of a black precipitate was observed in the reaction of **20a**. The acylation reaction of **17a** resulted in a dark reaction mixture and black precipitates. Trace amounts of what was suspected to be the acylated product were detected on TLC, but the compound decomposed during workup. This compound was not isolated or characterized conclusively. The acylation of **17a** was investigated further, as described in Section 4.4. The only complex with a substituent *meta* to the amino linker group that underwent the acylation cleanly without any complications was **19a**, bearing a fluoro substituent. After refluxing **19a** in AcOH with 10 equivalents of acetyl chloride for one hour, all of the starting material had been acylated, as confirmed by $^{1}$H NMR. The acylated product was collected in an 83% yield. The characterization of the acylated cycloplatinated complex **19b** is discussed in Chapter 5.

### 4.4 Use of Alternate Electrophiles

The use of anhydrous organic solvents like 1,2-dichloroethane and benzonitrile allow for electrophiles other than acetyl chloride to be used in the reaction. Benzoyl chloride is similar in reactivity to acetyl chloride, so it was used in acylation reactions with a few of the previously mentioned cyclometalated platinum complexes (**Scheme 13**). No reaction was observed when **6a** was refluxed in 1,2-dichloroethane with 10 equivalents of benzoyl chloride for five hours. All of the starting material was recovered, unreacted. Cycloplatinated complex **9a** was heated in 1,2-dichloroethane at reflux with 5 equivalents of benzoyl chloride, yielding the acylated complex **9c** in a 72% yield. Complex **17a** was acylated in benzonitrile with 20 equivalents of benzoyl

chloride forming bis-cyclometalated acylated complex **17b** in a 46% yield. The formation of **17b** is discussed further in Chapter 5.

**Scheme 13**. Acylation of cyclometalated platinum complexes with benzoyl chloride.



## 4.5 Experimental Procedures

*General:*

Tetrahydrofuran (THF) was distilled from sodium and benzophenone. All other anhydrous solvents used were purchased from Sigma-Aldrich with Sure Seal. All catalysts and reagents were purchased from Sigma-Aldrich, with the exception of $K_2PtCl_4$ which was purchased from Strem Chemicals. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. Preparative chromatography was performed on silica gel 60 (0.063-0.200 mm) purchased from EMD chemicals. Thin layer chromatography was performed with silica gel 60 $F_{254}$ plates, purchased from EMD chemicals. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker 400 MHz spectrometer at 298K. Chemical shifts were reported relative to TMS (0.0 ppm for 1H), dichloromethane-d2 (53.8 ppm for $^{13}C$), chloroform-d (77.0 ppm for 13C), DMSO-d6 (39.5 ppm for $^{13}C$) and coupling constants are in Hertz. Elemental analyses were performed in Atlantic Microlabs, Norcross, GA.

### Reaction Condition Optimization

*Reaction of **6a** in 1:1 AcOH:$Ac_2O$*

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **6a** (50 mg, 0.1 mmol), acetic acid (3 mL), and acetic anhydride (3 mL). The mixture was stirred and heated at reflux for 3 d. After cooling the reaction mixture to room temperature, it was extracted with dichloromethane and the organic phase was washed with brine and dried over $MgSO_4$. After filtration, the organic solvents were removed by rotary evaporator and the crude product was purified by column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 4/1): **6b**, yellow solid, 17.6 mg, 34%. $^{1}H$ NMR (400 MHz, DMSO) δ 9.61 (d, J = 5.1

Hz, 1H), 8.75 (d, J = 8.1 Hz, 1H), 8.59 (dd, J = 7.9, 1.7 Hz, 1H), 8.50 (d, J = 5.1 Hz, 2H), 8.41 (td, J = 8.0, 1.5 Hz, 1H), 7.96 (t, J = 6.7 Hz, 1H), 7.74 (t, J = 4.8 Hz, 1H), 7.33 (dd, J = 7.3, 1.7 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 2.73 (s, 3H).

*Reaction of **6a** and AcCl in AcOH*

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **6a** (50 mg, 0.1 mmol), acetyl chloride (1.0 mL, excess), and acetic acid (5 mL). The mixture was stirred and heated at reflux for 1 h. After evaporating the solvent, the crude product was dissolved in dichloromethane and purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): **6b**, yellow solid, 45.4 mg, 84%.

*Reaction of **6a** and AcCl in MeCN*

**General Procedure C**: To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **6a** (50 mg, 0.1 mmol), acetyl chloride (140 µL, 2 mmol), and acetonitrile (5 mL). The mixture was stirred and heated at reflux for 6 h. After evaporating the solvent, the crude product was dissolved in dichloromethane and purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): **6b**, yellow solid, 35%.

*Reaction of **6a** and AcCl in PhCN*

The reaction was run according to **General Procedure C**. The mixture was stirred and heated at 170$^{o}$C for 3 h. The product was precipitated by adding hexane (25 mL) and filtered, then washed with hexane, methanol, water, and ethyl acetate: **6b**, yellow solid, 75%.

*Reaction of **6a** and AcCl in 1,2-dichloroethane*

The reaction was run according to **General Procedure C**. The mixture was stirred and heated at reflux for 1 h. After evaporating the solvent, the crude product was dissolved in dichloromethane and purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): **6b**, yellow solid, 75%.

*Reaction of **6a** and AcCl in DMF*

The reaction was run according to **General Procedure C**. The mixture was stirred and heated at reflux for 1 h. No reaction or decomposition was observed on TLC, and the reaction was stopped.

*Reaction of **6a** and AcCl in THF*

The reaction was run according to **General Procedure C**. The mixture was stirred and heated at reflux for 3 h. No reaction or decomposition was observed on TLC, and the reaction was stopped. The solvent was evaporated and the starting material was recovered.

*Cascade cycloplatination-acylation of **6** in with AcCl in AcOH*

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **6** (40 mg, 0.16 mmol), $K_2PtCl_4$ (67 mg, 0.16 mmol) acetyl chloride (230 µL, 3.2 mmol), and acetic acid (6 mL). The mixture was stirred and heated at reflux for 18 h. After cooling the reaction mixture to room temperature, the precipitates were collected by suction filtration. The crude product was purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): **6b**, yellow solid, 50 mg, 59%.

## Acylation of Cycloplatinated Complexes

*Acylation of **4a** forming **4b***

**General Procedure D**: To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **4a** (30 mg, 0.063 mmol), acetyl chloride (91 µL, 1.3 mmol), and acetic acid (4 mL). The mixture was stirred and heated at reflux for 1 h. The mixture was cooled to room temperature. The precipitate was filtered and washed with hexane, methanol, water, and ethyl acetate: **4b**, orange solid, 25.8 mg, 86%. $^1$H NMR (400 MHz, DMSO) δ 13.70 (s, 1H), 9.71 (d, J = 5.6 Hz, 1H), 8.91 (d, J = 7.9 Hz, 1H), 8.67 (d, J= 8.2 Hz, 1H), 8.33 (t, J= 8.0 Hz, 1H), 8.24 (t, J= 7.5 Hz, 1H), 8.17 (d, J = 7.7 Hz, 1H), 7.93 (d, J = 7.8 Hz, 1H), 7.88 (t, J= 6.4 Hz, 1H), 7.49 (t, J= 8.3 Hz, 1H), 6.93 (t, J= 7.7 Hz, 1H), 2.73 (s, 3H). Anal. Calcd for $C_{18}H_{14}ClN_3OPt$: C, 41.67; H, 2.72; N, 8.10. Found: C, 41.46; H, 2.78; N, 7.94.

*Acylation of **5a** forming **5b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. The mixture was cooled to room temperature and the precipitates were filtered. The crude product was dissolved in dichloromethane and purified by column chromatography on silica gel with dichloromethane and methanol (v/v 20/1). The first band gave **5a**, yellow solid, 12% recovered. The second band gave **5b**, orange solid, 40%. $^1$H NMR (400 MHz, DMSO) δ 9.49 (d, J = 5.6 Hz, 1H), 8.67 (d, J = 8.2 Hz, 1H), 8.50 (d, J = 8.1 Hz, 1H), 8.40 (td, J = 7.9, 1.6 Hz, 1H), 8.24 (t, J = 8.0 Hz, 1H), 8.17-8.00 (m, 2H), 7.94 (t, J = 6.6 Hz, 1H), 7.60 (dd, J = 7.4, 1.5 Hz, 1H), 7.00 (t, J = 7.7 Hz, 1H), 2.63 (s, 3H).

*Acylation of **6a** forming **6b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. The mixture was cooled to room temperature and the precipitates were filtered. The crude product was dissolved in dichloromethane and purified by column chromatography on silica gel first with dichloromethane and then with dichloromethane and ethyl acetate (v/v 1/1): **6b**, orange solid, 77%.

*Reaction of **6a** with BzCl in 1,2-dichloroethane*

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **6a** (40 mg, 0.084 mmol), benzoyl chloride (97 µL, 0.84 mmol), and 1,2-dichloroethane (5 mL). The mixture was stirred and heated at reflux for 5 h, then cooled to room temperature and diluted with hexane (25 mL). No reaction or decomposition was observed on TLC. The solvent was evaporated and all of the starting material **6a** was collected.

*Acylation of **7a** forming **7b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 6 h. The mixture was cooled to room temperature and the precipitates were filtered and washed with water, methanol, ethyl acetate, and acetone: **7b**, yellow/brown solid, 68%. $^{1}$H NMR (400 MHz, DMSO) δ 9.37 (d, J = 5.5 Hz, 1H), 8.62 (d, J = 8.0 Hz, 1H), 8.46 (d, J = 8.1 Hz, 1H), 8.38 (td, J = 7.9, 1.6 Hz, 1H), 8.27 (t, J = 7.8 Hz, 1H), 8.03-7.86 (m, 2H), 7.79 (d, J = 7.8 Hz, 1H), 7.29 (dd, J = 7.6, 1.3 Hz, 1H), 6.93 (t, J = 7.6 Hz, 1H), 4.47 (s, 2H), 2.60 (s, 3H).

*Acylation of **8a***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 5 h. No reaction or decomposition was observed on TLC. The mixture was cooled to room temperature the starting material was recovered by suction filtration: **8a**, brown solid, 62% recovered.

*Acylation of **9a** forming **9b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 1 h. The mixture was cooled to room temperature and diluted with water. The precipitate was filtered and washed with water, methanol, ethyl acetate, and acetone: **9b**, red solid, 91%. $^{1}$H NMR (400 MHz, DMSO) δ 3.63 (s, 1H), 9.74 (d, J = 5.7 Hz, 1H), 8.77 (s, 1H), 8.68 (d, J = 8.2 Hz, 1H), 8.35 (td, J = 7.6, 1.6 Hz, 1H), 8.22 (t, J = 8.3 Hz, 1H), 8.15 (d, J = 7.5 Hz, 1H), 7.90 (t, J = 6.7 Hz, 1H), 7.75 (s, 1H), 7.46 (d, J = 8.5 Hz, 1H), 2.76 (s, 3H), 2.30 (s, 3H).

*Acylation of **9a** forming **9c***

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **9a** (40 mg, 0.081 mmol), benzoyl chloride (47 µL, 0.41 mmol), and 1,2-dichloroethane (5 mL). The mixture was stirred and heated at reflux for 24 h. After cooling to room temperature, the solvent was evaporated and the product was collected by suction filtration and washed with hexane, water, and methanol: **9c**, yellow solid, 35.2 mg, 72%. $^{1}$H NMR (400 MHz, DMSO) δ 12.58 (s, 1H), 9.76 (d, J = 5.6 Hz, 1H), 8.81 (s, 1H), 8.71 (d, J = 8.3 Hz, 1H), 8.37 (t, J = 7.7 Hz, 1H), 8.24 (t, J = 8.2 Hz, 1H), 8.19 (d, J = 8.0 Hz, 1H), 7.91 (t, J = 6.6 Hz, 1H), 7.73-7.50 (m, 6H), 7.14 (d, J = 2.1 Hz, 1H), 2.20 (s, 3H).

*Acylation of **10a** forming **10b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 1 h. The mixture was cooled to room temperature and diluted with water. The precipitate was filtered and washed with water and methanol: **10b**, red solid, 94%. $^{1}$H NMR (400 MHz, DMSO) δ 13.50 (s, 1H), 9.68 (d, J = 5.5 Hz, 1H), 8.88 (s, $^{3}J_{Pt–H}$ = 48.0 Hz, 1H), 8.69 (d, J = 8.3 Hz, 1H), 8.37 (td, J = 7.9, 1.6 Hz, 1H), 8.26 (t, J = 8.2 Hz, 1H), 8.19 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 2.4 Hz, 1H), 7.90 (t, J = 6.8 Hz, 1H), 7.49 (d, J = 8.2 Hz, 1H), 2.78 (s, 3H).

*Acylation of **11a** forming **11b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 1 h. The mixture was cooled to room temperature and diluted with water. The precipitate was filtered and washed with water, methanol, ethyl acetate, and acetone: **11b**, dark red solid, 69%. $^{1}$H NMR (400 MHz, DMSO) δ 13.49 (s, 1H), 9.72 (d, J = 5.6 Hz, 1H), 8.67 (d, J = 8.4 Hz, 1H), 8.65 (d, J = 3.1 Hz, 1H), 8.35 (td, J = 7.9, 1.7 Hz, 1H), 8.19 (t, J = 8.3 Hz, 1H), 8.12 (d, J = 7.6 Hz, 1H), 7.89 (t, J = 6.6 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 3.0 Hz, 1H), 3.80 (s, 3H), 2.77 (s, 3H).

*Acylation of **13a** forming **13b***

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **13a** (40 mg, 0.072 mmol), acetic acid (3 mL), and acetic anhydride (3 mL). The mixture was stirred and heated at reflux for 21 h. After cooling to room temperature, water (3 mL) were added and the precipitate was filtered and washed with hexane, methanol, water, and ethyl acetate: **13b**, orange solid, 35.4 mg, 75%. $^{1}$H NMR (400 MHz, DMSO) δ 13.76 (s, 1H), 9.72 (d, J = 5.7 Hz, 1H), 9.52 (d, J = 2.0 Hz, $^{3}J_{Pt–H}$ = 36.2 Hz, 1H), 8.71 (d, J = 8.1 Hz, 1H), 8.47 (d, J =

2.0 Hz, 1H), 8.37 (t, J = 8.0 Hz, 1H), 8.31 (t, J = 8.2 Hz, 1H), 8.28-8.22 (m, 1H), 7.92 (t, J = 6.6 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 4.35 (q, J = 7.2 Hz, 2 H), 2.81 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H).

*Acylation of **14a** forming **14b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 1 h. The mixture was cooled to room temperature and diluted with water. The precipitate was filtered and washed with water and methanol: **14b**, yellow solid, 90%. $^{1}$H NMR (400 MHz, DMSO) δ 9.59 (d, J = 5.7 Hz, 1H), 8.72 (d, J = 8.2 Hz, 1H), 8.52-8.28 (m, 4H), 7.93 (t, J = 6.6 Hz, 1H), 7.69 (t, J = 4.8 Hz, 1H), 7.11 (d, J = 2.1 Hz, 1H), 2.70 (s, 3H), 2.25 (s, 3H).

*Acylation of **15a** forming **15b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 24 h. The solvent was evaporated and the crude product was dissolved in dichloromethane and purified by column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 10/1). The first band gave **15a**, orange solid, 16% recovered. The second band gave **15b**, orange solid, 61%. $^{1}$H NMR (400 MHz, DMSO) δ 9.58 (d, J = 5.4 Hz, 1H), 8.72 (d, J = 8.1 Hz, 1H), 8.46 (d, J = 4.8 Hz, 2H), 8.40 (t, J = 7.7 Hz, 1H), 8.16 (s, $^{3}J_{Pt–H}$ = 52 Hz, 1H), 7.94 (t, J = 6.5 Hz, 1H), 7.69 (t, J = 4.8 Hz, 1H), 6.85 (d, J = 3.1 Hz, 1H), 3.75 (s, 3H), 2.73 (s, 3H).

*Acylation of **16a***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. No reaction was observed on TLC, but some black precipitates formed. The mixture was cooled to room temperature the starting material was recovered by suction filtration: **16a**, brown solid, 61% recovered.

*Acylation of **17a** forming **17b***

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added **17a** (40 mg, 0.085 mmol), benzoyl chloride (190 µL, 1.69 mmol), and benzonitrile (5 mL). The mixture was stirred and heated at reflux for 2 h, then cooled to room temperature and diluted with hexane (25 mL). The yellow precipitate was filtered and dried. The crude product was dissolved in dichloromethane and purified by column chromatography on silica gel with dichloromethane and methanol (v/v 40/1): **17b**, yellow solid, 22.3 mg, 46%. $^{1}$H NMR (400 MHz, DMSO) δ 12.75 (s, 1H), 8.98 (d, J = 5.0 Hz, 1H), 8.90 (d, J = 8.1 Hz, 1H), 8.46-8.38 (m, 2H), 8.29 (t, J = 7.7 Hz, 1H), 7.93 (t, J = 6.8 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 7.69-7.54 (m, 5H), 7.33 (d, J = 8.7 Hz, 1H), 6.76 (s, $^{2}J_{Pt–H}$ = 75.9 Hz, 2H), 6.49 (d, J = 8.7 Hz, 1H).

*Acylation of **18a***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. No reaction was observed on TLC. The mixture was cooled to room temperature the starting material was recovered by suction filtration: **18a**, orange solid, 88% recovered.

*Acylation of **19a** forming **19b***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. The mixture was cooled to room temperature and diluted with water. The precipitate was filtered and washed with water, methanol, and hexane: **19b**, orange solid, 94%. $^{1}$H NMR (400 MHz, DMSO) δ 13.64 (s, 1H), 9.67 (d, J = 5.6 Hz, 1H), 8.66 (d, J = 8.1 Hz, 1H), 8.38 (t, J = 7.7 Hz, 1H), 8.27-8.16 (m, 2H), 8.04-7.91 (m, 2H), 7.49 (d, J = 8.2 Hz, 1H), 6.69 (t, J = 8.8 Hz, 1H), 2.73 (s, 3H).

*Acylation of **20a***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. No reaction was observed on TLC, but some black precipitates formed. The mixture was cooled to room temperature the starting material was recovered by suction filtration: **20a**, orange solid, 66% recovered.

*Acylation of **21a***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. No reaction was observed on TLC. The mixture was cooled to room temperature the starting material was recovered by suction filtration: **21a**, orange solid, 61% recovered.

*Acylation of **22a***

The reaction was run according to **General Procedure D**. The mixture was stirred and heated at reflux for 3 h. No reaction was observed on TLC. The mixture was cooled to room temperature the starting material was recovered by suction filtration: **22a**, red-brown solid, 79% recovered.

CHAPTER 5: MECHANISTIC INSIGHTS

## 5.1 Identification of the Site of Acylation

Identifying the site of acylation was a key task in clarifying the mechanism of the acylation reaction. Depending on whether the acylation takes place at the metalated carbon or the unmetalated carbon (*ortho* to the linker group), different mechanisms must be considered. As previously mentioned, ligands were designed with substituents *meta* to the amino linker group to help gather this piece of information (Section 3.1, **Scheme 7**). The two possible sites of acylation, the sites on the phenyl ring *ortho* to the linker group, can be distinguished in such complexes (**16a**, **17a**, **18a**, **19a**, **20a**, **21a**). The reactions of these complexes with acetyl chloride in acetic acid had differing results (Section 4.3). The acylation of **19a**, the fluoro analog, proceeded cleanly and the acylated complex **19b** was isolated in an 83% yield. A quality NMR spectrum was difficult to obtain due to solubility issues, so the chloride ligand was replaced by a phenylacetylide to yield **19c** (**Scheme 14**), which was soluble enough in DMSO-$d_6$ to take a $^1$H NMR spectrum (**Figure 7**).

**Scheme 14**. Synthesis of **19c**.

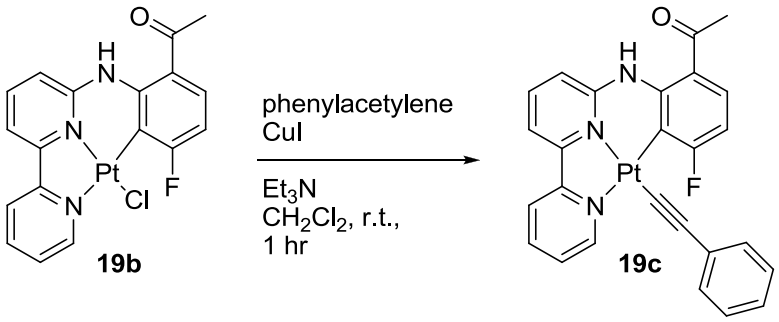
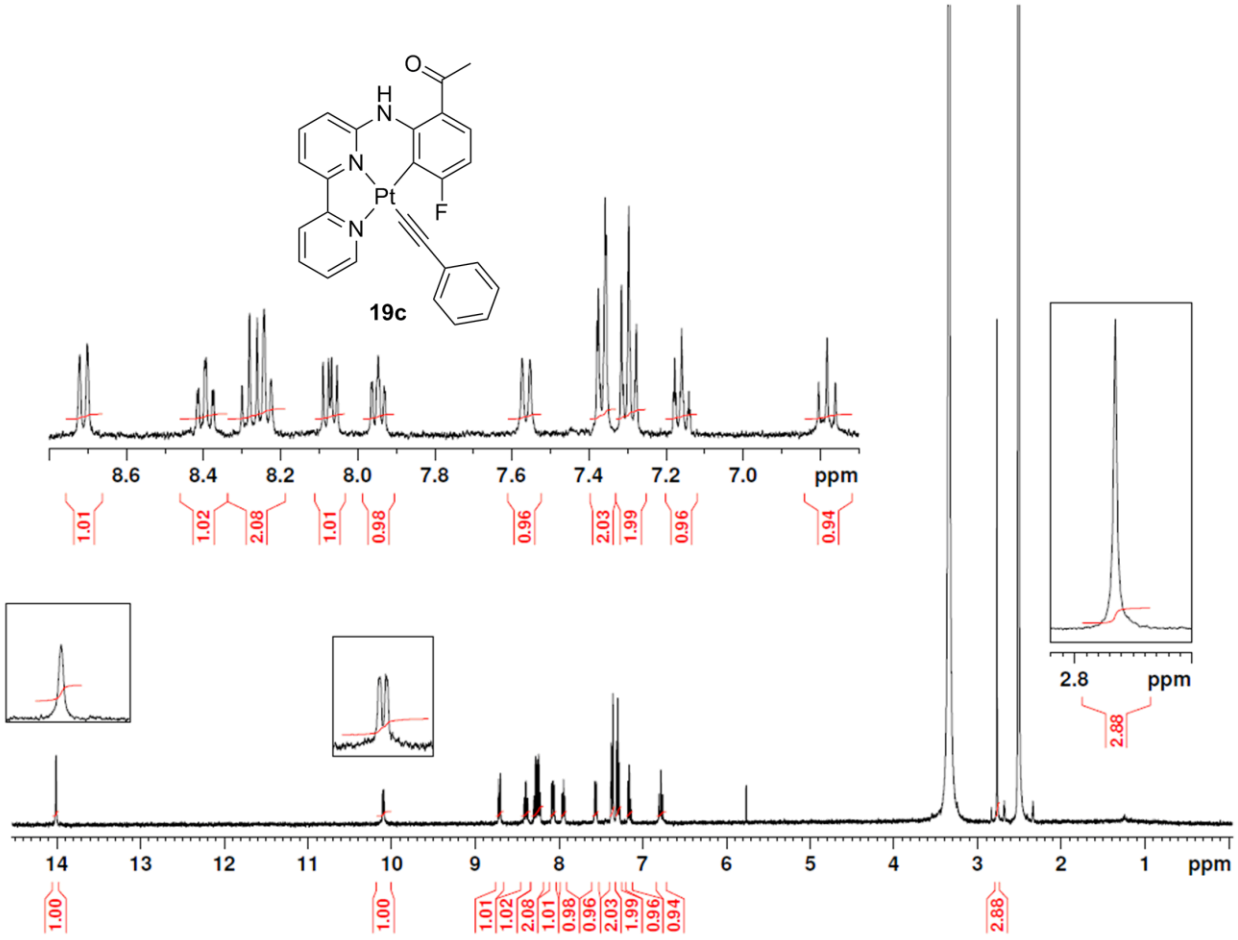


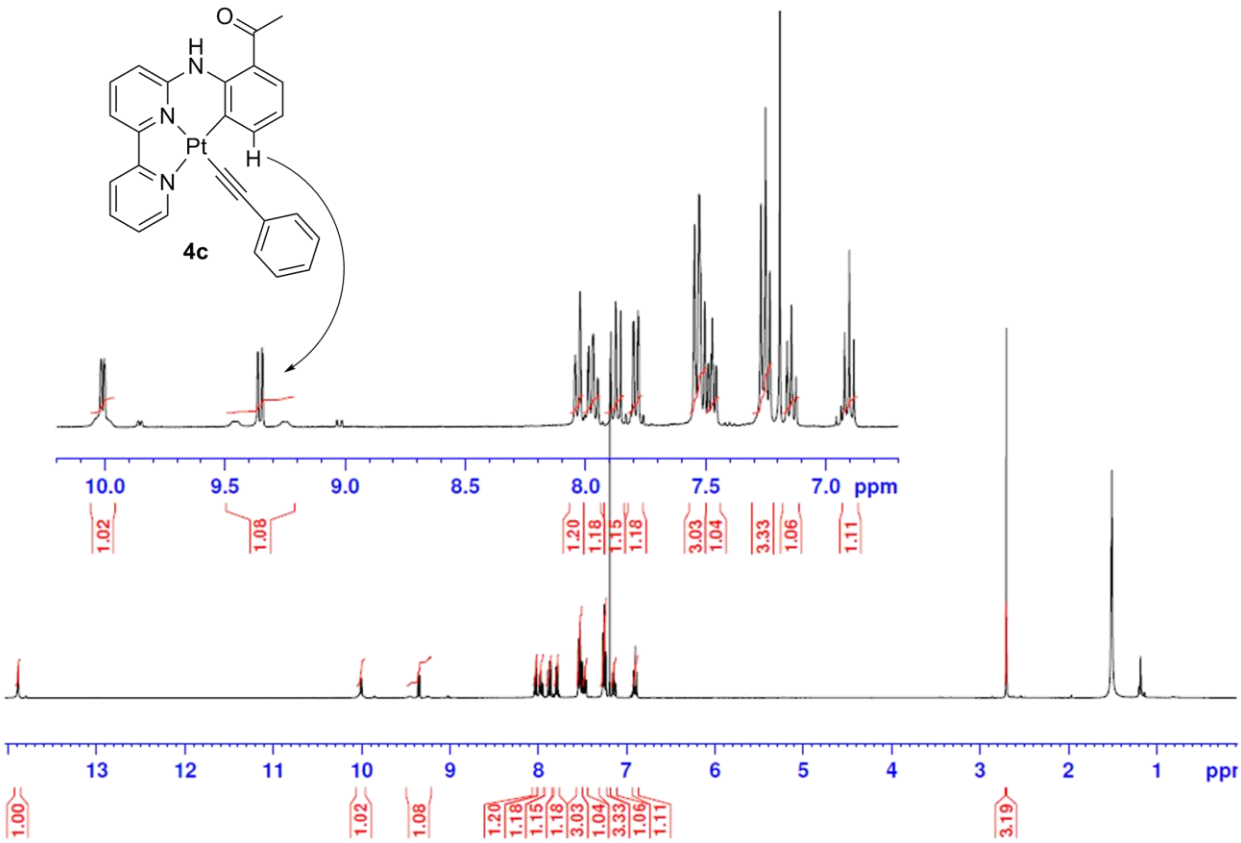
**Figure 7**. $^{1}$H NMR spectrum of **19c**.




The downfield shift of the amino proton (~14.0 ppm, 1 H) suggests that the complex was regioselectively acylated and hydrogen bonding with the carbonyl oxygen is deshielding this proton. The aromatic region showed signals from 14 protons, which is consistent with the structure of **19c**. More importantly, the aromatic proton signals displayed no signs of coupling to the platinum center. Platinum satellite peaks are typically observed for the proton *meta* to the linker group and *ortho* to the metalated carbon on the phenyl ring (see the Pt satellite peaks around the signal at 9.35 ppm in the $^{1}$H NMR spectrum of **4c**, **Figure 8**). The absence of any platinum satellite peaks in the spectrum suggests that the fluoro group is in the position *meta* to

the linker group and *ortho* to the metalated carbon. Thus, the acylation of **19a** most likely occurred at the metalated carbon.

**Figure 8**. $^{1}$H NMR spectrum of **4c**, showing platinum satellites.

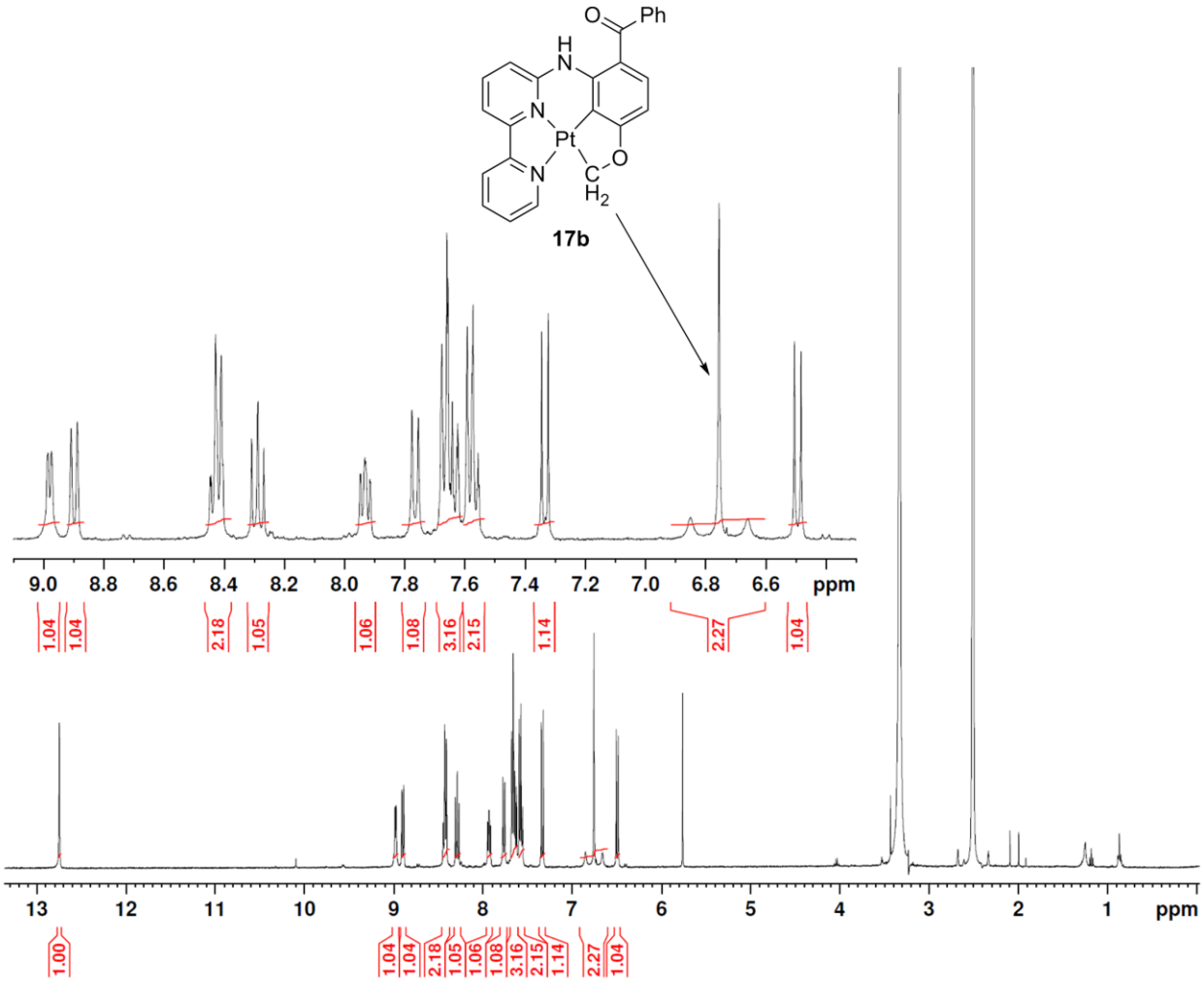



It is important to note the varied results of the acylation reactions of the complexes with halogens at the position *meta* to the linker group, namely **19a** (F), **20a** (Cl), and **21a** (Br). The difference in size of these substituents may contribute to the results of the reactions. Complex **19a** was completely converted to **19b** after only one hour. When the fluoro group was replaced with the larger chloro (**20a**) and bromo (**21a**) groups, no formation of the acylated complexes was observed and most of the starting materials were recovered. Additionally, **16a** and **18a** had substituents at this position with similar steric bulk, and these were not acylated. This data

suggests that the acylation of cycloplatinated complexes may be hindered by large substituents on the phenyl ring at the position *meta* to the linker group.

Further evidence to suggest the cyclometalated carbon as the site of acylation was found in the reaction of **17a** with 20 equivalents of benzoyl chloride in benzonitrile. The major product of this reaction was isolated and characterized as bis-cyclometalated platinum complex **17b**. The $^{1}$H NMR spectrum of **17b** (**Figure 9**) features the downfield-shifted amino hydrogen peak at 12.75 ppm. The methylene protons on the metalated carbon provide a signal at ~6.75 ppm, which is significantly shifted downfield compared to the signal from the corresponding methoxy protons in the 1H NMR spectrum of **17a**. The platinum satellite peaks observed around this peak suggest that this carbon is coordinated to the platinum. Coordination of the methoxy substituent to form bis-cyclometalated complex **17b** is only possible if acylation occurs at the cyclometalated carbon of the phenyl ring.

**Figure 9**. $^{1}$H NMR spectrum of **17b**.




## 5.2 Role of Hydrogen Bonding in the Acylation

The acylated complex **4c** displayed a strong hydrogen bonding interaction, as shown in the X-ray crystal structure (**Figure 1**). Ligands with different linker atoms or groups (**5** (S), **6** (O), **7** ($CH_2$), **8** (C=O)) were synthesized and cycloplatinated to test the effect of this hydrogen bonding on the acylation. Although complex **8a** was not acylated, complexes **5a**, **6a**, and **7a** were all acylated with the same regioselectivity. To confirm the regioselectivity, ligand **23** was synthesized by palladium-catalyzed Buchwald-Hartwig cross-coupling of 6-bromo-2,2'-

bipyridine and 4-hydroxyacetophenone. Ligand **23** was then refluxed in acetic acid with $K_2PtCl_4$ to yield complex **23a** (**Scheme 15**). This complex has an acetyl group *para* to the oxygen linker atom, making it a structural isomer of **6b**. Complex **23a** represents a possible product of the acylation of **6a**. This complex was compared to **6b** on TLC to show that they were distinct (it moved slightly faster up the TLC plate than **6b**). Their $^1$H NMR spectra also confirm that the isomers are distinct. The chemical shifts of the methyl signals are different, and there are distinct signals in the aromatic regions of the spectra. The protons on the phenyl ring have different splitting patterns based on the position of the acetyl group. Whereas the spectrum of **6b** consists of only doublets and triplets, **23a** shows a singlet at 9.12 ppm from the proton *ortho* to the metalated carbon. (**Figure 10**).

**Scheme 15**. Synthesis of **23** and **23a**.

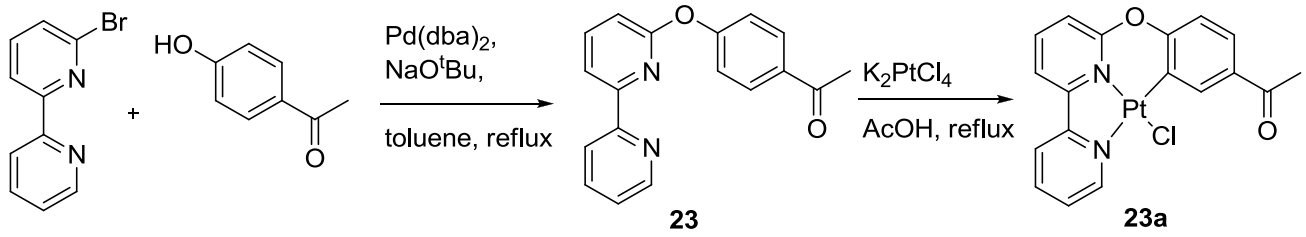
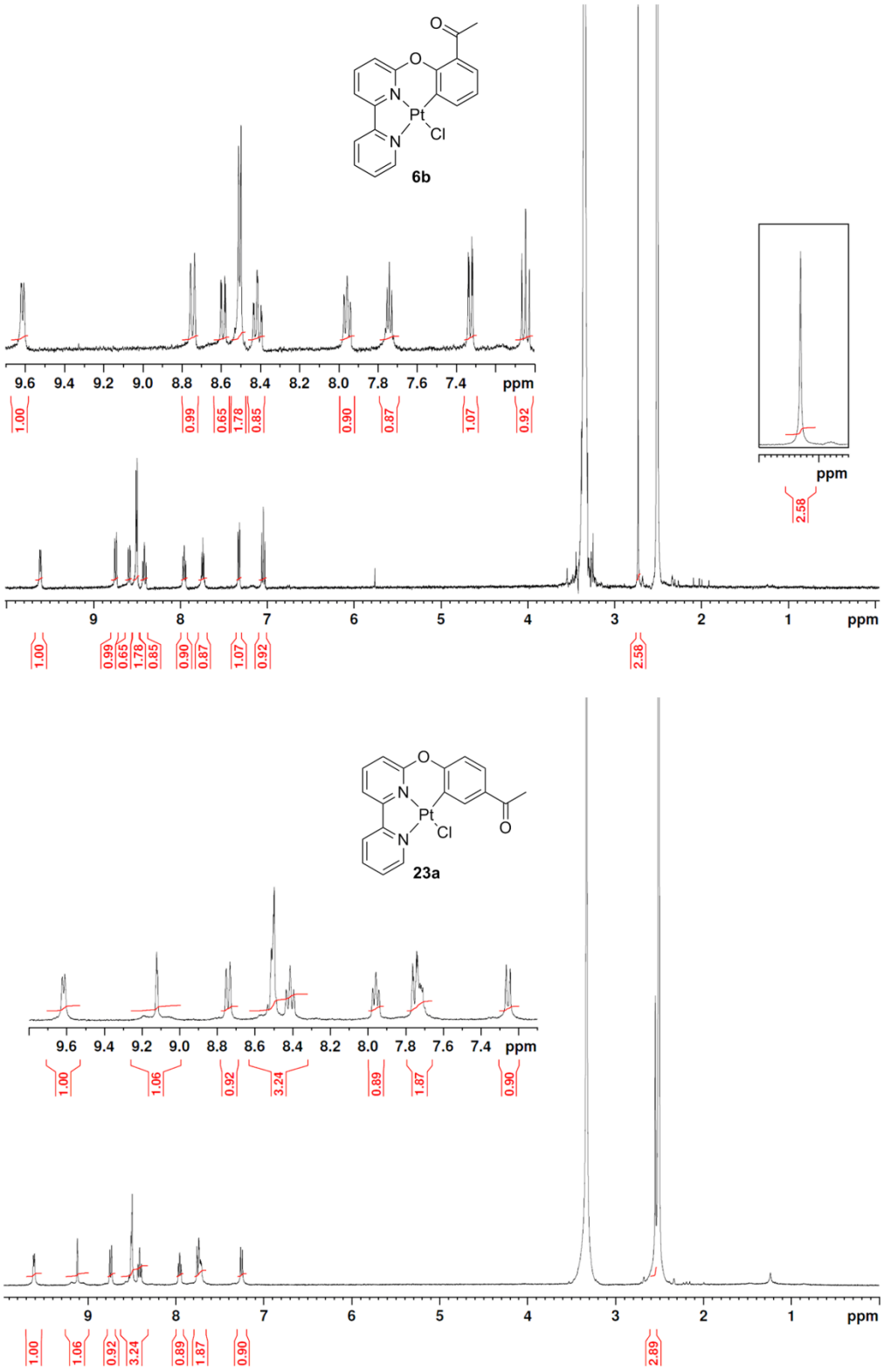


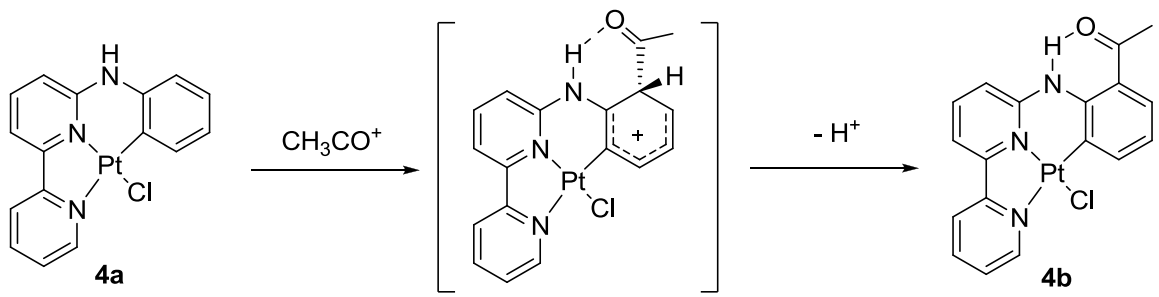
**Figure 10**. Comparison of **6b**'s (top) and **23a**'s (bottom) $^{1}$H NMR spectra.



## 5.3 Proposed Mechanisms

The information gathered in this study shed light on the mechanism of the regioselective acylation of cyclometalated platinum complexes. When the acylation of **4a** was first discovered, the simplest mechanistic explanation was a classical Friedel-Crafts acylation, shown in **Scheme 16**. Friedel-Crafts acylation is acid-catalyzed, which is consistent with the observation that the acylation is dependent on the presence of hydrogen chloride (Section 1.4). The regioselectivity of the reaction could be explained in the case of **4a** by hydrogen bonding of the acyl group with the amino hydrogen in the intermediate shown in **Scheme 16**.

**Scheme 16**. Proposed mechanism: Friedel-Crafts acylation.

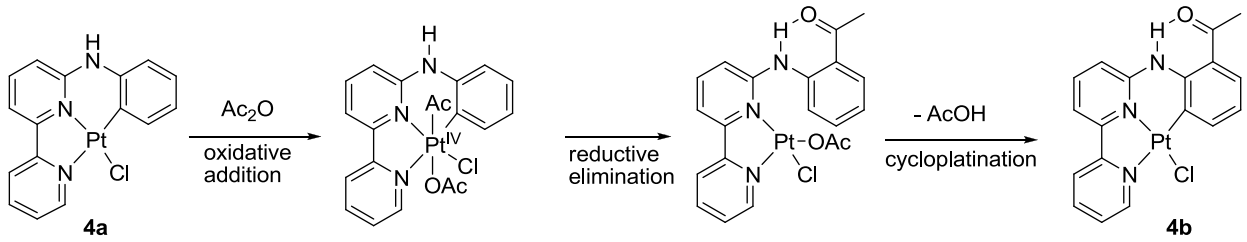



When considering the results of the acylations of **5a**, **6a**, and **7a**, hydrogen bonding likely is not necessary for directing the acylation (although it may serve to stabilize the acylated products with amino linker groups). Additionally, the proposed Friedel-Crafts mechanism involves acylation at the unmetalated *ortho*- carbon of the phenyl ring, which is unlikely considering the structures of acylated complexes **19b** and **17b** which were acylated at the metalated *ortho*-carbon.

The data reported in Section 5.1 suggests that acylation occurs at the metalated carbon of the cycloplatinated complexes, so the mechanism of the reaction must account for this. One possibility is oxidative addition of the acyl group to the platinum center, resulting in an

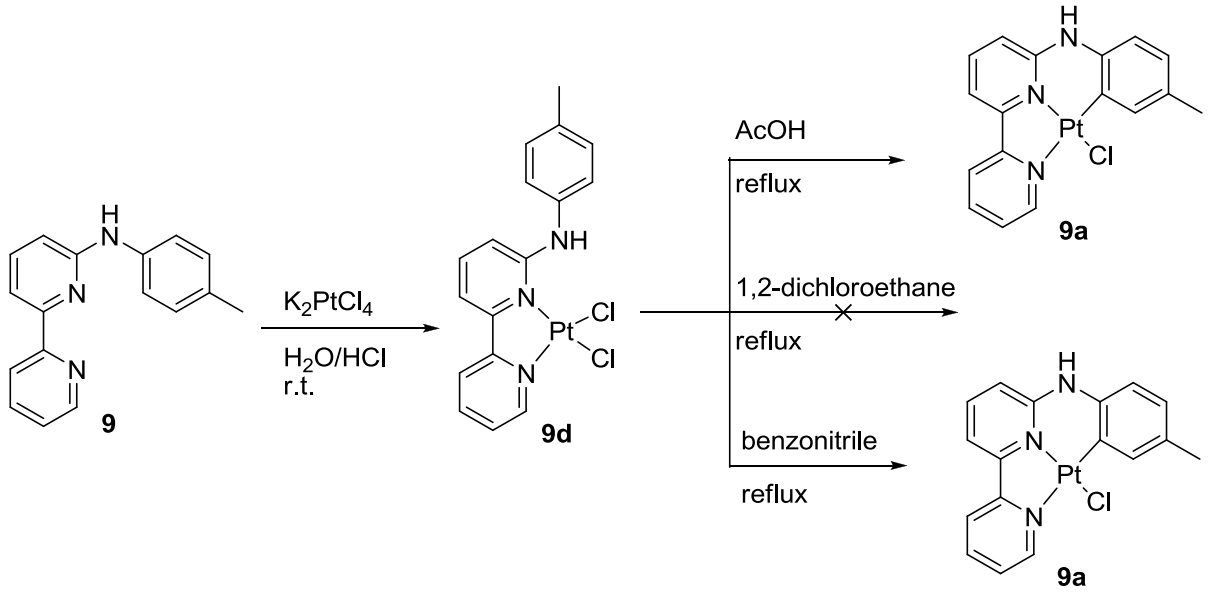
octahedral Pt(IV) species, followed by reductive elimination, acylating the phenyl ring at the metalated carbon, and then recycloplatination (**Scheme 17**). It can be noted that oxidative addition mechanisms were proposed for the regioselective acylation[43] and acetoxylation[44] of palladacycles, though no examples are reported for platinacycles. Like palladium, the +4 oxidation state of platinum is available, so formation of a Pt(IV) intermediate species is plausible.

**Scheme 17**. Proposed mechanism: oxidative addition-reductive elimination-re-cycloplatination.



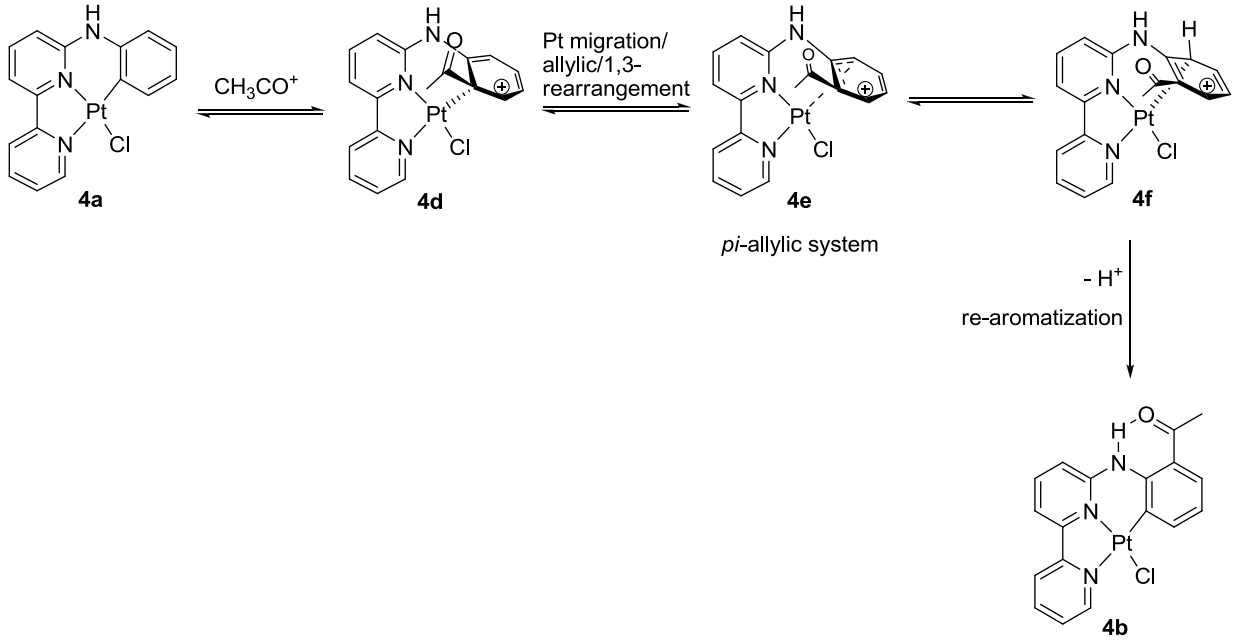

It was observed that compound **4a** was acylated to form **4b** when 1,2-dichloroethane or benzonitrile was used as the solvent, but it is unclear whether cyclometalation can take place in these solvents. To test this, compound **9d** was synthesized by stirring ligand **9** in dilute hydrochloric acid at room temperature. The dichloride complex **9d** was then refluxed in acetic acid, 1,2-dichloroethane, and benzonitrile to see if cyclometalation could occur (**Scheme 18**). As expected, cyclometalated product **9a** was detected by TLC analysis of the reaction mixture in which acetic acid was the solvent. Cyclometalation was also observed after refluxing **9c** in benzonitrile. However, no sign of cyclometalation was observed when 1,2-dichloroethane was used as the solvent. This result suggests that the mechanism of the acylation of cyclometalated platinum complexes, at least in 1,2-dichloroethane, does not involve re-cyclometalation.

**Scheme 18**. Synthesis of **9d** and its cyclometalation attempts.



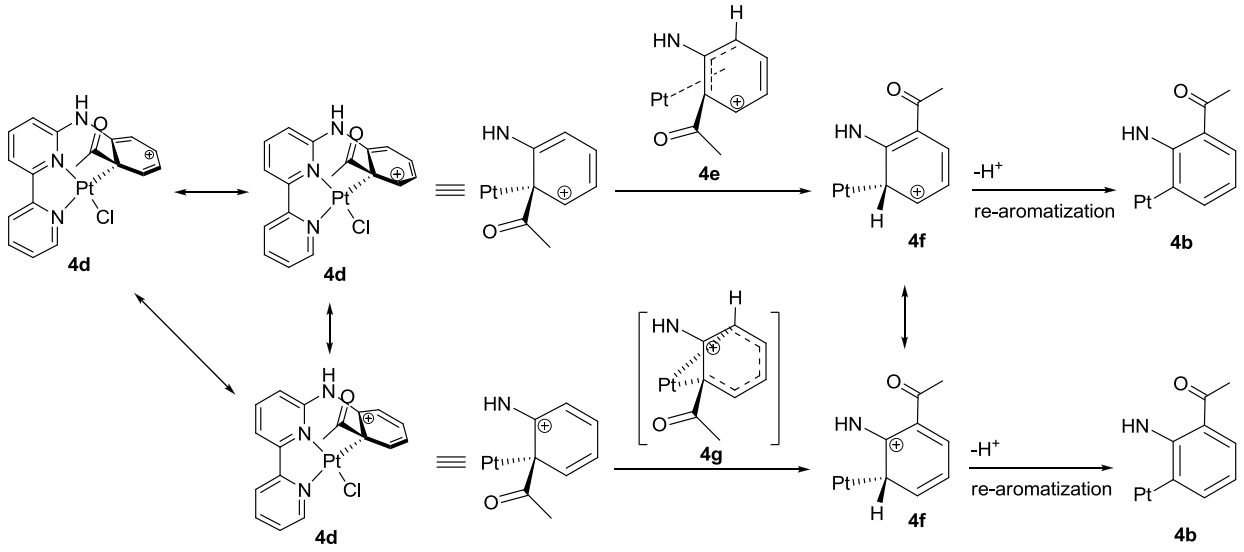

Another mechanism to consider is electrophilic attack at the metalated carbon, followed by allylic/1,3-rearrangement (platinum migration), then re-aromatization (**Scheme 19**). In this proposed mechanism, complex **4a** undergoes electrophilic attack by the acyl cation at the metalated carbon. The positive charge in the resulting intermediate **4d** is spread across the π-system of the benzene ring through resonance. The $sp^2$ metalated carbon would become $sp^3$ hybridized. However, platinum may bond to the benzene ring through the π-system, so the platinum would no longer be bound to a single carbon at this point, but rather to an allyl ligand (**Scheme 19**, **4e**). The benzene ring is perpendicular to the plane of the complex in these intermediates (**4d,e,f**). Following allylic/1,3- rearrangement, the newly metalated carbon is deprotonated and the aromaticity of the benzene ring is restored, affording the planar complex **4b**.

**Scheme 19**. Proposed mechanism: electrophilic attack-platinum migration-re-aromatization.




The platinum migration could also occur through another pathway that can be described as a 1,5-sigmatropic rearrangement (**Scheme 20**), depending on the location of the carbocation. This rearrangement would occur when the carbocation is at the carbon bonded to the amino linker. Structure **4g** could be a transition state with the platinum atom partially bonded to both carbons *ortho* to the amino linker group, rather than a π bond to the 5-centered, 6e-π system. A bond of the platinum to a 6e-π system is unlikely according to the 18-electron rule.

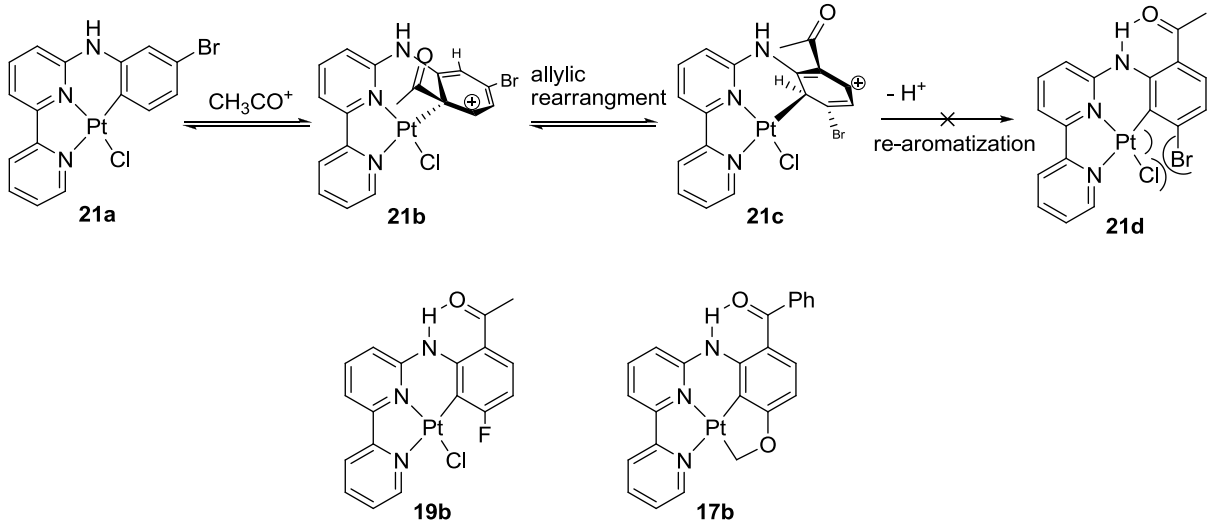
**Scheme 20**. Resonance structures of **4d** and possible platinum migrations forming **4f** (bipyridyl moiety and chloride ligand are omitted for clarity).




The electrophilic attack-platinum migration-re-aromatization mechanism is consistent with the data reported in this work. In this mechanism, acylation occurs at the metalated carbon, hydrogen bonding of the acyl group is not required, and re-cyclometalation does not take place. The inability of the acylation to occur in complexes with bulky groups *meta* to the linker group can also be explained in the context of this mechanism. For example, in the acylation of **21a**, most of the starting material was recovered, unreacted. It is possible that after electrophilic attack of the acyl group at the metalated carbon (**Scheme 21**, **21b**), platinum migration takes place, forming **21c**. The bromo group and the chloride ligand observe a steric interaction when the phenyl ring rotates further in the re-aromatization step, as shown in the structure of **21d**. The bromo group and the platinum atom are in **21d** are *ortho* to one another, which is another source of steric strain. This acts as a barrier to the further rotation of the ring for re-aromatization. Therefore, the acyl group is lost in the reverse reaction and the starting material **21a** remains. In

the case of **19a**, the fluoro group is small enough that its steric interaction with the chloride ligand is not enough to block the phenyl ring rotation. The bond length of $C_{ar}$–F bonds (1.363 Å) is comparable to the bond length of $C_{ar}$ –H bonds (1.083 Å), and considerably shorter than $C_{ar}$ – Cl (1.739 Å) and $C_{ar}$ –Br bonds (1.899 Å)[45]. Complex **17a** was able to avoid the deleterious steric effects associated with the chloride ligand by displacing it and forming bis-cyclometalated complex **17b**.

**Scheme 21**. Steric effects in the acylation of **21a**, **19a**, and **17a**.




## 5.4 Experimental Procedures

*General:*

All anhydrous solvents used were purchased from Sigma-Aldrich with Sure Seal. All catalysts and reagents were purchased from Sigma-Aldrich, with the exception of $K_2PtCl_4$ which was purchased from Strem Chemicals. Commercial reagent grade solvents and chemicals were used as obtained unless otherwise noted. Preparative chromatography was performed on silica gel 60 (0.063-0.200 mm) purchased from EMD chemicals. Thin layer chromatography was performed

with silica gel 60 $F_{254}$ plates, purchased from EMD chemicals. $^{1}H$ and $^{13}C$ NMR spectra were recorded on a Bruker 400 MHz spectrometer at 298K. Chemical shifts were reported relative to TMS (0.0 ppm for 1H), dichloromethane-d2 (53.8 ppm for $^{13}C$), chloroform-d (77.0 ppm for 13C), DMSO-d6 (39.5 ppm for $^{13}C$) and coupling constants are in Hertz. Elemental analyses were performed in Atlantic Microlab, Norcross, GA.

*Preparation of complex **19c***

To a 50 mL three-necked round-bottom flask under argon were added complex **19a** (100 mg, 0.19 mmol), phenylacetylene (61 µL, 0.66 mmol), copper iodide (2.8 mg, 0.015 mmol), triethylamine (1.7 mL, 12.1 mmol), and anhydrous dichloromethane (15 mL). The reaction mixture was stirred at room temperature for 1 h, then quenched with water (15 mL) and extracted with dichloromethane. The organic phase was washed with brine and dried over $MgSO_4$. After filtration, the solvent was removed and the crude product was purified by column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 3/1): red solid, 80 mg, 71%. $^{1}H$ NMR (400 MHz, $CDCl_3$): δ 14.01 (s, 1H), 10.10 (d, J = 5.5 Hz, 1H), 8.71 (d, J = 8.2 Hz, 1H), 8.39 (td, J = 7.9, 1.5 Hz, 1H), 8.31-8.20 (m, 2H), 8.07 (dd, J = 8.7, 5.7 Hz, 1H), 7.95 (t, J = 6.6 Hz, 1H), 7.56 (d, J = 8.3, 1H), 7.40-7.26 (m, 4H), 7.16 (t, J = 7.3 Hz, 1H), 6.78 (t, J = 8.7 Hz, 1H), 2.77 (s, 3H).

*Preparation of ligand **23***

To a 50 mL, dry, argon flushed, three-necked round-bottom flask were charged 6-bromo-2,2'-bipyridine (235 mg, 1.0 mmol), 4-hydroxyacetophenone (272 mg, 2 mmol), $NaO^tBu$ (115 mg, 1.2 mmol), $Pd(dba)_2$ (23.0 mg, 0.04 mmol), DPPF (22.2 mg, 0.04 mmol), and toluene (12 mL). The mixture was stirred and heated at reflux for 20 h. After cooling the reaction mixture to

room temperature, it was quenched with 10 mL of water. The mixture was extracted with ethyl acetate, and the organic phase was washed with brine and dried over $MgSO_4$. After filtration, the organic solvents were removed by rotary evaporator and the crude product was purified by column chromatography on silica gel with hexane and ethyl acetate (v/v 3/1): off-white solid, 33 mg, 11%. $^1$H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 4.7 Hz, 1H), 8.22 (d, J = 7.6 Hz, 1H), 8.09-8.03 (m, 3H), 7.87 (t, J = 7.9 Hz, 1H), 7.72 (td, J = 7.6, 1.8 Hz, 1H), 7.32-7.26 (m, 3H), 7.00 (d, J = 8.0 Hz, 1H), 2.64 (s, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) δ 197.1, 161.9, 158.5, 155.1, 154.4, 149.1, 140.7, 137.0, 133.2, 130.2 (2C), 123.9, 121.1, 120.5 (2C), 116.4, 112.2, 26.6.

*Complexation of ligand **23** forming complex **23a***

To a 25 mL three-necked round-bottom flask with condenser and drying tube were added ligand **23** (29 mg, 0.10 mmol), $K_2PtCl_4$ (42 mg, 0.10 mmol), and acetic acid (3 mL). The mixture was heated at reflux for 8 h. After the mixture was cooled to room temperature, the precipitate was collected by suction filtration, washed with water, methanol, hexane, and ethyl acetate: yellow solid, 27 mg, 51%. $^1$H NMR (400 MHz, DMSO) δ 9.62 (d, J = 5.6 Hz, 1H), 9.12 (s, $^3J_{Pt-H}$ = 53.6 Hz, 1H), 8.74 (d, J = 8.2 Hz, 1H), 8.59-8.46 (m, 2H), 8.41 (td, J = 7.8, 1.6 Hz, 1H), 7.96 (t, J = 6.8 Hz, 1H), 7.78-7.65 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 2.55 (s, 3H).

*Preparation of complex **9d***

To a 25 mL three-necked round-bottom flask open to atmosphere were added $K_2PtCl_4$ (79 mg, 0.19 mmol) and water (3 mL). Ligand **9** was dissolved in hydrochloric acid (2M, 1 mL) and transferred to the reaction flask. The homogenous reaction mixture was stirred at room temperature for 24 hours. The precipitate was collected by suction filtration and washed with water, hexane, and methanol: bright yellow solid, 75 mg, 75%. $^1$H NMR (400 MHz, DMSO) δ

9.22 (s, 1H), 8.71 (d, J = 4.4 Hz, 1H), 8.36 (d, J = 8.1 Hz, 1H), 8.08 (t, J= 7.4 Hz, 1H), 7.80-7.71 (m, 2H), 7.62 (d, J= 8.4 Hz, 2H), 7.54 (t, J = 6.2 Hz, 1H), 7.16 (d, J = 8.3 Hz, 1H), 6.92 (d, J= 7.9 Hz, 1H), 2.29 (s, 3H).

*Heating of **9d** in various solvents to test for cyclometalation*

Complex **9d** (10 mg, 0.019 mmol) was added to a 25 mL three-necked round-bottom flask with a drying tube open to atmosphere with 4 mL of solvent then heated (1,2-dichloroethane, reflux; acetic acid, reflux; benzonitrile, 170$^{o}$C). The reaction was monitored on TLC to test for formation of **9a**. Complex **9a** was detected when acetic acid and benzonitrile were used as the solvents, but not1,2-dichloroethane.

# CHAPTER 6: CONCLUSIONS

This research has demonstrated the scope and limitations of the regioselective acylation of cyclometalated platinum complexes. The acylation reaction proceeds in a number of solvents, such as acetic acid, 1,2-dichloroethane, benzonitrile, and acetonitrile. Through careful ligand design and synthesis, a variety of substrates with different linker atoms or groups, as well as substituents on different positions of the phenyl ring, were tested in the acylation reaction. It was determined that the acylation proceeds in complexes with amino, oxygen, sulfur, and methylene linker groups or atoms, but not with a carbonyl linker group. The acylation reaction proceeds with a range of electron-donating to electron-withdrawing substituents *para*- to the linker atom or group. The acylation was blocked when the substituents were located *meta*- to the linker group, though less sterically-demanding substituents like fluorine did not impede the acylation, as this complex was acylated cleanly. The use of alternate electrophiles in this reaction was demonstrated.

Some mechanistic aspects of the regioselective acylation of cycloplatinated complexes reported in this research were clarified. It was demonstrated that the site of acylation is the metalated carbon of the phenyl ring. The role of hydrogen bonding in the reaction mechanism was deemed non-essential by acylation of complexes with linker groups incapable of hydrogen bonding. Based on the mechanistic studies conducted, the most likely mechanism of the acylation reaction involves electrophilic attack at the metalated carbon, platinum migration, and re-aromatization.

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# APPENDIX A

ORGANOMETALLICS

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# Reaction of *N*-Isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine with $K_2PtCl_4$: Selective C−H Bond Activation, C−N Bond Cleavage, and Selective Acylation

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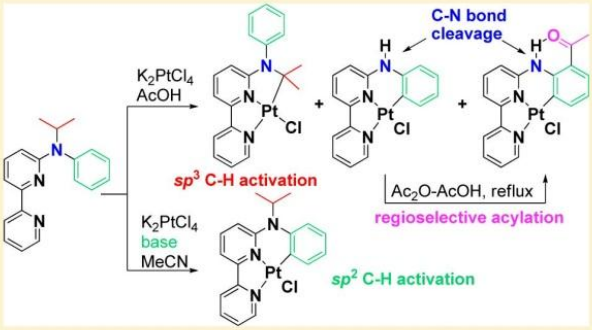
Supporting Information

**ABSTRACT:** The selective C−H bond activation of *N*-isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine promoted by Pt(II) was complicated by the low selectivity of $sp^2$ C−H bond activation in acetonitrile and low yield of $sp^3$ C−H activation in acetic acid. The use of a base was found to effectively suppress the competing $sp^3$ C−H bond activation in acetonitrile, improving the selectivity of $sp^2$ C−H bond activation from 70% to 99%. In the reaction in acetic acid, the low yield was due to the competing C−N bond cleavage. The use of a base reduced the C−N bond cleavage, but not completely. The reaction of *N*-*tert*-butyl-*N*-phenyl-2,2′-bipyridin-6-amine with $K_2PtCl_4$ in acetic acid produced the cyclometalated complex with complete C−N bond cleavage and its acylated derivative. These results indicated that the C−N bond cleavage might proceed via heterolytic C−N bond dissociation. The acylation following the C−N cleavage in the reaction in acetic acid is regioselective. Further experiments showed that the reaction of *N*-phenyl-2,2′-bipyridin-6-amine with $K_2PtCl_4$ in acetic acid produced the cyclometalated complex, while the reaction in a mixture of acetic anhydride and acetic acid produced the acylated cyclometalated complex. An X-ray crystal structure study revealed strong intramolecular H bonding in the acylated complexes. The regioselectivity was explained in terms of H bonding and the electron distribution predicted by the DFT calculations.




## INTRODUCTION

Cyclometalation is an important process in organometallic chemistry, which involves chelation-assisted carbon−metal bond formation.[1] Cyclometalation via the cleavage of a C−H bond to form the metallacycle is the intramolecular version of organometallic C−H bond activation.[2] Since the chelation can significantly improve the thermal stability of organometallic compounds, many of the cyclometalated complexes are very stable and can be isolated and fully characterized. This makes them extremely important in studying fundamental mechanistic issues associated with C−H bond activation.[1,2] Some key active intermediates involved in or proposed for the C−H bond activation may be stabilized by the chelation so that they can be fully studied. For example, an agostic interaction is conceived to be an important process in intermolecular C−H bond activation but could not be fully characterized. With chelation stabilization, complexes displaying an agostic interaction have been isolated and fully characterized.[3,4] On the other hand, cyclometalated complexes have found applications in a wide range of areas, from catalysis[5,6] to advanced materials.[7]

One of the fundamental issues in chemical transformations is the selectivity. A selective reaction allows the formation of one compound out of two or more possibilities. For cyclopalladation and cycloplatination, it is generally observed that the activation of an $sp^2$ C−H bond is preferred over the activation of an $sp^3$ C−H bond; however, there have been many reports on the competing $sp^2/sp^3$ C−H activation in cyclopalladation.[8] Remarkably, in some cases either of the two C−H activations can be achieved through a switch of the selectivity. One of the earliest examples of the selectivity switch was reported by Yoshida et al.,[8a] who observed that the cyclopalladation of *N*-thiobenzoylpyrrolidine with $PdCl_2$ in methanol occurred at the phenyl ring while a similar reaction in hexamethylphosphoramide (HMPA) resulted in metalation at the $CH_2$ group next to the nitrogen of the pyrrolidine ring. The preference in the competing $sp^2/sp^3$ C−H bond activation can also be influenced by other factors such as the ring size of the metallacycle,[8b,f,i] metal precursors,[8d,f−h] and the reaction temperature.[8b,f] In contrast, reports on the competing $sp^2/sp^3$ C−H bond activation via cycloplatination are very rare.[3] In the cycloplatination of 6-(1-methylbenzyl)-2,2′-bipyridine and 6-

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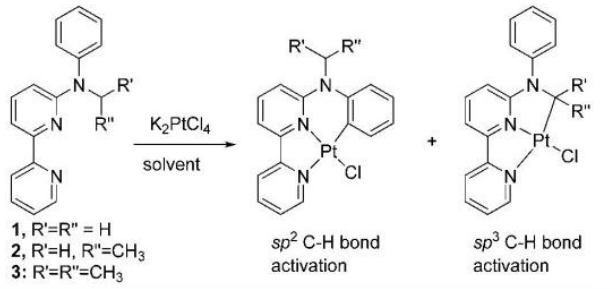
(1,1-dimethylbenzyl)-2,2′-bipyridine, metalation was reported to occur at the phenyl ring rather than the methyl groups,[9a,b] although forced $sp^3$ C−H bond activation in cycloplatination of 6-alkyl-2,2′-bipyridine is known.[9c,d] Recently, we have discovered a solvent-controlled switch of selectivity between intramolecular $sp^2$ and $sp^3$ C−H bond activation mediated by platinum,[10] in which the reaction of *N*-alkyl-*N*-phenyl-2,2′-bipyridin-6-amine (alkyl = Me (**1**), Et (**2**), *i*-Pr (**3**)) with $K_2PtCl_4$ in acetic acid produced predominantly $sp^3$ C−H activation products, while interestingly, the reaction in acetonitrile gave selectively $sp^2$ C−H activation products (Scheme 1). Further experiments suggested that the switch of

**Scheme 1. Reaction of *N*-Alkyl-*N*-phenyl-2,2′-bipyridin-6-amine with $K_2PtCl_4$**




selectivity could be attributed to kinetic or thermodynamic control under different conditions. The degree of the selectivity control is quite remarkable except for the reaction of *N*-isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine (**3**), which produced a 70:30 mixture of both $sp^2$ and $sp^3$ activation products **4** and **5** in acetonitrile (Table 1). In addition, the reaction in acetic acid gave the product **5** resulted from exclusive $sp^3$ C−H bond activation, but only in 38% yield. In this paper, we report our effort to improve the control of the selectivity of this reaction and to gain an insight into the competing side reactions associated with the C−N bond cleavage.

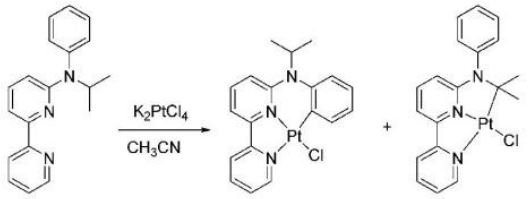
## ■ RESULTS AND DISCUSSION

There are two issues with the C−H bond activation of *N*-isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine (**3**) by platinum: namely the low selectivity of **4** formation in the reaction in acetonitrile and the low yield of **5** in the reaction in acetic acid. This is in sharp contrast with the reaction of *N*-methyl-*N*-phenyl-2,2′-bipyridin-6-amine (**1**), which exhibited both high selectivity and high yield of $sp^2$ C−H bond activation in acetonitrile and $sp^3$ C−H bond activation in acetic acid.[10]

**Selectivity of $sp^2$ C−H Bond Activation.** The cause of the lower selectivity may be complicated; however, two factors may be significant. First of all, the intrinsic reactivity of different types of $sp^3$ C−H bonds is different. Generally, the bond strength decreases in the order methane, primary, secondary, and tertiary C−H bonds,[11] which indicates that the secondary C−H bond in *N*-isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine (**3**) may be more reactive than the methyl C−H bond in *N*-methyl-*N*-phenyl-2,2′-bipyridin-6-amine. Therefore, the $sp^3$ C−H activation becomes relatively more competitive under kinetically controlled conditions of the reaction of **3** in acetonitrile, resulting in lower selectivity of **4**. It should be mentioned that the relative reactivity of primary, secondary, and tertiary C−H bonds depends on the nature of the reactions and other factors and a reverse order is known in cyclometalation chemistry.[1a]

On the other hand, since the formation of **4** was considered to be kinetically controlled,[10] the isomerization of **4** to **5** is at least one major contributor to the poor selectivity. The isomerization likely proceeds via the cleavage of the $sp^2$ C−Pt bond of **4** by the HCl generated from the cyclometalation reaction; therefore, the use of a base may terminate this pathway by neutralizing the HCl. We may not be able to alter the intrinsic reactivity of the C−H bond but certainly can use an HCl scavenger in the reaction. The choice of the HCl scavenger could be critical; a strong base may coordinate strongly to the platinum and inhibit the reaction, while a weak base may not bind to the proton strongly enough to block the protonolysis of the $sp^2$ C−Pt bond. A strong but bulky base may be the best choice. Nonetheless, a few different bases were examined in the reaction of **3** with $K_2PtCl_4$ in acetonitrile, and the results are summarized in Table 1.

**Table 1. Effect of Bases on the Selectivity of Reaction of 3 with $K_2PtCl_4$ in Acetonitrile[a]**



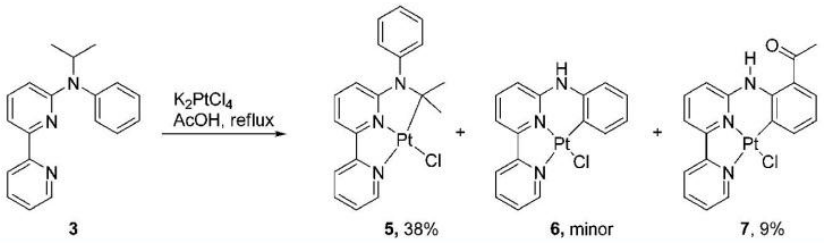

3 4 5

| entry | base | amt, equiv | time (days) | yield (%)[b] | selectivity (4:5) |
|---|---|---|---|---|---|
| 1 | none | | 3 | 36[c] | 70:30 |
| 2 | sodium acetate | 1 | 10 | 64 | 99:1 |
| 3 | triethylamine | 1 | 5 | 52 | 98:2 |
| 4 | triethylamine | 1 | 10 | 91 | 94:6 |
| 5 | DABCO[e] | 1 | 10 | 58 | 98:2 |
| 6 | TMP[d] | 1 | 2 | 41 | 97:3 |
| 7 | TMP | 2 | 3 | 34 | 90:10 |
| 8 | $Na_2CO_3$ | 1 | 5 | trace | |
| 9 | NaOH | 1 | 5 | trace | |
| 10 | **3** | 1 | 1 | 83 | 99:1 |

[a]Reactions were run with equimolar amounts of the ligand **3** and $K_2PtCl_4$ in acetonitrile at reflux. [b]Isolated yield of the mixture of **4** and **5** by flash column chromatography. [c]Isolated yield of pure **4** by recrystallization.[10] [d]2,2′-6,6′-Tetramethylpiperidine. [e]1,4-Diazabicyclo-[2.2.2]octane.

It can be seen from Table 1 that the effect of the bases is quite remarkable. Excellent to perfect selectivity was achieved with the use of a proper base. When sodium acetate was used, the reaction appeared to be much slower in comparison with the reaction in the absence of a base. A reasonable conversion could be attained after 10 days of reaction at reflux; however, a nearly perfect control of selective $sp^2$ C−H bond activation (99%) was achieved. The slower reaction rate may be attributed to the acetate ion, which may bind to the platinum and deactivate the platinum complex toward C−H bond activation. When triethylamine was used, again, the reaction was slow but the selectivity was high. It was also found that the selectivity decreased slightly as the conversion increased with prolonged heating (entry 4). 1,4-Diazabicyclo[2.2.2]octane (DABCO) displayed a similar effect (entry 5). For comparison, a sterically hindered secondary amine, 2,2,6,6-tetramethylpiperidine (TMP), was tested. When 1 equiv of TMP was used, after 2

**Scheme 2. Reaction of 3 with $K_2PtCl_4$ in Acetic Acid**[10]



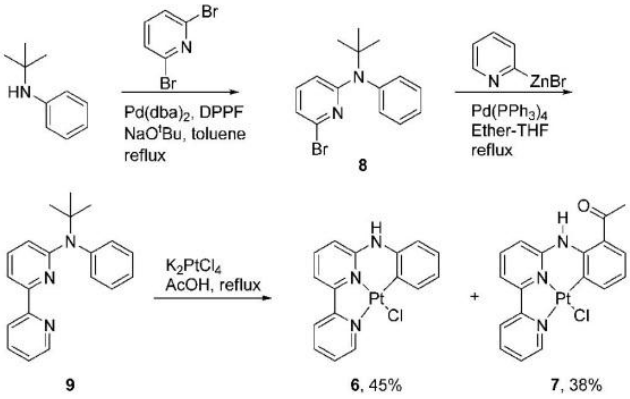

days, the product **4** was isolated in moderate yield (41%) with high selectivity (97%). When 2 equiv of TMP was used, the reaction was much slower. After 3 days of reaction, a mixture of **4** and **5** was isolated in 34% yield with a ratio of 90:10. It appears that the tertiary amines are a better choice, perhaps because of the stronger basicity and greater bulkiness of the tertiary amine. It should be pointed out that when the amount of other bases used in the reaction was increased, the reaction became very sluggish. When sodium carbonate and sodium hydroxide were used, only a trace of cyclometalation product(s) could be detected by the TLC analysis and the reaction did not proceed further to produce more of the product(s) after the first day of the reaction. The formation of black precipitates was observed, likely due to the reduction of platinum(II) to platinum(0). Finally, the use of another 1 equiv of the ligand **3** resulted in nearly exclusive formation of **4** without a low reaction rate (entry 10).

**C–N Bond Cleavage.** The second issue with the C–H bond activation of *N*-isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine (**3**) by platinum is the low yield of **5**, although there was no presence of **4** in the products of the reaction.[10] A careful analysis of the reaction mixture by TLC showed that there were two other compounds accompanying the major desired product **5**. The two byproducts are more polar and moved much more slowly than **5** on TLC. The proton NMR spectra of the two compounds did not show any signals that could be assigned to the isopropyl group, suggesting that the C–N bond was cleaved. In particular, one of the two byproducts, which is less polar and moved more quickly on TLC, showed a singlet proton signal appearing at significantly low field (DMSO-$d_6$, 13.70 ppm) and a singlet at 2.76 ppm, which could be assigned to a methyl group according to the integration. We proposed that the two byproducts were the cyclometalated compound **6** with the C–N bond cleavage and its acylated derivatives **7**, as shown in Scheme 2. Complex **6** was formed in a very small amount and could not be recovered from column chromatographic separation.

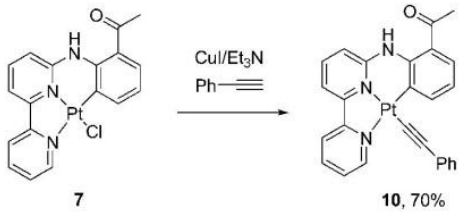
To gain further information on the C–N bond cleavage, the ligand *N*-*tert*-butyl-*N*-phenyl-2,2′-bipyridin-6-amine (**9**) with a *tert*-butyl group was prepared by consecutive palladium-catalyzed C–N[12] and C–C[7b,13] bond cross-coupling reactions, as shown in Scheme 3. The cross coupling of *N*-*tert*-butylaniline with an excess amount of 2,6-dibromopyridine produced intermediate **8**. Palladium-catalyzed Negishi coupling of **8** with 2-pyridylzinc bromide produced the ligand **9**. The reaction of **9** with $K_2PtCl_4$ in acetic acid resulted in exclusive C–N bond cleavage, producing **6** and **7** in 45% and 38% isolated yields, respectively (Scheme 3).

Compounds **6** and **7** have very poor solubility. An attempt to grow suitable crystals of compound **7** for an X-ray structure determination was unsuccessful. Therefore, compound **7** was converted into its phenylacetylide derivative **10** by treating **7** with phenylacetylene in the presence of CuI and triethylamine[14] (Scheme 4). A crystal suitable for X-ray crystallographic analysis was obtained by diffusing hexanes into a solution of **10** in dichloromethane.

**Scheme 3. Preparation of 9 and Its Reaction with $K_2PtCl_4$ in Acetic Acid**




**Scheme 4. Reaction of 7 with Phenylacetylene**




The crystal data are summarized in Table S1 (Supporting Information), and the molecular structure is depicted in Figure 1. The results confirmed the proposed structure of **10**, which also substantiates the structure of **7** as well as the C–N bond cleavage in the reaction of **3** and **9** with $K_2PtCl_4$ in acetic acid. The platinum complex adopts a square-planar geometry with a C(16)–Pt(1)–N(1) bite angle of 173.76°, being close to 180°, similar to those for cyclometalated platinum complexes with a 5–6-fused metallacycle reported previously.[7b,13,14b] The Pt–C(sp) bond is shorter than the Pt–C($sp^2$) bond, as expected. The Pt–N bond *trans* to the Pt–C($sp^2$) bond is slightly longer than the other Pt–N bond that is *trans* to the Pt–C(sp) bond, indicating a stronger structural *trans* effect[15] induced by an $sp^2$ carbon donor. The phenyl ring of the phenylacetylide is slightly twisted from the coordination plane with a dihedral angle of 24.7°. It is noteworthy that there exists a strong intramolecular hydrogen bond between the carbonyl oxygen and the hydrogen attached to the amino nitrogen. The hydrogen bond length is 1.81 Å, well within the range of a typical hydrogen bond of

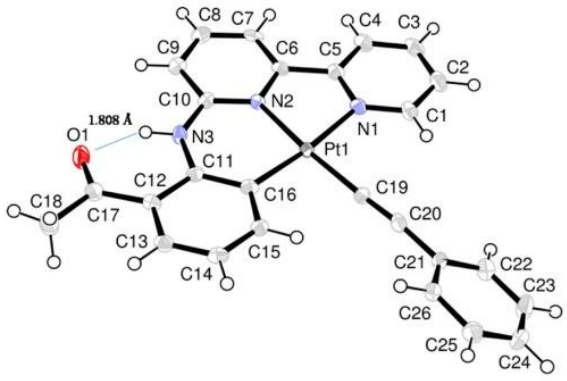


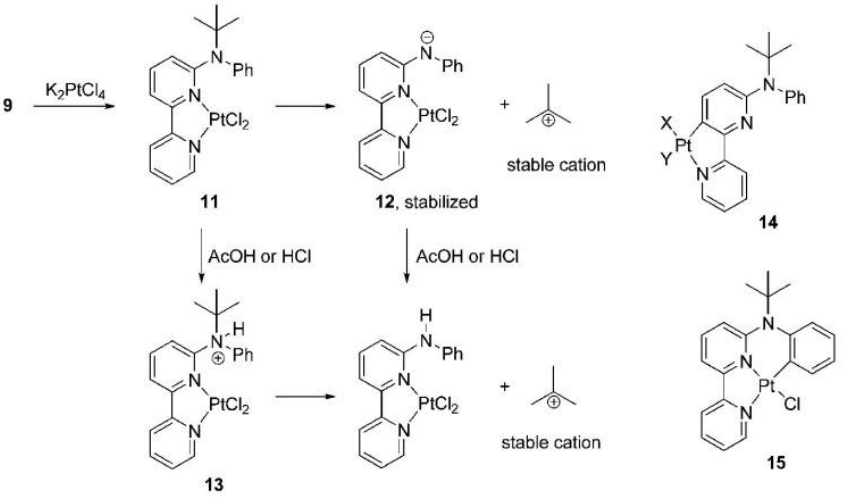

**Figure 1.** Perspective drawing of the molecular structure of **10**. Selected bond lengths (Å): Pt(1)−C(19) = 1.961(4), Pt(1)−C(16) = 2.006(4), Pt(1)−N(2) = 2.029(3), Pt(1)−N(1) = 2.084(3). Selected bond angles (deg): C(19)−Pt(1)−C(16) = 92.08(16), C(19)−Pt(1)−N(2) = 173.38(15), C(16)−Pt(1)−N(2) = 94.32(14), C(19)−Pt(1)−N(1) = 93.89(15), C(16)−Pt(1)−N(1) = 173.76(14), N(2)−Pt(1)−N(1) = 79.77(13).

1.6−2.0 Å. This intramolecular hydrogen bond may explain the unusual downfield proton signal observed in the NMR spectrum of **7**. This proton in **10** appeared at 13.89 ppm ($CDCl_3$). In contrast, the NH proton in **6** appeared at 10.69 ppm (DMSO-$d_6$).

The C−N cleavage may be attributed to the heterolytic dissociation of the alkyl C−N bond. In general, C−N bond dissociation is an unfavorable process, because the amide is a strong base and thus a poor leaving group. However, with stabilization of the anion and the cation, C−N bond dissociation is possible. In a classical Hoffman elimination, a quaternary ammonium salt has to be formed to create a reasonably good leaving group. Under strongly acidic conditions, elimination of tertiary alkyl groups from alkylanilines by hydrolysis was reported.[16] Therefore, the C−N cleavage in the reaction of **3** and **9** may benefit from several factors, including stabilization of the amide anion by the bipyridyl ring, the increasing stability of the isopropyl and *tert*-butyl carbocation, and the protonation of the amino nitrogen by the HCl generated from the C−H bond activation. The complete C−N bond cleavage in the reaction of **9** is consistent with the extraordinary stability of the *tert*-butyl cation. The fact that the reactions of **1** and **2** with $K_2PtCl_4$ in acetic acid were not accompanied by C−N bond cleavage is also supportive of a heterolytic cleavage of the C−N bond in the reactions of **3** and **9** with $K_2PtCl_4$, because the methyl and ethyl cations that would be formed from the heterolytic C−N dissociation of **1** and **2**, respectively, are too unstable to be formed. Another fact that the C−N cleavage occurred readily in acetic acid but not in acetonitrile provides additional support of the heterolytic C−N bond dissociation process, which is favored in protic solvents. It should be noted that transition-metal-assisted C−N bond cleavage through oxidative addition[17] and $\beta$-hydrogen abstraction[18] has been proposed. In the former case, the cleavage of the methyl C−N bond,[17d,e] allyllic C−N bonds,[17a] benzylic C−N bonds,[17b] and strained aziridines[17c] appears more common. A $\beta$-hydrogen is required in the latter case.[18]

The role of acid in the C−N bond cleavage has also been examined. When ligand **3** alone was heated at reflux in acetic acid, no C−N bond cleavage was observed. The cyclometalation produced HCl as the side product, thus, the HCl might facilitate the C−N bond dissociation. However, even with addition of a few drops of concentrated hydrochloric acid to the reaction of **3** in acetic acid, C−N bond cleavage was not observed. These results indicated that the presence of the platinum salt and/or the cyclometalation process may play a role in the C−N bond cleavage. Complexation of platinum to the bipyridyl motif would further stabilize the amide anion, thus promoting the C−N dissociation as shown in Scheme 5. Complexation of **9** with the platinum (**9** to **11**) not only improves the planar geometry of the bipyridine for better electron delocalization of the amide anion **12** but also makes the bipyridine more electron deficient, both of which would lead to the stabilization of **12**. The protonation of the amino nitrogen could also precede the C−N bond cleavage to form **13** and the heterolytic C−N bond cleavage of **13** would be facilitated by the electron delocalization of the developing lone pair at the nitrogen. C−N bond cleavage may also occur following the cycloplatination, producing the intermediates **14** and **15** rather than the coordination giving **11**. The C−N bond cleavage likely results from a cooperative action of stabilization of the amide anion or delocalization of the lone pair at the

**Scheme 5. Proposed Pathways for C−N Bond Cleavage in the Reaction of 9 with $K_2PtCl_4$ in Acetic Acid**



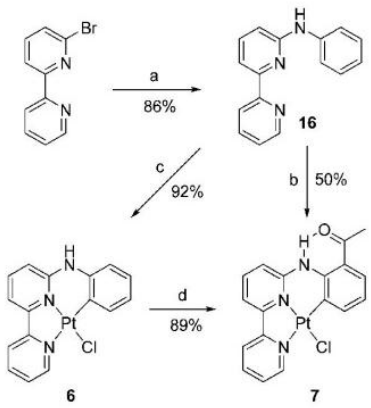
nitrogen, protonation of the amino nitrogen, and stabilization of the carbocation (Scheme 5).

To suppress this unwanted process in the formation of **5**, the use of a base to neutralize the HCl generated from the C−H bond activation may be necessary. Therefore, the use of NaOAc in the reaction of **3** with $K_2PtCl_4$ in acetic acid was examined. It turned out that the addition of 1 equiv of NaOAc slowed the reaction and suppressed the C−N bond cleavage to some extent, and an isolated yield of 50% for **5** was achieved. When an extra 1 equiv of NaOAc was used, the reaction was even slower, and the C−N bond cleavage still could not be suppressed completely. Apparently the presence of HCl was not a necessary factor in the C−N bond cleavage but might accelerate the process. Furthermore, the use of excess base led to the decomposition of the platinum complexes, as a black precipitate was observed. An attempt to use 2-ethoxyethanol as the solvent and sodium bicarbonate as the base for the reaction resulted in mainly decomposition of the complexes to black precipitates, which is likely the reduced platinum metal. Finally, **4** was completely isomerized to **5** when it was heated in acetic acid at reflux for 3 h, producing **5** in 72% isolated yield, but was accompanied by the decomposition to black platinum metal. The formation of **6** was also detected by TLC, and the ratio of **6** and **5** was determined to be 5:95 from the $^1$H NMR spectrum of the reaction mixture, which further indicates that C−N bond cleavage could be effected under the reaction conditions without the presence of HCl. The isomerization of **4** to **5** is an intramolecular process. It should be noted that the proton-assisted intermolecular ligand exchange in cyclopalladation and cycloplatination has been reported.[19]

**Regioselective Acylation.** It was also found that the presence of HCl is responsible for the formation of the acylation product **7** in the reaction of **3** with $K_2PtCl_4$ in acetic acid, because there was no acylation detected when NaOAc was used in the reaction to neutralize the HCl and the isomerization of **4** to **5** in acetic acid was accompanied by **6** but not **7**. We speculate that a classical Friedel−Crafts acylation might be the mechanism of this reaction, because hydrogen chloride generated in the cyclometalation can catalyze the Friedel−Crafts acylation by promoting the formation of the acyl cation from acetic acid. To gain more information on the acylation reaction, compound **16** was synthesized and subject to a series of reactions as shown in Scheme 6. The reaction of **16** with $K_2PtCl_4$ in acetic acid produced cyclometalation product **6** in 89% yield. As acetic anhydride is a good reagent for the Friedel−Crafts reaction, the cyclometalation of **16** with $K_2PtCl_4$ in pure acetic anhydride was attempted. However, no reaction proceeded, as the platinum salt remained undissolved in the solvent even after 24 h of refluxing. Surprisingly, when water was added to the reaction mixture, the reaction proceeded to form **7** cleanly, which suggests that acetic acid is needed for this reaction. Indeed, when a mixture of acetic acid and acetic anhydride was used as the solvent, the acylation product **7** was the only product detected by TLC and there was no **6** present. Furthermore, when **6** was heated in the mixed solvent of acetic acid and acetic anhydride, complete acylation of **6** was observed. The lack of **7** in the reaction of **16** in acetic acid may be attributed to the poor solubility of **6** in acetic acid. Once precipitated, **6** was essentially insoluble in acetic acid.

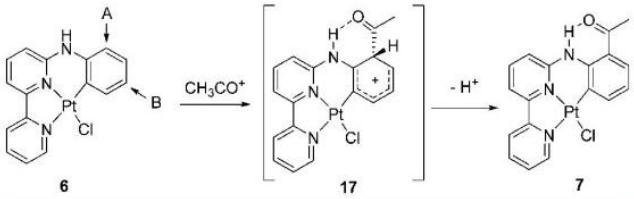
It is also noteworthy that the acylation is regioselective. There are two competitive sites on the phenyl ring of **6** that could be acylated, labeled A and B, as shown in Scheme 7. The electronic effects of the substituents are expected to be similar

**Scheme 6. Cycloplatination of 16 and Related Reactions**[a]




[a]Reagents and conditions: (a) aniline (2 equiv), $Pd(dba)_2$ (2%), DPPF (2%), NaO$^t$Bu (1.2 equiv), toluene, reflux; (b) $K_2PtCl_4$ (1 equiv), AcOH/$Ac_2O$ (1/1), reflux.; (c) $K_2PtCl_4$ (1 equiv), AcOH, reflux; (d) AcOH/$Ac_2O$ (1/1), reflux.

**Scheme 7. Proposed Mechanism for the Selective Acylation of 6**




for both positions, so why did the acylation occur exclusively at the position A that is *ortho* to the amino nitrogen? A possible explanation could be that the regioselective acylation is directed by the hydrogen bond between the incoming carbonyl oxygen and the proton attached to the nitrogen (Scheme 7). The hydrogen bond not only stabilizes the product **7** and proposed intermediate **17** but may also stabilize the transition state leading to the intermediate in the rate-determining step.

To gain information on the electron distribution of the compound **6**, particularly in the phenyl ring, DFT (density functional theory) calculations were performed on **6** and the optimized geometry is depicted in Figure 2. The optimized structure of **6** displays a nearly perfect square-planar geometry, similar to that of **7** revealed by X-ray crystallography (Figure 1). Notably, all atoms of the molecule are coplanar. The C−Pt bond is 2.015 Å. The Pt−N(1) bond (2.132 Å), which is *trans* to the carbon donor, is significantly longer than the Pt−N(2) bond (2.038 Å) *trans* to the chlorine, indicating a much stronger structural *trans* effect induced by a carbon donor.[15] The valence angle is 174.32°. At the optimized geometry, the atomic charges were calculated at the CCSD level of theory. Net charges on the carbons of the metalated phenyl ring are shown in Figure 2. There is net negative charge on both A and B carbons, indicating that both sites are activated toward the electrophilic aromatic substitution reaction; however, the negative charge on carbon A (−0.056) *ortho* to N3 is much larger than that on carbon B (−0.025) *para* to the N3, which further explains the preferential substitution at the A carbon. It should be mentioned that regioselective aromatic substitution of cyclometalated iridium(III) complexes has been reported,[20,21] but the carbon of the cyclometalated phenyl ring that was substituted is *para* to the iridium.

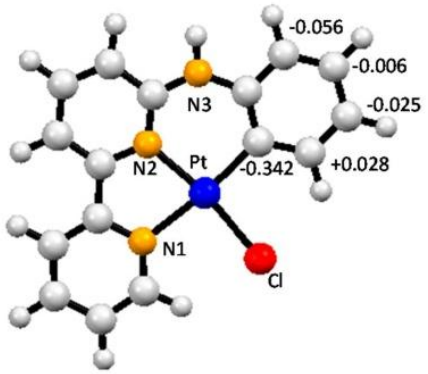



**Figure 2.** Optimized geometry of **6** in the ground state and net charges on the carbons of the phenyl ring. Selected bond lengths (Å): Pt−Cl = 2.345, Pt(1)−C = 2.015, Pt−N(1) = 2.132, Pt−N(2) = 2.038. Selected bond angles (deg): Cl−Pt−C = 94.04, Cl−Pt−N(2) = 170.76, C−Pt−N(2) = 95.2, Cl−Pt−N(1) = 91.64, C−Pt−N(1) = 174.32, N(2)−Pt(1)−N(1) = 79.12.

An alternative mechanism involving oxidative addition of acetic anhydride to the platinacycle **6** could also be proposed for the selective acylation, as shown in Scheme 8. Reductive elimination of the intermediate **18**, which is a Pt(IV) species, would be expected to proceed readily, leading to the acylated intermediate **19**. A subsequent cycloplatination of **19** would occur to produce **7**. Although not reported in the cycloplatinated complexes, regioselective acylation[22] and acetoxylation[8f] of palladacycles have been observed and an oxidative addition mechanism was proposed for the reactions.[22a] Since the selective acylation of **6** is an isolated special case, further investigations would be necessary to gain a deeper understanding of the reaction mechanism.

## ■ CONCLUSION

The use of a proper base was found to improve the selectivity of the $sp^2$ C−H bond activation of *N*-isopropyl-*N*-phenyl-2,2′-bipyridin-6-amine by platinum(II) in acetonitrile, from 70% up to 99%. However, the selective $sp^3$ C−H bond activation in acetic acid was complicated by the cleavage of the C(isopropyl)−N bond. The use of a base retarded the C−N bond cleavage but did not block it completely. The fact that the reaction of *N*-*tert*-butyl-*N*-phenyl-2,2′-bipyridin-6-amine with $K_2PtCl_4$ in acetic acid resulted in completely C−N bond cleavage suggested that the C−N bond cleavage proceeded via heterolytic C−N bond dissociation. Further investigations showed that the acylation of platinacycle **6** occurred regioselectively at the *N*-phenyl ring to form complex **7**, possibly via a Friedel−Crafts reaction facilitated by intramolecular H bonding, although other mechanisms are also possible.

## ■ EXPERIMENTAL SECTION

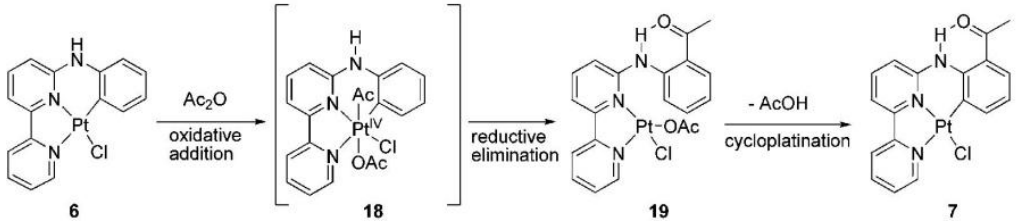
**Synthesis.** All reactions involving moisture- and/or oxygen-sensitive organometallic complexes were carried out under a nitrogen or argon atmosphere and anhydrous conditions. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium and benzophenone under nitrogen before use. All other anhydrous solvents were purchased from Aldrich Chemical Co. and were used as received. *N*-*tert*-Butylaniline[23] and 6-bromo-2,2′-bipyridine[24] were prepared according to the literature procedures. All other reagents were purchased from chemical companies and were used as received. NMR spectra were measured on a Bruker 400 or a Varian 500 spectrometer. Spectra were taken in $CDCl_3$ or $CD_2Cl_2$ using tetramethylsilane as the standard for $^1$H NMR chemical shifts and the solvent peak ($CDCl_3$, 77.0 ppm; $CD_2Cl_2$, 53.8 ppm) as the standard for $^{13}$C NMR chemical shifts. Coupling constants ($J$) are reported in Hz. Elemental analyses were performed at Atlantic Microlab, Inc., Norcross, GA.

**Reaction of 3 with $K_2PtCl_4$ in the Presence of a Base. General Procedure.** In a dry 50 mL three-necked flask were added **3** (36 mg, 0.125 mmol), $K_2PtCl_4$ (52 mg, 0.125 mmol), and acetonitrile (5 mL). A few crystals of tetrabutylammonium chloride were added to the mixture. The reaction mixture was refluxed for 10 days and then cooled to room temperature. The solvent was removed by rotary evaporation. The crude product was analyzed by $^1$H NMR spectroscopy, which showed that the ratio of **4** and **5** was 99:1. The crude product was purified by flash column chromatography on silica gel first with dichloromethane then with a mixture of dichloromethane and ethyl acetate (v/v, 50/1) to give **4**: orange solid, 38 mg, 64%. It should be mentioned that, under the column chromatographic conditions, there was no enrichment in either **4** or **5**.

**Preparation of 6-Bromo-*N*-*tert*-butyl-*N*-phenylpyridin-2-amine (8).** In a dry, nitrogen-flushed, 100 mL three-necked round-bottom flask were charged 2,6-dibromopyridine (2.49 g, 10.5 mmol), *N*-*tert*-butylaniline (1.05 g, 7 mmol), NaOtBu (0.81 g, 8.4 mmol), toluene (14 mL), bis(dibenzylideneacetone)palladium ($Pd(dba)_2$, 0.16 g, 0.28 mmol), and 1,1′-bis(diphenylphosphino)ferrocene (DPPF, 0.16 g, 0.28 mmol). The mixture was stirred and heated at reflux for 26 h. After it was cooled to room temperature, the mixture was diluted with 10 mL of ethyl acetate. The organic layer was washed with 20 mL of water and dried over $MgSO_4$. After filtration, the organic solvents were removed by rotary evaporation and the crude product was purified by column chromatography on silica gel with hexanes and dichloromethane (v/v 1/1) as the mobile phase: colorless crystalline solid, 0.66 g, 31%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.35 (t, $J$ = 7.2, 2 H), 7.27 (t, $J$ = 7.3, 1 H), 7.04 (d, $J$ = 7.1, 2 H), 6.86 (t, $J$ = 7.9, 1 H), 6.55 (d, $J$ = 7.4, 1 H), 5.59 (d, $J$ = 8.4, 1 H), 1.43 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 159.4, 144.0, 138.3, 137.7, 131.2 (2C), 129.7 (2C), 127.5, 114.4, 109.6, 57.9, 31.0 (3C). Anal. Calcd for $C_{15}H_{17}BrN_2$: C, 59.03; H, 5.61; N, 9.18. Found: C, 58.54; H, 5.71; N, 8.77.

**Preparation of *N*-*tert*-butyl-*N*-phenyl-2,2′-bipyridin-6-amine (9).** Under nitrogen flushing, a 100 mL three-necked round-bottom flask equipped with a condenser was dried with a heat gun. A solution of nBuLi in hexanes (1.6 M, 3 mL, 3.8 mmol) was added to the flask via a syringe, and the flask was cooled to −78 °C with a dry ice/acetone bath. Under nitrogen, in a 25 mL dried flask was prepared a solution of 2-bromopyridine (0.58 g, 4 mmol) in diethyl ether (5 mL).

**Scheme 8. Alternative Mechanism for the Selective Acylation of 6**



The solution was cooled with a dry ice/acetone bath. The cold solution was added dropwise into the solution of nBuLi with stirring. After 10 min, the reaction mixture was warmed to 0 °C, and then a solution of $ZnCl_2$ in diethyl ether (1 M, 4 mL) was added and the mixture was warmed to room temperature. To the in situ generated 2-pyridylzinc reagent were added 6-bromo-*N*-*tert*-butyl-*N*-phenylpyridin-2-amine (0.59 g, 2 mmol), $Pd(PPh_3)_4$ (119 mg, 0.1 mmol), and THF (15 mL). The mixture was stirred at reflux for 20 h and then cooled to room temperature. Ethylenediaminetetraacetic acid (EDTA, 2.3 g) was used to facilitate aqueous workup. The crude product was purified on a silica gel packed column with dichloromethane and ethyl acetate (v/v 30/1) as eluting solvents: colorless crystalline solid, 0.51 g, 84%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.58 (d, $J$ = 4.8, 1 H), 8.35 (d, $J$ = 8.0, 1 H), 7.75 (td, $J$ = 7.7, 1.8, 1 H), 7.61 (d, $J$ = 7.4, 1 H), 7.35 (t, $J$ = 7.3, 2 H), 7.27 (t, $J$ = 7.4, 1 H), 7.20 (t, $J$ = 8.5, 1 H), 7.19 (t, $J$ = 7.5, 1 H), 7.11 (d, $J$ = 8.3, 2 H), 5.80 (d, $J$ = 8.5, 1 H), 1.54 (s, 9H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 159.6, 157.4, 152.7, 148.9, 145.2, 136.8, 131.8 (2C), 129.6 (2C), 127.1, 123.0, 120.9, 109.2, 57.3, 29.6 (3C). Anal. Calcd for $C_{20}H_{21}N_3$: C, 79.17; H, 6.98; N, 13.85. Found: C, 78.72; H, 6.98; N, 13.51.

**Reaction of 9 with $K_2PtCl_4$ in Acetic Acid.** A mixture of **9** (153 mg, 0.5 mmol) and $K_2PtCl_4$ (207 mg, 0.5 mmol) in acetic acid (20 mL) was refluxed for 22 h. The solvent was removed by rotary evaporation, and the residue was dissolved in dichloromethane. The solution was run through a silica gel column with dichloromethane and ethyl acetate (v/v 15/1) as eluting solvents. Two major bands were resolved and collected. After removal of the solvents, the first band gave 0.1 g of **7** (38%). $^1$H NMR (400 MHz, DMSO): $\delta$ 13.70 (s, 1 H), 9.71 (d, $J$ = 5.6, 1 H), 8.91 (d, $J$ = 7.9, 1 H), 8.67 (d, $J$ = 8.2, 1 H), 8.33 (t, $J$ = 8.0, 1 H), 8.24 (t, $J$ = 7.5, 1 H), 8.17 (d, $J$ = 7.7, 1 H), 7.93 (d, $J$ = 7.8, 1 H), 7.88 (t, $J$ = 6.4, 1 H), 7.49 (t, $J$ = 8.3, 1 H), 6.93 (t, $J$ = 7.7, 1H), 2.73 (s, 3 H). Anal. Calcd for $C_{18}H_{14}ClN_3OPt$: C, 41.67; H, 2.72; N, 8.10. Found: C, 41.46; H, 2.78; N, 7.94. The second band produced 0.12 g of **6** (45%). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 10.69 (s, 1 H), 9.74 (d, $J$ = 5.5, 1 H), 8.64 (d, $J$ = 8.3, 1 H), 8.60 (d, $J$ = 7.7, 1 H), 8.32 (t, $J$ = 7.3, 1 H), 8.14 (t, $J$ = 7.4, 1 H), 8.05 (d, $J$ = 7.4, 1 H), 7.86 (t, $J$ = 6.9, 1 H), 7.49 (d, $J$ = 8.5, 1 H), 7.09 (t, $J$ = 12.4, 1 H), 6.78 (t, $J$ = 7.2, 1 H). $^{13}$C NMR (75 MHz, DMSO-$d_6$): $\delta$ 155.4, 152.5, 147.8, 144.7, 139.6, 139.2, 135.6, 134.9, 126.5, 124.5, 123.0, 120.3, 118.2, 115.2, 115.0, 113.6. Anal. Calcd for $C_{16}H_{12}ClN_3Pt$: C, 40.30; H, 2.54; N, 8.81. Found: C, 40.49; H, 2.52; N, 8.79.

**Preparation of Platinum Complex 10.** In a 25 mL dry, argon-flushed flask was charged complex **7** (40 mg, 0.08 mmol), phenylacetylene (25 mg, 0.24 mmol), CuI (1.2 mg, 0.006 mmol), $Et_3N$ (0.7 mL), and dichloromethane (20 mL). The mixture was stirred under argon at room temperature for 24 h. After removal of the solvents, the crude material was purified by flash chromatography on silica gel with dichloromethane and ethyl acetate (v/v 50/1) to give a bright orange solid: 32 mg, 70%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 13.89 (s, 1H), 10.01 (d, $J$ = 5.6, 1 H), 9.35 (dd, $J$ = 3.8, 1.5, $^3J_{Pt-H}$ = 41.3, 1 H), 8.03 (d, $J$ = 8.03, 1 H), 7.97 (t, $J$ = 7.4, 1 H), 7.87 (t, $J$ = 8.0, 1 H), 7.79 (d, $J$ = 7.8, 1 H), 7.56–7.42 (m, 3 H), 7.47 (t, $J$ = 6.4, 1 H), 7.29–7.21 (m, 3 H), 7.14 (t, $J$ = 7.5, 1 H), 6.90 (t, $J$ = 7.7, 1 H), 2.70 (s, 3 H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 204.4, 155.5, 153.1, 153.0, 151.3, 145.0, 137.2, 136.8, 135.1, 131.6 (2 C), 129.6, 129.0, 128.0 (2 C). 125.9, 125.2, 121.5, 120.4, 120.2, 118.5, 118.2, 113.6, 103.8, 100.7, 28.7. Anal. Calcd for $C_{26}H_{19}N_3OPt$: C, 53.42; H, 3.28; N, 7.19. Found: C, 53.13; H, 3.26; N, 7.24.

**Isomerization of 4 in Acetic Acid.** A mixture of **4** (92 mg, 0.18 mmol) in acetic acid (8 mL) was refluxed for 3 h. $^1$H NMR analysis of the reaction mixture showed that **4** was completely isomerized to **5** with the presence of a small amount of **6**. The ratio of **5** and **6** was determined to be 95:5. After removal of acetic acid by rotary evaporation, the residue was dissolved in dichloromethane (30 mL) and the solution was washed with water and brine, dried over $Na_2SO_4$, and filtered. The filtrate was concentrated, and the crude product was purified by flash column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 80/1) to give **5** as an orange solid: 66 mg, 72%.

**Preparation of *N*-Phenyl-2,2′-bipyridin-6-amine (16).** In a dry, argon-flushed, 50 mL three-necked round-bottom flask were charged 6-bromo-2,2′-bipyridine (0.94 g, 4 mmol), aniline (0.73 mL, 8 mmol), NaO$^t$Bu (0.46 g, 4.8 mmol), toluene (15 mL), $Pd(dba)_2$ (92 mg, 0.16 mmol), and DPPF (89 mg, 0.16 mmol). The mixture was stirred and heated at reflux for 19 h. After it was cooled to room temperature, the mixture was diluted with 10 mL of ethyl acetate and filtered through a disk of Celite. The filtrate was extracted with ethyl acetate, and the organic phase was washed with brine and dried over $MgSO_4$. After filtration, the organic solvents were removed and the crude product was purified by column chromatography on silica gel first with dichloromethane and hexanes (v/v 5/1) then with hexanes and ethyl acetate (v/v 3/1): off-white crystalline solid, 0.83 g, 85%. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 8.60 (d, $J$ = 4.8, 1 H), 8.26 (d, $J$ = 8.0, 1 H), 7.77 (d, $J$ = 7.5, 1 H), 7.74 (td, $J$ = 7.7, 1.8, 1 H), 7.57 (t, $J$ = 8.0, 1 H), 7.37 (d, $J$ = 8.5, 2 H), 7.29 (t, $J$ = 7.4, 2 H), 7.22 (t, $J$ = 6.2, 1 H), 6.99 (t, $J$ = 7.3, 1 H), 6.81 (d, $J$ = 8.2, 1 H), 6.59 (s, 1 H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 156.3, 155.4, 154.7, 149.1, 140.6, 138.6, 136.9, 129.2 (2 C), 123.5, 122.6, 121.0, 120.1 (2 C), 112.6, 108.9. Anal. Calcd for $C_{16}H_{13}N_3$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.47; H, 5.31; N, 16.86.

**Reaction of 16 with $K_2PtCl_4$ in Acetic Anhydride–Acetic Acid.** A mixture of **16** (62 mg, 0.25 mmol) and $K_2PtCl_4$ (104 mg, 0.25 mmol) in acetic anhydride (5 mL) and acetic acid (5 mL) was refluxed for 24 h. After removal of the solvents, the residue was dissolved in dichloromethane and purified by flash column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 5/1) to give **7**: bright orange solid, 60 mg, 50%.

**Reaction of 16 with $K_2PtCl_4$ in Acetic Acid.** A mixture of **16** (40 mg, 0.16 mmol) and $K_2PtCl_4$ (66 mg, 0.16 mmol) in acetic acid (6 mL) was refluxed for 24 h. After the mixture was cooled to room temperature, the precipitates were collected by filtration, washed with acetic acid, water, methanol, and ethyl acetate, and dried in air to give a yellow solid of **6**: 67 mg, 89%.

**Reaction of 6 with Acetic Anhydride in Acetic Acid.** Complex **6** (30 mg, 0.063 mmol) was suspended in a mixture of acetic anhydride (4 mL) and acetic acid (4 mL). The mixture was heated at reflux for 24 h, and then the solvents were removed by rotary evaporation. The residue was dissolved in dichloromethane and purified by flash column chromatography on silica gel with dichloromethane and ethyl acetate (v/v 5/1) to give **7**: bright orange solid, 30 mg, 92%.

**X-ray Crystallography.** All crystals were grown by diffusing hexanes into dichloromethane solutions of the complexes. A suitable crystal was selected and mounted on a glass fiber. All measurements were made using graphite-monochromated Cu K$\alpha$ radiation (1.54178 Å) on a Bruker-AXS three-circle diffractometer, equipped with a SMART Apex II CCD detector. In each case, initial space group determination was based on a matrix consisting of 120 frames. The data were reduced using SAINT+,[25] and empirical absorption correction was applied using SADABS.[26] Structures were solved using direct methods. Least-squares refinement for all structures was carried out on $F^2$. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and allowed to be refined isotropically as riding models. Structure solution, refinement, and calculation of derived results were performed using the SHELXTL package of computer programs.[27]

**DFT and CCSD Calculations.** Geometry optimizations were performed for the ground state using density functional theory (DFT) with Gaussian 03[28] and the B3LYP exchange-correlation functional.[29] The DEF2_TZVP basis set[30] was used for platinum, while the cc-pvdz basis set[31] was used for all other atoms. At the optimized geometry with the same basis sets, the atomic charges were calculated at the CCSD (coupled-cluster with single and double excitations) level of theory.[32]

## ■ ASSOCIATED CONTENT

### Supporting Information

A CIF file giving crystallographic data for complex **10**, tables giving crystal data and refinement details for **10** and Cartesian coordinates of the optimized geometry of complex **6**, and figures giving an $^1$H NMR analysis of ratio of **4** and **5** formed in the reaction of **3** with $K_2PtCl_4$ in acetonitrile in the presence of a base and NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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