PLATINUM CATALYZED SYNTHESIS OF ALPHA-KETOESTER VIA C-H FUNCTIONALIZATION

by

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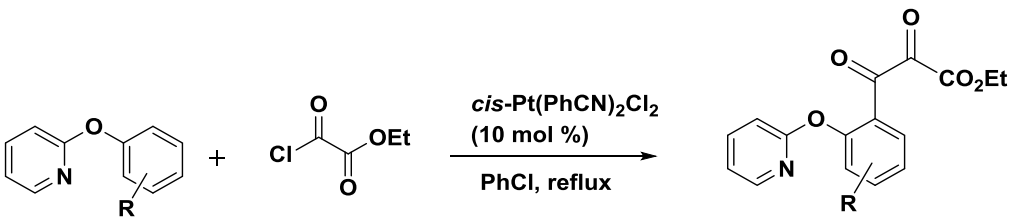
Alpha-ketoesters have proven to be useful in a variety of fields. They have found wide spread applications in pharmaceuticals, photochemistry, and biology. Additionally, they are of great interest in synthetic chemistry and are frequently used as a precursor to many useful organic compounds including alpha-keto acids, alpha-hydroxy acids, and alpha-amino acids. Numerous methods have been reported for synthesizing alpha-ketoesters but they all amount to a few notable drawbacks. Herein reported is a potentially more effective transition metal catalyzed reaction to synthesize alpha-ketoester via C-H functionalization.

A series of ligands with structural modifications have been designed, synthesized and acylated to shed light on the scope and limitations of the reaction. An inexpensive and readily accessible reagent namely ethyl chlorooxoacetate was employed as the acylating reagent. Reaction conditions were optimized by screening various solvents and catalysts. A variety of solvents were found useful in this reaction, including chlorobenzene, benzonitrile, toluene, and m-xylene although the best results were obtained when chlorobenzene was used. The reaction showed great tolerance to both electron withdrawing and donating groups on the phenyl ring however some electronic effects were observed and it was found that the presence of electron withdrawing group on the phenyl ring decelerated the acylation reaction. Experimental results of the acylation reaction will be reported and the mechanistic implications of these results will be discussed.



R= OMe, Cl, Br, F, CO_2Et,, Me, NO_2 , NMe_2,$C_{10}H_8$

PLATINUM CATALYZED SYNTHESIS OF ALPHA-KETOESTER VIA C-H FUNCTIONALIZATION

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In Partial Fulfillment of the Requirements for the Degree

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by

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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^tBu	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)
$Pd(OAc)_2$	palladium(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

LIST OF SCHEMES

CHAPTER 1: INTRODUCTION AND BACKGROUND

1.1 Importance and Applications of Heterocyclic Compounds

Heterocyclic compounds are one of the most active classes of compounds as they possess applications in a wide spectrum of areas including synthetic pharmaceuticals[1-6], agrochemicals[7-8], catalysis[9-10], and biology.[11-12] They can also be found as a key structural unit in numerous drugs[13-15], vitamins[16-17], and natural products.[18-19] Additionally, they compose the core structure of the four DNA bases that establish the genetic code in human body.[20] Recent developments have also shed light on their widespread therapeutic uses such as antibacterial[21-23], antifungal[24], anticancer[25-27], antimalarial[28], and insecticidal agents.[29] More notably, heterocyclic compounds are of great significance in synthetic chemistry due to their utility as intermediates, organocatalysts, and metal ligands in asymmetric catalysts.[30-37]

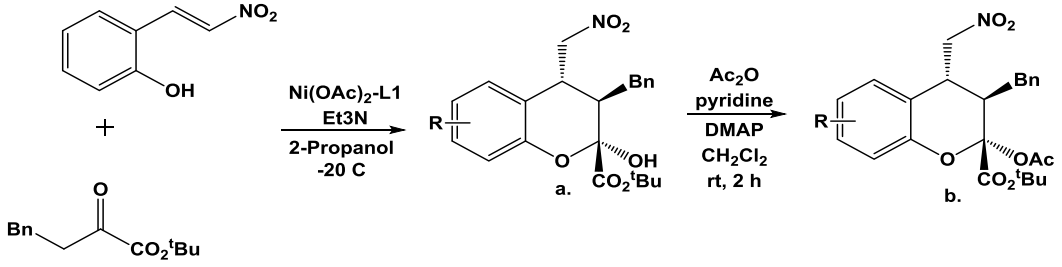
1.2 Importance and Applications of Alpha-ketoesters

Alpha-ketoesters in particular have proven to be very useful in the synthesis of heterocyclic compounds.[28-42] Due to their reactive carbonyl functionality, alpha-ketoesters are susceptible to all types of reactions, such as Paal–Knorr reaction[43], Michael addition[44], hydrogenation reaction[45], aldol reaction[46], Pfitzinger-type condensation[47], 1,3-dipolar cycloaddition reaction[48] etc. Consequently they are conveniently used as a precursor to numerous organic compounds including alpha-keto acids, alpha-hydroxy acids, and alpha-amino acids. Furthermore alpha-ketoesters are ubiquitous in nature and have found applications in pharmaceuticals[49], bioactive natural products[50] and biomolecules.[51]

As previously mentioned, alpha-ketoesters are susceptible to all types of reaction and although great achievements have been achieved, there are still some drawbacks for the existing methods,

such as low atom efficiency, expensive and/or hazardous reagents, extreme temperature, multiple steps etc. Recently Chen and Yang reported a Michael/Hemiacetalization cascade reaction of alpha-ketoester with 2-(2-nitrovinyl)phenol to generate a range of structurally diverse polysubstituted chromanes.[52] Chromane cores are a structural feature of many complex heterocyclic compounds and are found in many pharmaceuticals with biological activities, such as vitamin E, diversonol, afzelechin, cordotolide A, lotthanongine, and flavonoids.[53] Although Chen and group successfully achieved an array of chiral chromane compounds in good yields, their developed method lacked efficiency. The reaction employs a strong base and is required to be carried out at a low temperature of -20 °C. Additionally, the alpha-ketoesters used in this reaction was prepared using Grignard reagents, which are known to be highly reactive and unstable.

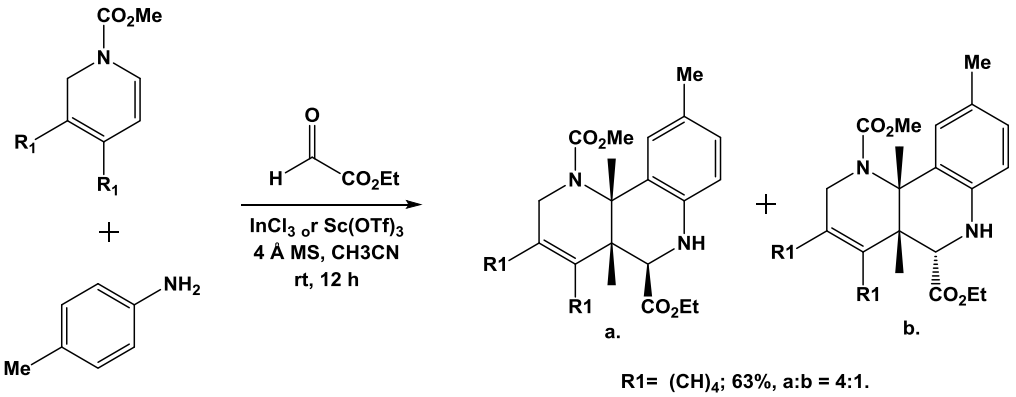
Scheme 1: Michael/Hemiacetalization cascade reaction of Alpha-ketoesters with 2-(2-nitrovinyl) phenols



Heterocyclic compounds, namely naphthyridine derivatives represent an important class of heterocycles as these ring systems occur in various natural products, such as ascididemine, amphimedine, and cystoditins. Additionally, fused pyridines are also found in the many biologically active compounds and pharmaceuticals, such as cartazolate, etazolate, and tracazolate.[54] Lavella and group reported a Lewis acid-catalyzed formal [4 + 2] cycloaddition reaction using ethyl glyoxylate.[55] The reaction was carried out by adding 4 Å MS and Lewis acid

($InCl_3$ or $Sc(OTf)_3$) (20 mol %) to a solution of an equimolar amount of ethyl glyoxalate and p-toluidine in dry CH_3CN, followed by addition of DHPs (1 equiv). The reaction was stirred overnight under N_2 atmosphere to give naphthyridines in a combined yield of 63%. Apart from low atom efficiency, the reaction employed the use of molecular sieves, which can prove to be costly.

Scheme 2: Lewis acid-catalyzed formal [4 + 2] cycloaddition reaction using ethyl glyoxylate



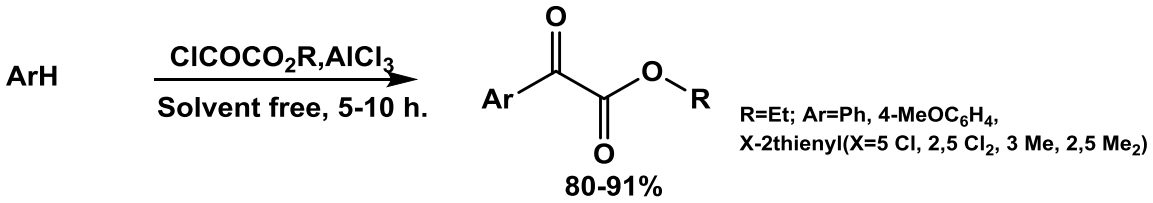
Apart from the growing importance and significance of heterocyclic compounds with an alpha-ketoester functionality, the drawbacks of the current methods underscore the need for developing a novel one-pot reaction that not only employs easily available starting material but also eliminates the use of harsh bases and additives.

1.3 Methods for Synthesizing Alpha-ketoesters

Aromatic keto-esters can be synthesized in a variety of ways, including the traditional Friedel-Crafts method as well as via newly developed cross-coupling reactions. Over the years, Friedel-Crafts acylation has been conveniently employed as a useful synthetic method to introduce acyl group to aromatic rings and is acknowledged as a critical step in the synthesis of many useful

compounds. Typically, stoichiometric amounts of strong Lewis acids, such as $AlCl_3$, must be present for the reaction to occur. However, recently catalytic Friedel-Crafts reactions employing rare-earth metals have also been reported. Xiang and Li reported the synthesis of arylglyoxalates via Friedel–Crafts reaction of substituted aromatic compounds with ethyl oxalyl chloride using $AlCl_3$ under solvent-free conditions[56] (**scheme 3**). Despite this method being straightforward, it comes with a variety of limitations. Friedel-Crafts acylation reactions are not compatible with electron-withdrawing groups, including carbonyl groups, as they deactivate the aromatic ring. This prevents acylation from occurring thus a narrow scope of substrates is available for these reactions.

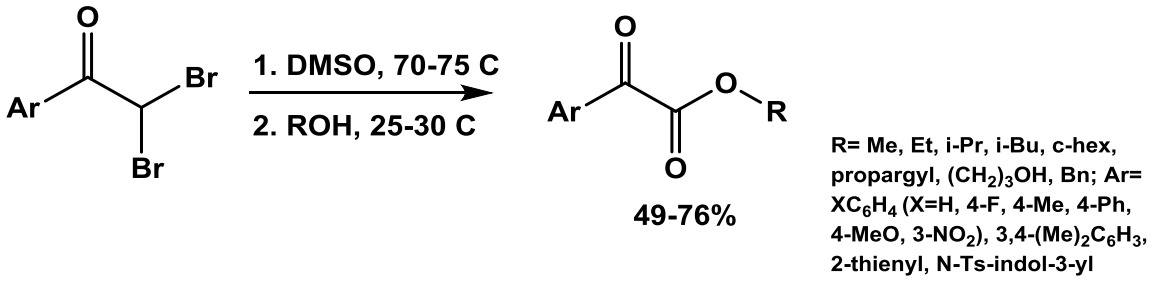
Scheme 3 Friedel–Crafts reaction of substituted aromatic compounds with ethyl oxalyl chloride



Additionally, Friedel-Crafts acylation reactions are not exclusively regioselecitve, introducing the acyl group to either ortho or para positions with respect to the activating group. Another useful alternative for synthesizing alpha-ketoesters is oxidative esterification. Unlike the traditional Friedel-Crafts method, it utilizes alcohol rather than strong acids. Raghunadh and group reported the use of 2 2-dibromo-1-(het)-arylethanones to synthesize arylglyoxalate derivatives via oxidative esterification[57] (**scheme 4**). The reaction was proceeded by heating 2,2-dibromo-1-(het)- arylethanones in DMSO at 70−75 °C for 14−16 h. It was then cooled to room temperature and treated with alcohol to give 35-76% yield. However, this method lacks efficiency as α,α-

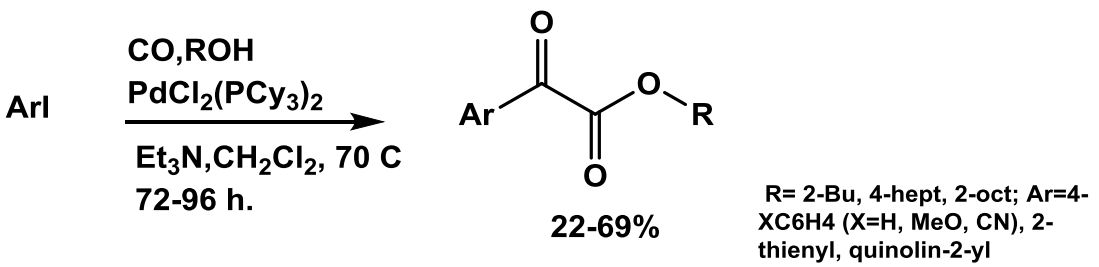
dibromoketones, the starting materials used for this reaction are not readily accessible and have to be made.

Scheme 4 Synthesis of arylglyoxalate derivatives via Oxidative esterification



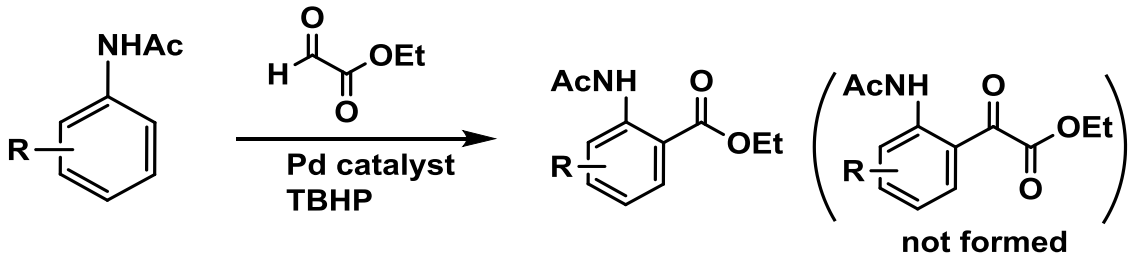
Copious amounts of cross-coupling reactions have also been reported for the synthesis of alpha-ketoesters. Ozawa and group reported the synthesis of alpha-ketoester via carbonylation of aryl iodide using a palladium catalyst and trimethylamine base[58] (**scheme 5**). Similarly, many other transition metal-catalyzed reactions have been reported and interestingly they all require the use of additives such as a base and/or an oxidant. The purpose of the additives and/or oxidants is to regenerate the catalyst and/or to oxidize the acylation reagent. Ozawa and group used a trimethylamine base to remove hydrogen iodide generated in the reaction, which was essential for the acylation reaction to proceed. In addition to employing a hazardous base like trimethylamine, they also reported that high level of CO pressure was required to obtain alpha-ketoesters in higher yields

Scheme 5 Synthesis of alpha-ketoester via carbonylation of aryl iodide



The Pd-catalyzed direct C-H functionalization is a powerful synthetic tool for the formation of carbon-carbon bonds; however, some issues with efficacy remain. Wang and group reported an attempt to synthesize alpha-ketoester compounds through a Pd-catalyzed acylation using ethyl glyoxylate as the acylating reagent and TBHP as the oxidant[59]. Unfortunately, instead of the desired product, decarbonylative ester products were obtained (**Scheme 6**). Decarbonylation is one of the most common drawbacks of metal-catalyzed acylation reactions, particularly when acyl chlorides are employed.

Scheme 6 Synthesis of alpha-ketoester via Pd-catalyzed acylation using ethyl glyoxylate

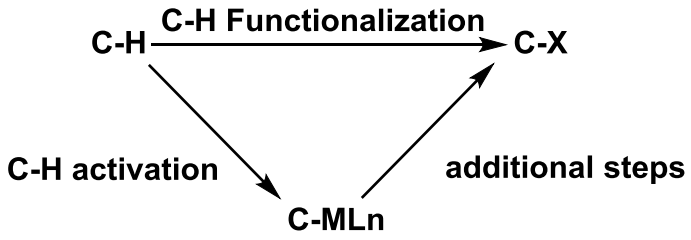


Other methods reported for the synthesis of alpha-ketoesters include oxidative cleavage of tartrate esters[60], the reaction of organometallic species with oxalic ester derivatives[61], hydrolysis[62], and esterification of acyl cyanides[63]. However, all of these methods suffer from lengthy procedures or lack of generality. Nevertheless, metal-catalyzed C-H functionalization is a desirable synthetic method. Recently, the Huo group reported a Pt-catalyzed acylation reaction of 2-aryloxypyridines through C-H functionalization[64]. This reaction required no additives and proceeded without any side reactions. Further detail on this reaction are reported in section 1.5.

1.4 Metal-Catalyzed C-H Functionalization

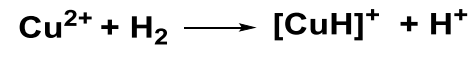
Transition metal-catalyzed C-H functionalization is regarded as the "holy grail" of organic chemistry and remains one of the most sought out synthetic pathways by organic chemists. It is a fundamental organic transformation where the hydrogen is replaced with a functional group to form C-C and carbon-heteroatom bonds (**Scheme 7**). Metal catalyzed functionalization employs the use of a wide range of organic compounds, including alkanes, alkenes, and arenes. Additionally, it functionalizes the previously inert C-H bond, consequently eliminating the pre-functionalization steps of a reaction. This revolutionary method has streamlined synthetic pathways in developing various useful organic molecules of medicinal and biological interest.[65]

Scheme 7: General scheme for C-H functionalization



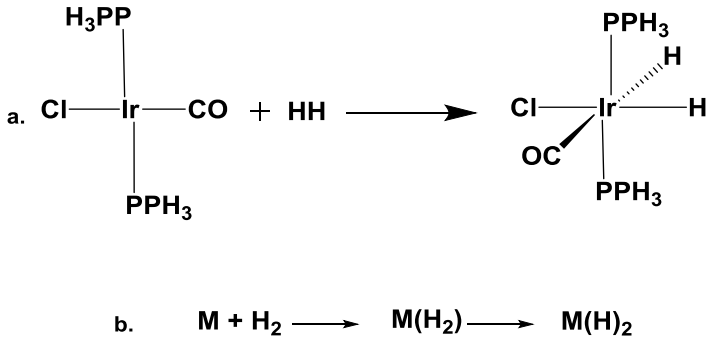
Research on C-H functionalization can be dated back to the late 1800s. Although findings from the initial research conducted did not make significant contributions to C-H functionalization, however they did provide several seminal observations that suggested a possible pathway for C-H activation. In 1955, Halpern reported that Cu^{2+} could heterolytically cleave H_2 (**scheme 8**). This finding was quite interesting because in terms of polarity and bond strength, H-H bond is the closest relative to the C-H bond. Based on their similarity it was assumed that if a transition metal could cleave a H-H bond, it should also potentially cleave a C-H bond.[66]

Scheme 8. Reaction scheme reported in 1955 by Halpern proposing Cu^{2+} catalyzed cleavage of H-H bond



In 1962, Vaska reported oxidative addition of H_2 to $Ir(PPh_3)_2(CO)Cl$. His findings shed light on the possible mechanism of the reaction. He proposed that the reaction was oxidative and proceeded via the formation of an intermediate dihydrogen complex[67] (**Scheme 9**).

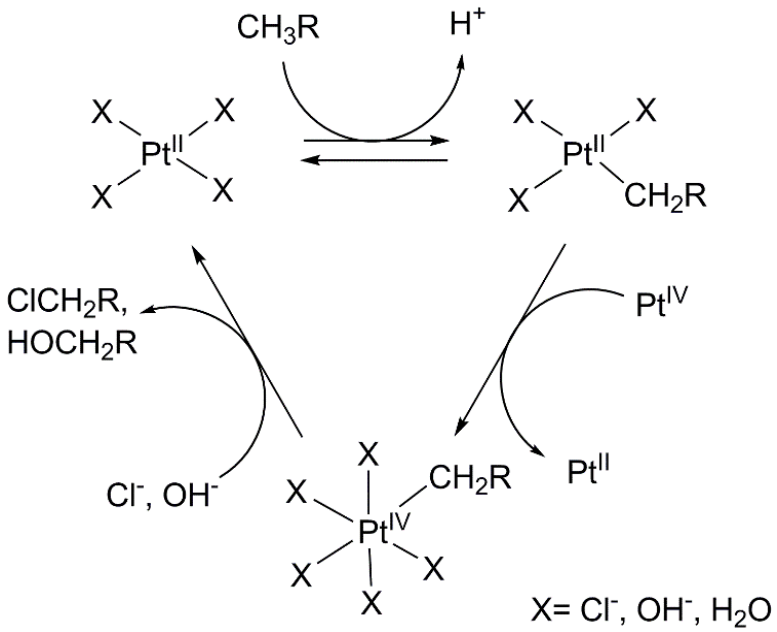
Scheme 9. a. Reaction scheme reported in 1962 proposing oxidative addition of H_2 to $Ir(PPh_3)_2(CO)Cl$ as a possible pathway b. general reaction scheme for metal catalyzed cleavage of H-H bond.



The first "true" transition metal-catalyzed C-H activation reaction was reported in 1961 by Joseph Chatt.[68] He reported C-H activation of a ligand, phosphine methyl group and functionalization of C-H bond of naphthalene using a ruthenium complex, $Ru(0)(dmpe)_2$. These reactions were clear examples of oxidative addition, making Vaska's findings more credible. Around the same time, Wilkinson discovered a rhodium coordination complex, commonly known as Wilkinson's catalyst.[69] He proposed that the mechanism explicitly involved the reductive elimination of a C-H bond and formation of Rh (I) and Rh (III) intermediates.

Shortly after, Shilov reported the use of the platinum complexes for alkane activation.[70] He converted a hydrocarbon to an alcohol by reacting methane with water and proposed that the reaction proceeded via electrophilic activation of the C-H bond (**Figure 1**). More recently, the Shilov system was modified to employ stoichiometric amounts of Cu(II) along with Pt(II) to hydroxylate aliphatic amines.

Figure 1. Shilov system

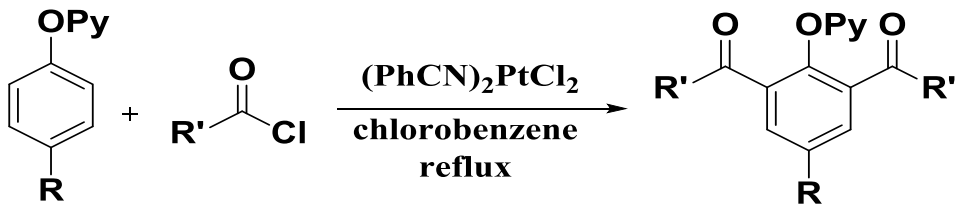


Following the Shilov System, there has been a vast amount of research and advancements directed towards transition metal-catalyzed C-H functionalization. Many metals including palladium, ruthenium, copper, etc., have played a vital role in the development of C-H functionalization. Despite the significant involvement of platinum in exploring stoichiometric C-H activation, it's rarely reported in catalytic C-H functionalization.[70] Instead, its analog palladium is frequently employed in C-H functionalization, mainly due to C-Pt bond being relatively stronger than C-Pd bond.

1.5 Research Relevance

Recently, a platinum catalyzed acylation reaction of 2-(aryloxy)pyridines with acyl chlorides was reported by the Huo Lab. This C-H functionalized acylation reaction was remarkable in that the reaction employed catalytic amount of platinum, required neither an oxidant nor any additives, and allowed double acylation to produce diacylated products, all of which are not common in the literature (**scheme 10**).

Scheme 10. C-H activation and acylation reaction



In order to allow for the most efficient application of the acylation reaction, various solvents and catalysts were screened to employ optimal reaction conditions. Reaction optimization included determination of catalyst load as well as amount of solvent required for the reaction to proceed. Additionally the effect of running the reaction under argon vs exposed to air were also observed.

It was found that the best results were achieved when chlorobenzene was used as the solvent along with platinum as the catalyst. The air sensitivity of the reaction was tested and open-air conditions were found to have negligible effects on the reaction. The catalyst loading however was found to significantly affect the reaction. An experiment was conducted using 5% platinum catalyst with 2-phenoxypyridine and benzoyl chloride and it showed significant decrease in conversion compared to the experiment conducted using 10% catalyst. Therefore the catalyst load was established as 10%.

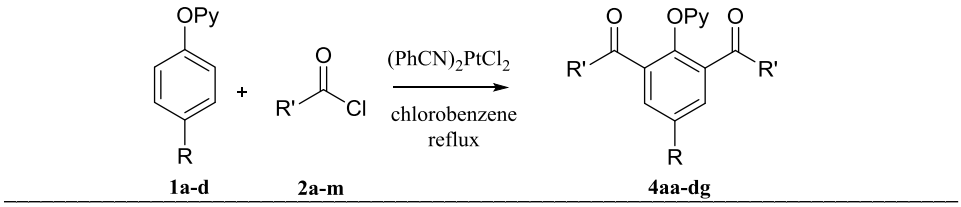
Further experiments were carried out to explore this interesting reaction. The acylation of 2-aryloxypyridines was examined with respect to four different substrates: 2-phenoxypyridine, with substitutions para to the oxygen linker consisting of methyl, methoxy, and chloro groups. It should be noted that while the formation of monoacylated product was detected, the reaction conditions seemed to favor the formation of diacylated product. The general scheme for this synthesis, along with their product yields, are summarized in **Table 1**

The platinum-catalyzed double acylation reaction accommodated all types of acyl chlorides, including aliphatic, aromatic, heteroaromatic, and α,β-unsaturated acyl chlorides. Steric and electronic effects were of particular interest in the acylation reaction. Although aroyl chlorides with either a strongly electron-withdrawing group or a strongly electron-donating group worked satisfactorily to give diacylated products in high yields, electron-withdrawing aroyl chlorides were demonstrated to be more reactive.

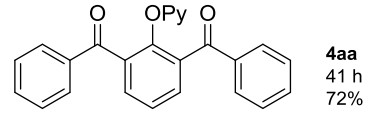
In addition, the removal of the directing pyridyl group was reported. This was exciting as it increases the utility of the acylation reaction by expanding synthetic options. The removal of the pyridyl group was carried out by methylating the pyridyl group using trifluoromethanesulfonate to form a pyridinium ion followed by treating the reaction mixture with a solution of sodium dissolved in methanol. The reaction mixture was then subjected to acidification followed by aqueous workup and finally the product was purified via column chromatography. The product was isolated with a high yield of 86%.

The mechanism of the acylation reaction was proposed based on the comprehensive insights gathered from the general reaction. It was suggested that the reaction proceeded via sequential cyclometalation followed by the acylation of the formed cyclometalated platinum complex.

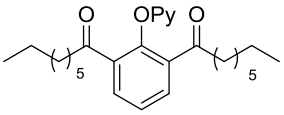
Table 1: Pt-catalyzed *ortho* double acylation of 2-aryloxypyridines



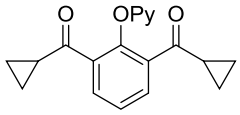
1a-d **2a-m** **4aa-dg**



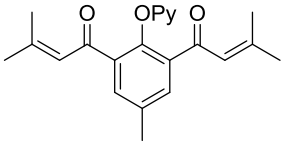
4aa
41 h
72%



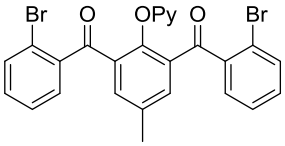
4ac
19 h
69%



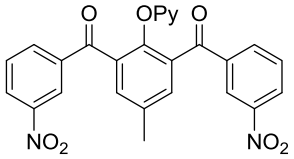
4ae
9 h
57%



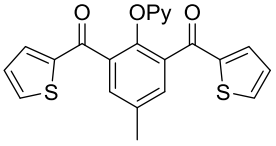
4bf
3 h
54%



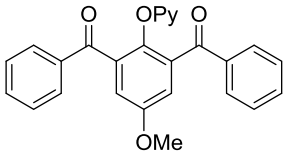
4bh
14 h
55%



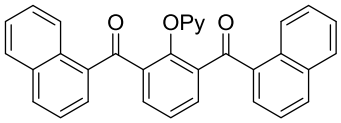
4bj
27 h
77%



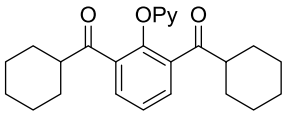
4bl
46 h
52%



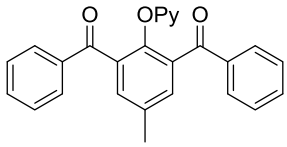
4ca
60 h
76%



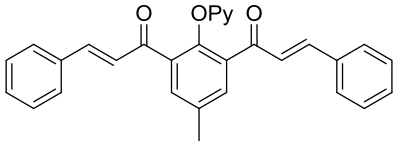
4ab
22 h
71%



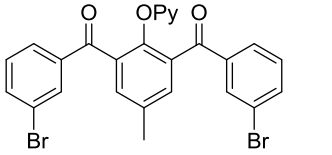
4ad
24 h
54%



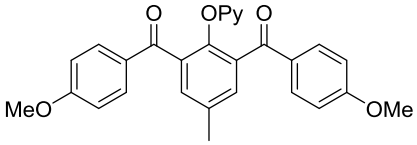
4ba
48 h
82%



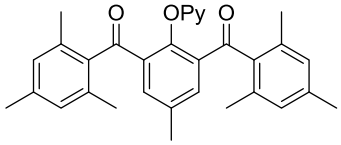
4bg
3 h
79%



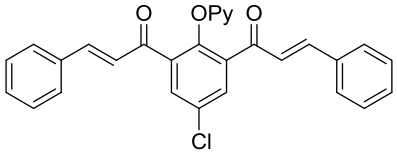
4bi
23 h
76%



4bk
44 h
52%



4bm
40 h
74%



4dg
6 h
64%

[a]Conditions: 2-(aryloxy)pyridine (1.0 mmol), acyl chloride (5.0mmol), Pt(PhCN)2Cl2 (0.1 mmol), chlorobenzene (3 mL), reflux. The reaction time was not optimized. Yields are isolated yields.

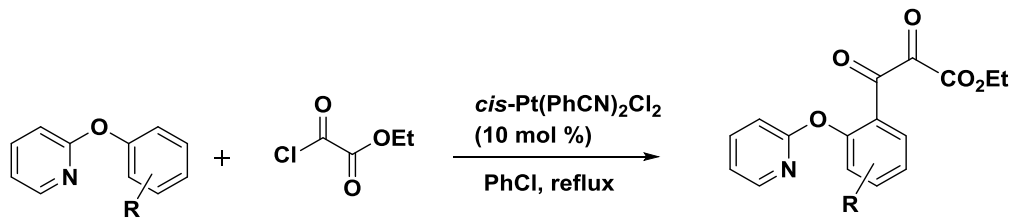
CHAPTER 2: RESEARCH OBJECTIVE

Keto-esters have many important applications in organic synthesis as reported in chapter 1.2. Development of essential methods for the introduction of an alpha-ketoester functional group is thereby of great importance. Encouraged by the previously discovered acylation reaction (Chapter 1.5), the objective of this research was to develop a straightforward and efficient method for the synthesis of novel alpha-ketoester compounds via platinum catalyzed C-H acylation.

This research was carried out to accomplish three general goals in regard to the acylation reaction for the synthesis of alpha-ketoester: optimization of reaction condition, examination of the scope and limitations of the reaction, and elucidation of the mechanism of the reaction. A variety of solvents and catalysts have been explored to allow for the most optimal reaction conditions. For the purpose of this research, ethylchlorooxoacetate, a cheap commercial bio-chemical with a keto-ester functionality, was chosen as the acylating agent. The use of chlorooxoacetate in C-H functionalization reactions is rarely reported most likely due to the possibility of the decarbonylation side reaction.

A series of 2-aryloxypyridines were designed with structural variations to shed light on the scope and limitations of the acylation reaction. Structural variations of the ligands included varied substituents on different position of aryl pyridine. The acylation reaction of the substrates with ethyl chlorooxoacetate to afford alpha-ketoester compounds is shown in **scheme 11**. The results of the acylation reaction are reported in chapter 4. Experimental results from the acylation reaction were used to understand the mechanism of the reaction. A possible reaction mechanism is proposed in chapter 5.

Scheme 11. General scheme for the acylation reaction with ethyl chlorooxoacetate

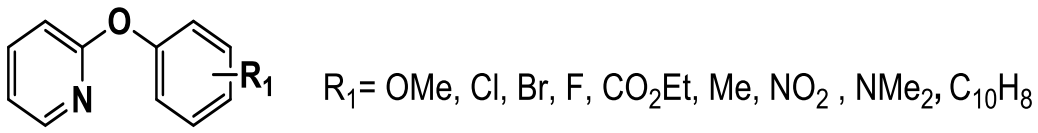


R= OMe, Cl, Br, F, CO_2Et, Me, NO_2 , $NMe_2C_{10}H_8$

CHAPTER 3: LIGAND DESIGN AND SYNTHESIS

A variety of substrates with a pyridine moiety were designed to determine the scope of the acylation reaction. The ligands synthesized had various functional groups at each position on the phenyl ring (**figure 2**). Substrates with other heteroaryl compounds namely pyrimidine and quinoline, were also synthesized. Synthesis of the ligands along with their experimental data is described in this chapter.

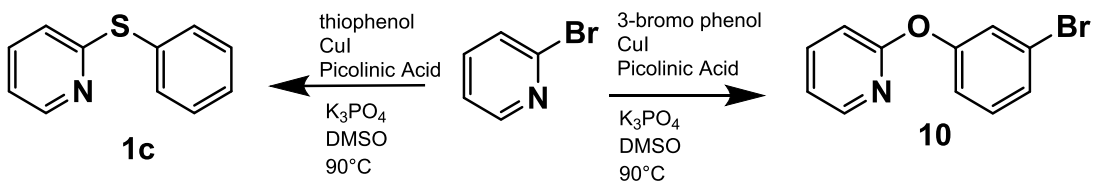
Figure 2: General structure of ligands with various substituents on the phenyl ring



3.1 Ligand design

For the purpose of this research, 2-phenoxy pyridine was chosen as a suitable substrate for the acylation reaction. The presence of nitrogen as a directing group facilitates C-H bond cleavage by inducing pre-association between the metal and the substrate. Moreover, 2-phenoxy pyridine, a bidentate ligand, would bind less tightly to the metal complex as opposed to a tridentate ligand, which comprise of two available nitrogen's to coordinate with. The two linker atoms compared in this study include sulfur and oxygen. The linker atoms serve the additional purpose of affecting the electron-richness of the phenyl ring, as the more electron-rich the phenyl ring is, the more prone it is to acylation.

Scheme 12: Synthesis of ligands with different linker groups



Oxygen and sulfur have similar electron configuration and therefore form compounds that are analogs of each other.(**Table 2**) To examine the different effects of sulfur and oxygen as a linker group on the acylation reaction, compounds **1c** and **10** were synthesized **(scheme 12**) and subjected to acylation reaction. It was found that acylation reaction of **10** with ethyl chlorooxoacetate resulted in satisfactory yield whereas ligand **1c** retarded the reaction. Further detail of both the reactions is reported in chapter 4.

Table 2. Analogous oxygen/sulfur compounds

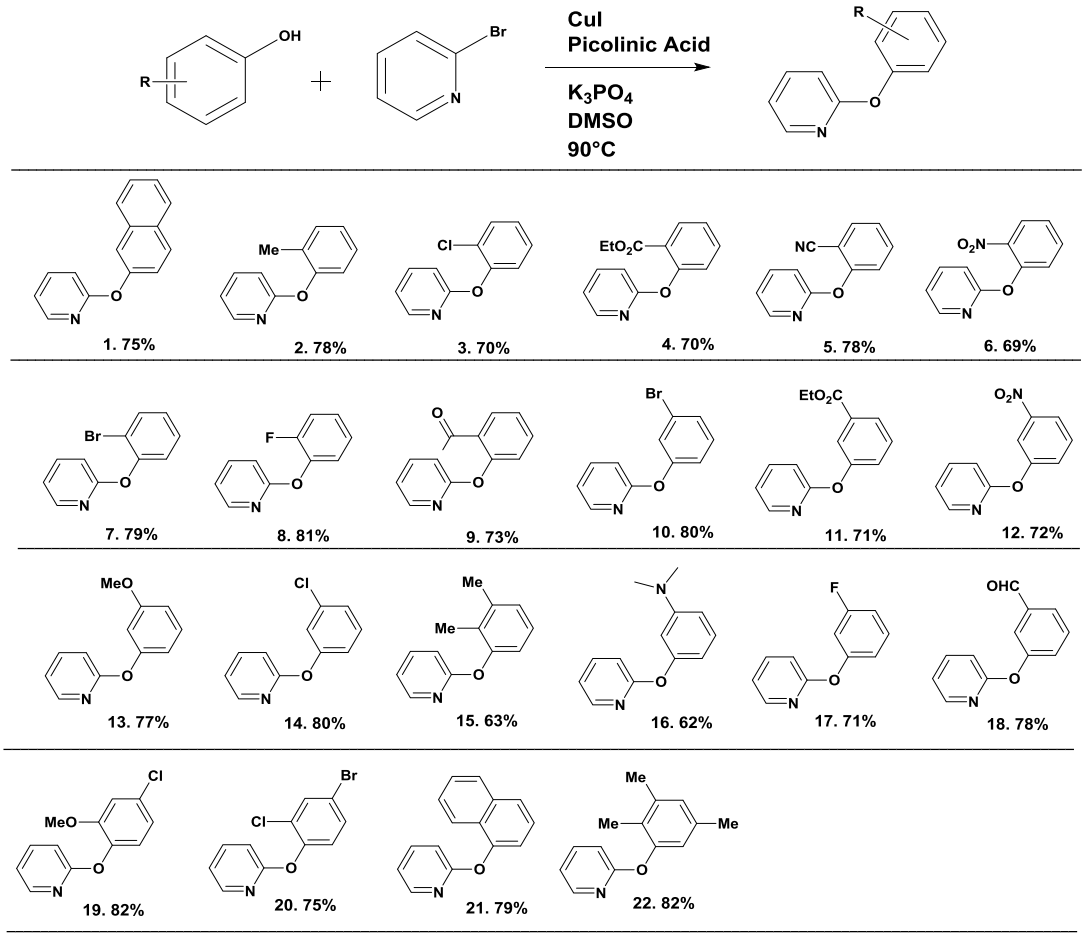
Oxygen Compounds	**Sulfur Compounds**
Na_2O (sodium oxide)	Na_2S (sodium sulfide)
H_2O (water)	H_2S (hydrogen sulfide)
O_3 (ozone)	SO_2 (sulfur dioxide)
CO_2 (carbon dioxide)	CS_2 (carbon disulfide)
OCN- (cyanate)	SCN- (thiocyanate)
$OC(NH_2)_2$ (urea)	$SC(NH_2)_2$ (thiourea)

3.2 Synthesis of the ligands

A series of ligands were designed with different functional groups on the phenyl ring to shed light on the scope of the acylation reaction. The substituents selected offer a range of electron withdrawing and electron donating abilities, which may provide insights on the mechanism of the acylation reaction.

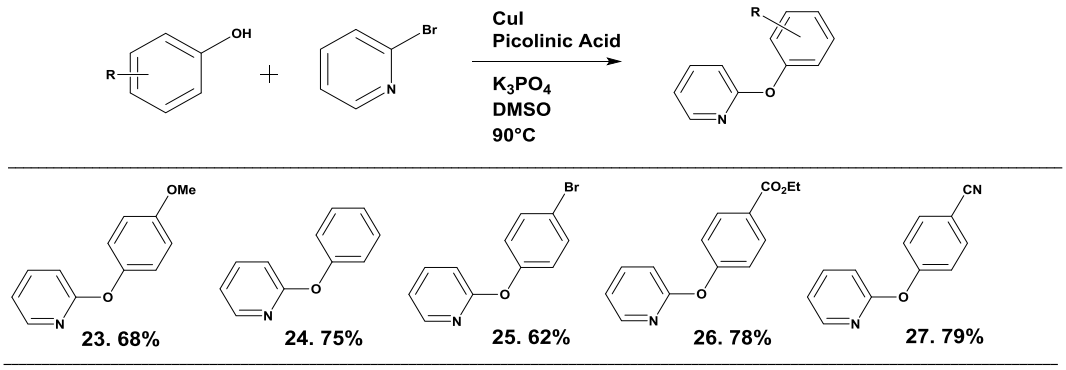
Ligands with substituents ortho and/or meta position relative to the oxygen linker atom were synthesized. Ligands with substituents at the ortho position are more likely to block the acylation at that particular carbon. Similarly, meta substituted ligands are likely to sterically hinder the acylation at the carbon ortho to the substituent. The general scheme for these synthesis, along with their respective yields, are reported in **Table 3**. All compounds were isolated in good yields and were characterized using ^{1}H NMR.

Table 3: Structure of ligands with substituents on the position otho and/or meta to the linker group



Ligands designed with a substituent on the position para to the linker atom are of particular interest as both positions ortho to the linker group are available and steric hindrance by the substituent is unlikely from this position on the phenyl ring. The general scheme for these synthesis, along with their respective yields, are reported in **Table 4**. All the compounds were isolated in good yields and were characterized using ^{1}H NMR.

Table 4: Structure of ligands with substituents on the position para to the linker group

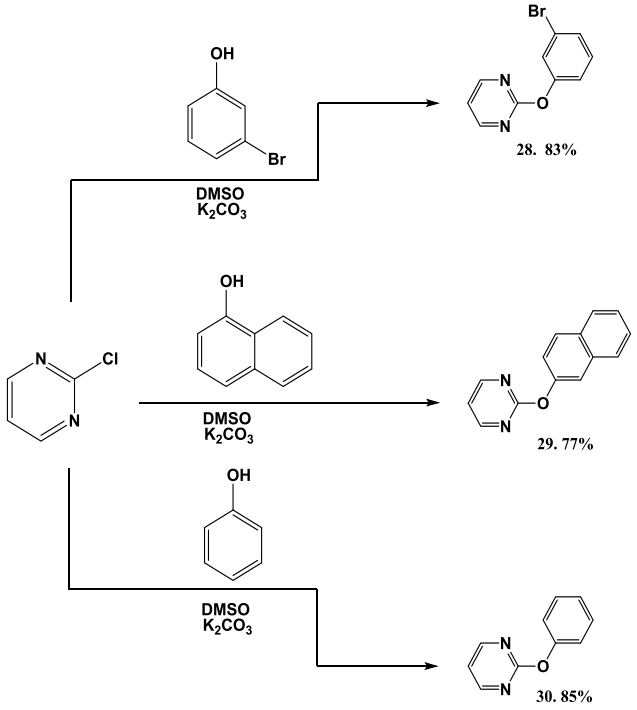


To further investigate the scope of the acylation reaction, hetero aryl ethers with a pyrimidine (**Scheme 13**) and quinolone (**Scheme 14, 15**) moiety were synthesized. Synthesis of ligands **28-32** called for a different synthetic procedure than the procedure used to synthesize phenoxypyridine. Ligands **28-30** were synthesized by reacting 2-chloro pyrimidine and the respective phenol in DMSO and presence of K_2CO_3. The reaction was stirred and heated at 90°C under argon for 24-48 h. The resulting crude mixture was subjected to aqueous workup and the product was isolated via column chromatography. Ligands **31-32** were synthesized following the same procedure.

Pyrimidine

Pyrimidines are an important class of natural products, such as nucleotides, caffeine, thiamine (vitamin B1), and alloxan and are found in many marketed drugs, including uramustine, tegafur, floxuridine, fluorouracil, cytarabine, trimethoprim.

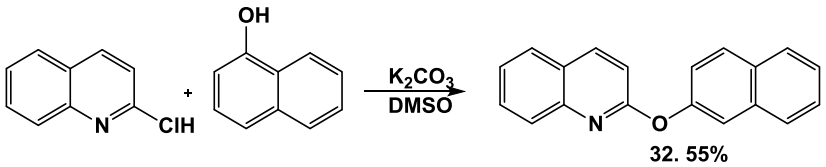
Scheme 13 Synthesis of ligands with a pyrimidine moiety



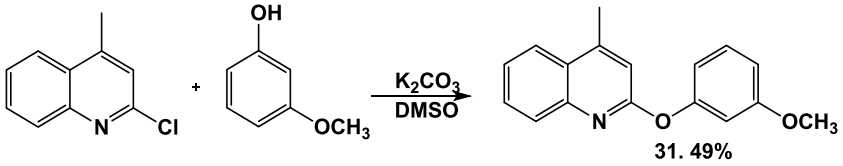
Quinoline

Quinoline can be found in the structure of many pharmaceuticals such as chloroquine, amodiaquine, mefloquine, and camptothecin. Additionally it has applications in biomolecules and many natural products, such as quinine, quinidine.

Scheme 14 Synthesis of ligand 32



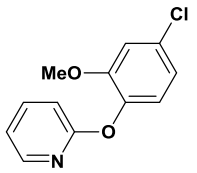
Scheme 15 Synthesis of ligand 33



3.3 Experimental

General Experimental Information

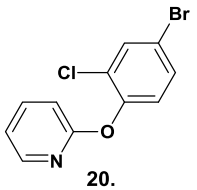
All reactions involving moisture- and/or oxygen-sensitive compounds were carried out under argon atmosphere and anhydrous conditions. All anhydrous solvents were purchased from Aldrich Chemical Co. and were used as received. Thin layer chromatography was performed with silica gel 60 F_{254} plates, purchased from EMD chemicals. Gas chromatography was performed on a Shimadzu GC-2010 AFC equipped with FID detector. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer at 298K using $CDCl_3$. Chemical shifts were reported relative to TMS (0.0 ppm for ^{1}H). Melting points were measured on a Mel-temp apparatus. A general procedure was described for the synthesis and characterization of compounds 19, 20, 22.



19.

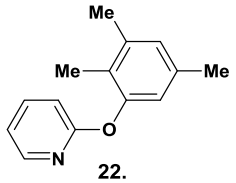
Synthesis of 2-(4-chloro-2-methoxyphenoxy)pyridine (**19**). **General Procedure A**: A 250 ml, three-necked round-bottom flask with a condenser was dried and purged with argon and then charged with 4-chloro-2-methoxyphenol (4.38 ml, 36 mmol), 2-bromopyridine (2.86 ml, 30 mmol), CuI (0.57 g, 3 mmol), picolinic acid (0.74 g, 6 mmol), K_3PO_4 (12.70 g, 60 mmol), and anhydrous DMSO (60 mL). The mixture was stirred and heated at 90°C under argon for 24 h. The progress of the reaction was monitored via thin layer chromatography and GC analysis. The mixture was cooled to room temperature and quenched with H_2O (100 ml). The aqueous layer was extracted with ethyl acetate (3 · 50 ml). Combined organic layer was washed with H_2O (3 · 50 ml), 3 M NaOH (2 · 10 ml), brine (3 · 25 ml) and dried over anhydrous Na_2SO_4. The organic solution was filtered, concentrated via rotary evaporator, and purified by recrystallization from hexanes. Light brown solid, 4.98 g, 70.6% yield. Melting point: 66-68 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.15 (dd, J = 3.6, 1.3 Hz, 1H), 7.72-7.66 (m, 1H), 7.09 (d, J = 8.3 Hz, 1H), 7.02-6.94 (m, 4H), 3.77 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 163.5, 152.4, 147.5, 141.3, 139.3, 130.8, 123.9, 121.0, 118.3, 113.6, 110.9, 56.3. **MS** Calculated for $C_{12}H_{11}ClNO_2$ ($M+H^+$) 236.7; Found: 236.6. **Anal**. Calculated for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found C, 60.96; H, 4.42; N, 5.85

The following compounds were prepared using General Procedure A.



20.

Synthesis of 2-(4-bromo-2-chlorophenoxy)pyridine (**20**)*:* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow solid, 69.1% yield. Melting point: 65-67 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.18-8.13 (m, 1H), 7.78-7.70 (m, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.45 (dd, J = 6.3, 2.3 Hz, 1H), 7.13 (d, J = 8.6 Hz, 1H), 7.06-7.00 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 162.7, 149.2, 147.5, 139.7, 133.2, 131.0, 128.6, 125.2, 118.9, 118.2, 111.3. **MS** Calculated for $C_{11}H_8BrClNO$ ($M+H^+$) 236.0, 238.0; Found: 236.1, 238.1. **Anal**. Calculated for $C_{11}H_7BrClNO$: C, 46.43; H, 2.48; N, 4.92. Found C, 46.37; H, 2.44; N, 4.99.



22.

Synthesis of 2-(2, 3, 5-trimethylphenoxy)pyridine **(22):** Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): brown solid, 76.4% yield. Melting point: 54-56 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23-8.19 (m, 1H), 7.70-7.64 (m, 1H), 6.93-6.87 (m, 1H), 6.89 (s, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.75 (s, 1H), 2.30 (s, 6H), 2.05 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.2, 152.0, 148.0, 139.3, 138.3, 136.1, 127.8, 126.1, 120.0, 117.7, 110.6, 20.95, 20.1, 12.2. **MS** Calculated for $C_{14}H_{16}NO$ ($M+H^+$) 214.1; Found: 214.2. **Anal**. Calculated for $C_{14}H_{15}NO$: C, 78.84; H, 7.09; N, 6.57. Found C, 79.00; H, 7.24; N, 6.56.

CHAPTER 4: SYNTHESIS OF ALPHA-KETOESTERS

As mentioned in chapter 1, the acylation reaction discovered by the Huo Lab was quite remarkable as it required neither an oxidant nor any additives and proceeded to give diacylated complexes in good yield. Thus using the insights gathered from the previously published acylation reaction a compelling road map for this study was strategized.

Prior to optimizing the reaction conditions the reaction time for each acylation reaction was optimized. Initially, the reactions were conducted on a small scale (0.5 mmol) and monitored over a duration of 1-9 h via TLC and gas chromatography. It was found that almost all reactions were completed within 1-2 h. It is important to note that after 2-3 h, the reaction started to degrade and turn black in color. Further details regarding reaction degradation are reported in section 4.1 of this chapter. After the establishing the optimized reaction time of each reaction, they were repeated on a 1 mmol scale and collected in satisfactory yields. Herein reported are the details and results of the platinum catalyzed acylation reaction along with the experimental procedure and characterization data.

4.1 Reaction Optimization

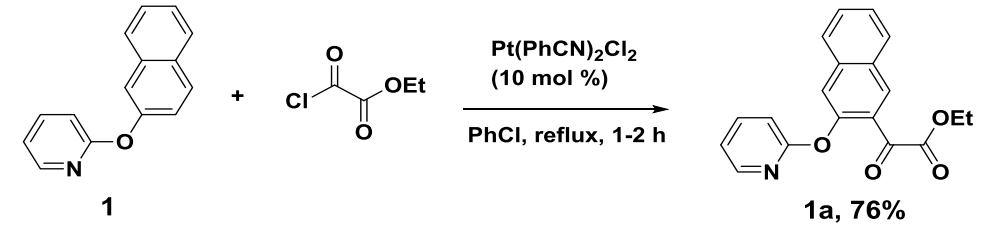
Reaction of **1a** was used as a model for optimizing reaction conditions of the acylation reaction. (**Scheme 16**). Various solvents and catalysts were employed for the reaction of ligand **1** with ethylchlorooxoacetate. **Table 5** outlines the effects of each solvent and catalyst tested during the screening process.

Table 5. Optimization of conditions for the reactions of 1a with ethyl chlorooxoacetate.[a]

Entry	Catalyst (%)	Solvent	T (°C)	t (h)	Remark	Conversion (%)
1	*cis*-$Pt(PhCN)_2Cl_2$ (10)	PhCl	reflux	3		85
2	*cis*-$Pt(PhCN)_2Cl_2$ (10)	PhCl	reflux	1		80
3	*trans*-$Pt(PhCN)_2Cl_2$ (10)	PhCl	reflux	3		30
4	*cis*-$Pt(PhCN)_2Cl_2$ (10)	MeCN	reflux	12	NR	
5	*cis*-$Pt(PhCN)_2Cl_2$ (10)	AcOH	reflux	12	NR	
6	*cis*-$Pt(PhCN)_2Cl_2$ (10)	Toluene	reflux	6		30
7	*cis*-$Pt(PhCN)_2Cl_2$ (10)	m-Xylene	reflux	3		80
8	*cis*-$Pt(PhCN)_2Cl_2$ (10)	PhCN	150	6		30
9	$PdCl_2$ (10)	PhCl	reflux	12	NR	
10	$Pd(OAc)_2$ (10)	PhCl	reflux	12	NR	
11	$Pd(MeCN)_2Cl_2$ (10)	PhCl	reflux	12	NR	
12	Cu(I)Br (10)	PhCl	reflux	12	NR	
13	$Cu(II)Cl_2$ (10)	PhCl	reflux	12	NR	
14	$Pt(DMSO)_2Cl_2$ (10)	PhCl	reflux	12	NR	
15	$PtCl_2$ (10)	PhCl	reflux	6		80
16	$RbClO_4$ (10)	PhCl	reflux	12	NR	

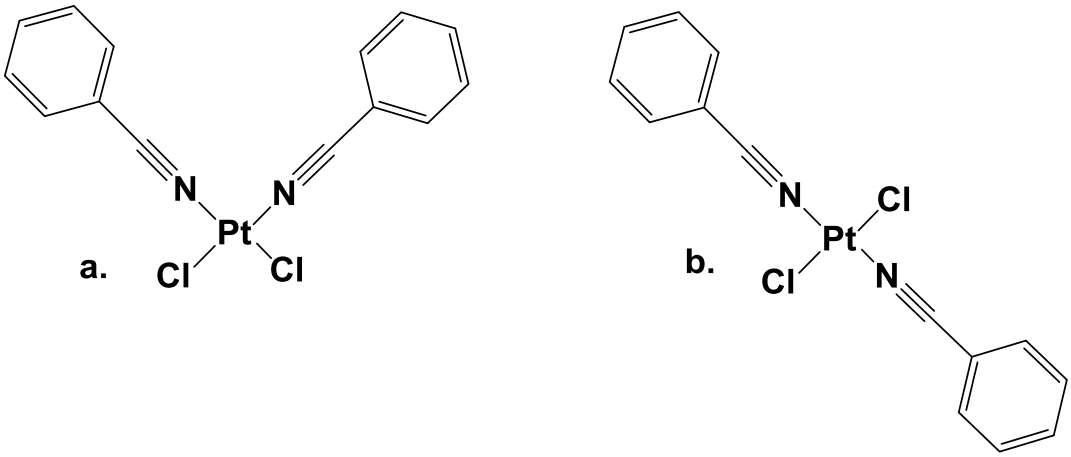
General conditions: Substrate (0.5 mmol), ethylchlorooxoacetate (1.5 mmol), solvent (2 mL). MeCN = acetonitrile; AcOH = acetic acid; PhCN = benzonitrile; PhCl = chlorobenzene

Scheme 16: Pt-Catalyzed C-H Acylation with Ethyl Chlorooxoacetate



A variety of transition metals were screened, however platinum proved to be the most efficient metal to catalyze the acylation reaction smoothly. It should be noted that when the cis isomer of the $Pt(PhCN)_2Cl_2$ complex was utilized, the reaction was completed within 2 h with the conversion rate of 85% as opposed to only 30% conversion and a much slower reaction when the trans isomer of $Pt(PhCN)_2Cl_2$ complex was used. Further experiments and computational studies will be required to better understand the difference in catalytic activity of both isomers. (**Figure 3**)

Figure 3 a. cis isomer of the $Pt(PhCN)_2Cl_2$ b. trans isomer of $Pt(PhCN)_2Cl_2$



Solvents that have been screened include chlorobenzene, acetonitrile, acetic acid, benzonitrile, toluene, and m-xylene. Reactions conducted using both benzonitrile and toluene progressed at a slow rate and showed only 30% starting material conversion. The use of chlorobenzene and m-xylene showed significant improvement in reaction time and conversion rate, 85% and 80% respectively with both reactions reaching completion within 2 h. While reactions using acetic acid and acetonitrile did not proceed at all, no degradation of the starting material was observed either. Since chlorobenzene showed the best results it was chosen as the solvent for all further acylation reactions.

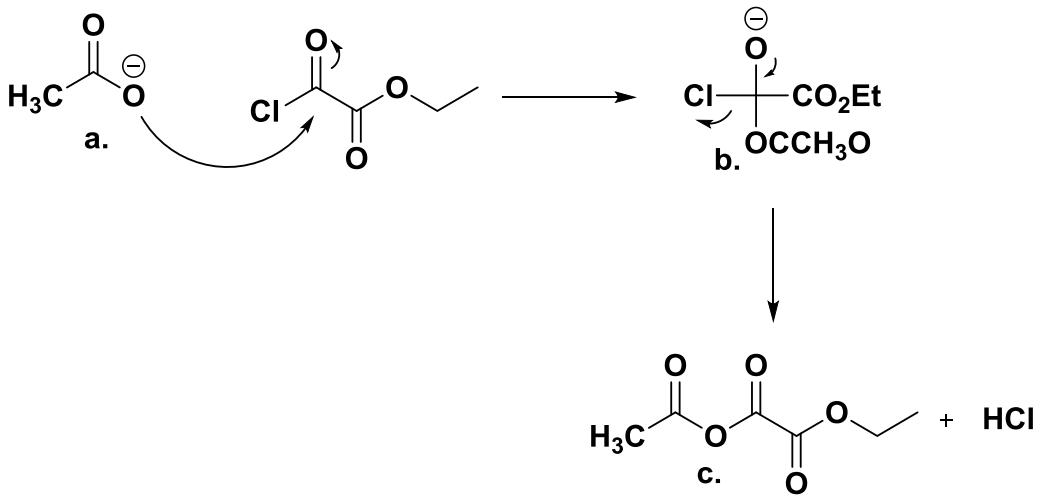
Table 6.The effect of the temperature on the progress of the reaction

Solvent	Temp	B.P. (℃)	Conversion (%)
PhCN	reflux	191	30
m-xylene	reflux	139	80
PhCl	reflux	132	85
AcOH	reflux	117.9	no reaction
Toluene	reflux	110.6	30
MeCN	reflux	82	no reaction

The varying results observed with each choice of solvent may have several contributing factors. The rate and progress of the reaction, when heated at reflux are effected by the solvents boiling point (**Table 6**). The most suitable temperature for this specific acylation reaction seemed to be in the range of 130-140 ℃. This trend can be seen in the poor conversion rate of the reactions where solvents with boiling point lower than that range were used. The boiling points of chlorobenzene and m-xylene are relatively closer in range, hence their conversion rate is similar.

Another contributing factor to the low % conversion with certain solvents is likely due to the possibility of competing or parallel reactions. The poor reaction of ligand **1** when acetic acid was used as a solvent indicates a possible competing reaction between ligand **1** and acetic acid to react with ethyl chlorooxoacetate. The substrate **1** could abstract a proton from acetic acid to form the corresponding anion, **a.** The carboxylate anion's negatively charged oxygen would then attack the carbonyl carbon of ethyl chlorooxoacetate, forming a tetrahedral intermediate. Finally, chloride (a good leaving group) would be eliminated to yield an acid anhydride and thus retarding the intended acylation reaction (**scheme 17**)

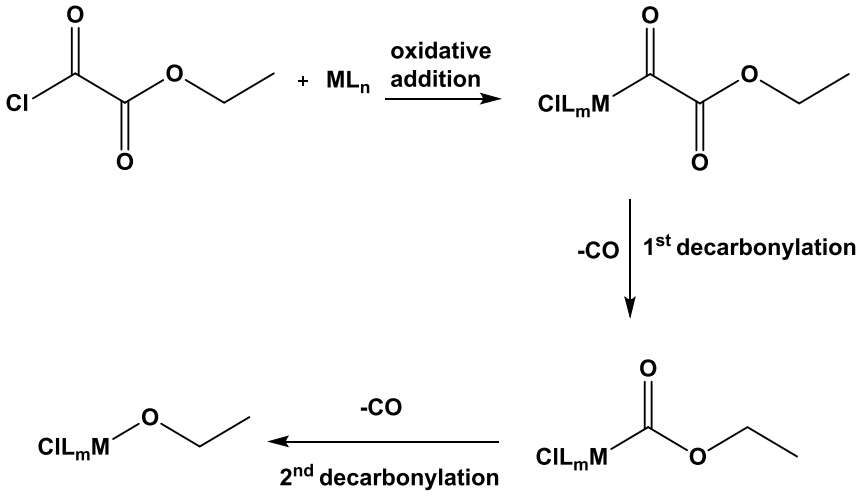
Scheme 17 Mechanism for the possible formation of acid anhydride



Another possibility for the failed acylation reaction when both nitriles were employed as the solvents can be due to the solvent's competitive binding to the catalyst and preventing the cyclometalation reaction from proceeding.

As mentioned previously in chapter 2, the use of ethylchlorooxoacetate was a major concern for this research because of the possibility of decarbonylation side reaction. A potential scheme for double decarbonylation is illustrated in **scheme 18.** However, the reaction of ligand **1** with ethylchlorooxoacetate, under optimized reaction conditions, formed no decarbonylative byproducts. This was confirmed by careful GC analysis of the crude reaction mixture and characterization of the isolated product via NMR spectroscopy.

Scheme 18: Proposed Mechanism for double decarbonylation of ethyl chlorooxoacetate

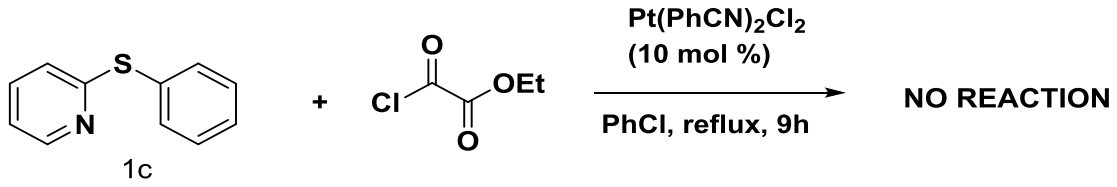


4.2 Sulfur vs Oxygen – the best linker atom

Under optimized reaction conditions, ligand **1c** and ligand **10** were subjected to the acylation reaction with ethylchlorooxoacetate. Both reactions were heated to reflux under anhydrous conditions and carried out using 10% cis-$Pt(PhCN)_2Cl_2$ along with chlorobenzene as the solvent and tetradecane as an internal standard for GC analysis. The reaction of **1c** (**scheme 19**) was

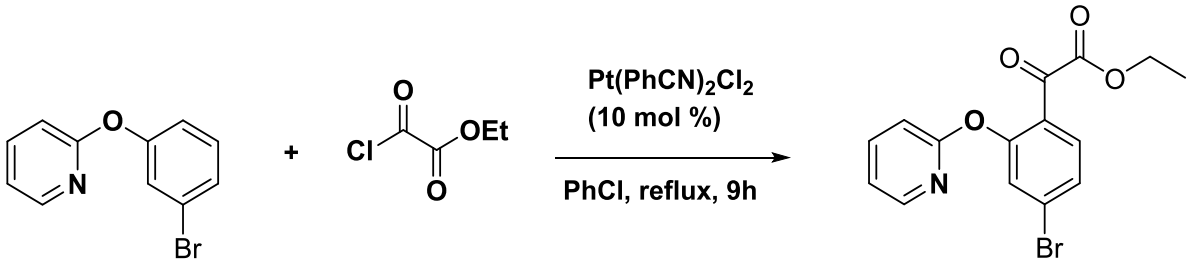
checked on TLC and GC after one hour, no product formation was detected. It was further monitored periodically for the next 4 h, however the reaction didn't seem to proceed and was eventually stopped.

Scheme 19 Reaction of 1c with ethyl chlorooxoacetate



On the contrary, the reaction of the substrate with an oxygen atom (**10**) proceeded smoothly and had almost all of the starting material converted to the desired product within the initial h only. (**Scheme 14**) Despite the completion of the reaction, it was further monitored on TLC and GC periodically for an additional 5 h. within the first 3 h. not much difference in the GC chromatograms were observed. The reaction was very clean with GC analysis of the crude reaction mixture only showing the product peak and a very small amount of starting material peak along with some solvent peaks. However, after 3 h., slight degradation of the product peak was observed and the reaction mixture gradually changed colors from deep yellow to almost tar like blackish brown. A significant decrease in the product peak was observed after 6 h. The degradation of the reaction might be associated with the degradation of the Pt catalyst, reducing from Pt (II) to Pt (0).

Scheme 20 Reaction of 10 with ethyl chlorooxoacetate

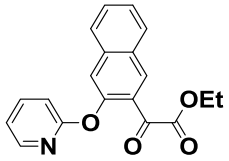
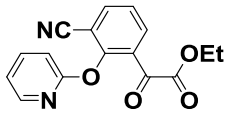
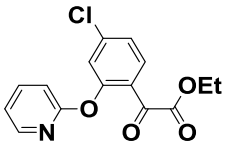
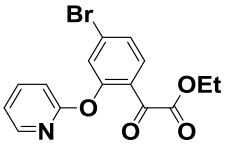


4.3 Formation of Monoacylated Alpha-ketoester Compounds

Under previously optimized reaction conditions, ligand **1** was reacted with ethylchlorooxoacetate for the synthesis of **1a**. (**Scheme 20**) As mentioned above, the reaction proceeded smoothly, with no side reaction, and was completed within 2 h. Despite the reaction proceeding smoothly and looking clean on GC, the product was isolated in poor yield of 56.0%. Similarly, compounds **5**, **10** and **14** all had undesirable yields when reacted with ethylchlorooxoacetate, despite GC analysis showing otherwise. This issue was closely examined and remedied to improve the percent yield of the acylated complexes.

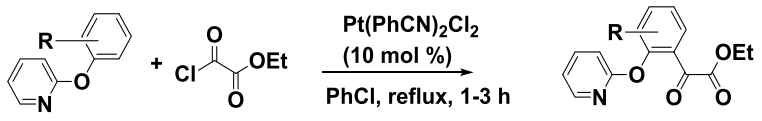
Upon making vigilant observations and extensively analyzing the reaction mixture, the low recovery was attributed to the platinum complex coordinating with some of the product and making it immobile during column chromatography. After isolating and evaluating the silica from the column it was confirmed that the product was indeed coordinated to the catalyst. The coordination between the two is likely due to the interaction between sp^2 lone pair electrons of nitro group on the product and the platinum complex. In an attempt to release the product from platinum, pyridine was employed to facilitate with ligand exchange. It was found that, after the completion, treating the acylation reaction mixture with **1** equivalent of pyridine prior to the aqueous workup increased the yield by about 20 %. (**Table 7**)

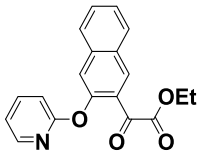
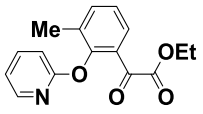
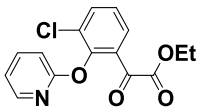
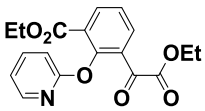
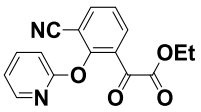
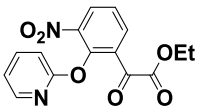
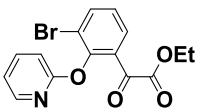
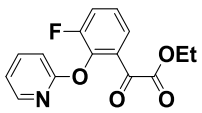
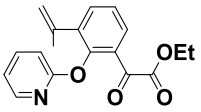
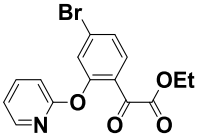
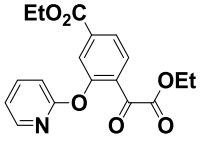
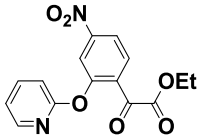
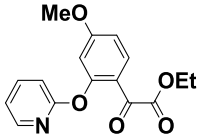
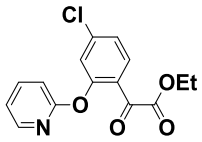
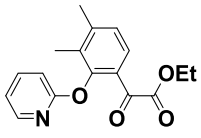
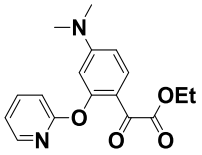
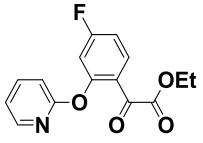
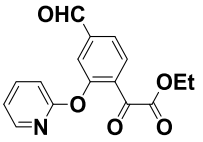
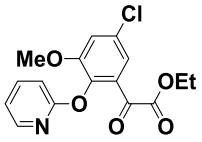
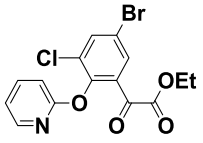
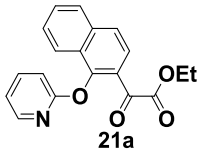
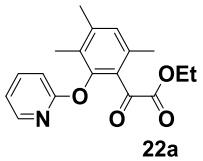
Table 7: Percent Yield comparison of 1a, 5a, 15a, and 10a when prepared using procedure B (without pyridine) vs. procedure C (with pyridine)

	Procedure B	Procedure C
	56.0%	76.4%
	58.4%	84.2%
	51.5%	76.7%
	66.7%	86.1%

The formation of monoacylated alpha-ketoester was examined based on the electron-richness of 2-aryloxypyridine with substituents ranging from strongly electron-donating group to strongly electron-withdrawing group. The general scheme for these syntheses, along with their respective yields, is reported in **Table 8**. Most of the products were synthesized in satisfactory yields except for a few, namely compounds **7a**, **8a**, **9a**, **12a**, **16a**, **17a**, and **22a**. For all other compounds, the acylation reaction was not significantly affected by the difference in electron-richness of the phenyl ring, and were isolated in high yields (**Table 9**).

Table 8. Acylation of ortho/meta substituted ligands



 1a 76%	 2a 75%	 3a 87%	 4a 75%
 5a 84%	 6a 80%	 7a 0%	 8a 0%
 9a 0%	 10a 86%	 11a 47%	 12a 0%
 13a 84%	 14a 77%	 15a 71%	 16a 0%
 17a 0%	 18a 0%	 19a 84%	 20a 75%
 21a 78%	 22a 0%		

For ortho-substituted 2-phenoxypyridine **4** (with an ester group) and **6** (with nitro group), alpha-ketoester was introduced on the ortho position to give monoacylated alpha-ketoester **4a** and **6a** with 75% and 80% yield, respectively. However, when meta substituted 2-phenoxypyridine **11** (with an ester group) and **12** (with nitro group) were utilized a sharp contrast in the results was observed. While reaction with **11** produced **11a** with a poor yield of 47%, reaction with **12** retarded the reaction, and no product was formed. This indicated that electronic effect of the meta-substituents are more pronounced than that of ortho-substituents of the aryloxypyridines.

It is important to note the varied results of the acylation reactions of 2-phenoxypyridine with halogens at the position ortho to the linker group, namely **3** (Cl), **7** (Br), and **8** (F), as well as at the position meta to the linker group, namely **14** (Cl), **10** (Br), and **17** (F). Compound **3** was mostly converted to **3a** after only one hour and was isolated with 87% yield. When the chloro group was replaced with bromo (**7**) and fluoro (**8**) group, no formation of the acylated complexes was observed. Similarly when compound **17** (meta substituted fluoro group) was subjected to the acylation reaction, no product formation was observed. However when the fluoro group was replaced with bromo (**10**) and chloro (**14**) groups at the meta position, a clean and smooth acylation reaction was observed with high isolated yields of 86% and 77%, respectively. This data suggests that electronic effects of compounds with a bromo or fluoro group are more pronounced than of compounds with a chloro group, particularly at the ortho position. However, since meta-bromo substituted compound **10** reacted to give compound **10a** in good yield, there may be other causes associated with the inactivity of ortho-bromo substituted compound **7** towards the catalytic acylation reaction. Additionally, the poor reaction with fluoro group can also be attributed the so called “fluorine effect”. Despite fluorine being the most electronegative atom, its atomic size is the same as the size of a hydrogen atom. This similarity in size allows for a convenient replacement

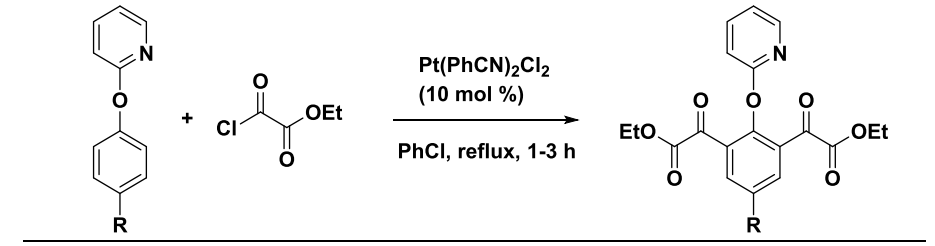
by fluorine of virtually any hydrogen atom in organic molecules without causing any significant steric effects. However, this causes organic molecules to be highly stable and inert. The high electronegativity of fluorine causes profound changes in the electronic structure and properties of organofluorine compounds, preventing the acylation from occurring, as can be seen with compounds **8** and **17**.

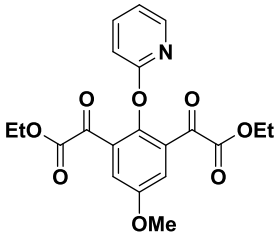
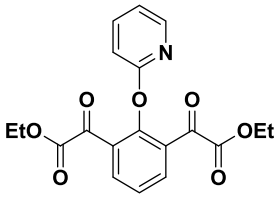
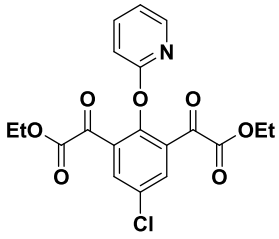
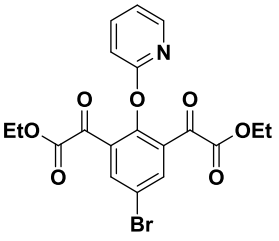
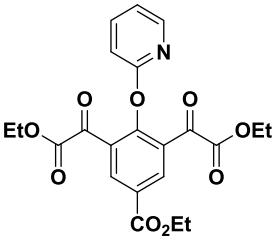
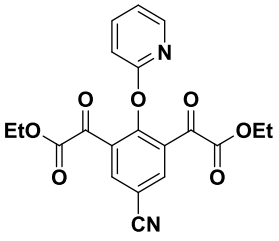
Substrates with multiple substituents, namely **15**, **19**, **20**, and **2**1 all participated in the acylation reaction to give the desired product in high yields (**15a**, **19a**, **20a**, and **21a**). The reaction of 2-(2,3,5-Trimethylphenoxy)pyridine (**22**) however did not produce the acylation product **22a** (0% yield), clearly indicating that the meta-substituent prevents the acylation from occurring at its adjacent ortho position of the phenyl ring due to steric effects.

4.4 Formation of Diacylated Alpha-ketoester Compounds

Acylation of para-substituted phenoxypyridine was interesting as it allowed for double acylation. Except for **28**, all other para substituted ligands participated in the acylation reaction and the desired double acylated products were isolated in high yields (**table 9**). It should be noted that while the formation of monoacylated product was detected on GC, the reaction conditions seemed to favor the conversion of the mono-acylated product to the di-acylated product, therefore isolation of only diacylated product was possible.

Table 9 Acylation of para substituted ligands



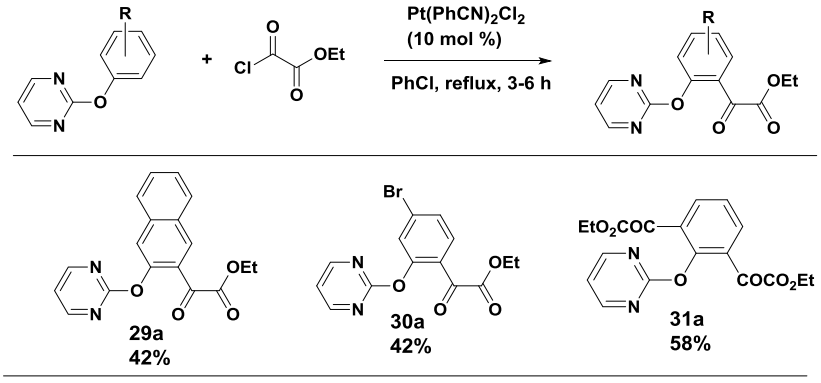
		
23a **68%**	**24a** **87%**	**25a,** **69%**
		
26a **87%**	**27a** **65%**	**28a** **0%**

Para-substituted compounds with substituent including methoxy, chloro, bromo, and ester groups were are tolerated in the double acylation reaction. However, more strongly electron-withdrawing cyano group (**28**) prohibited the reaction. In this case, neither double nor mono acylation reaction was observed. This is in sharp contrast with the acylation of ortho-substituted 2-phenoxypyridines in which both cyano-substituted and nitro-substituted substrates **5** and **6** underwent acylation smoothly to give the desired alpha-ketoester **5a** and **6a** in high yields. This may be due to the ortho-substituents not exerting efficient electronic effect, particularly resonance effect.

4.5 Acylation Reaction with Heteroaryl ethers

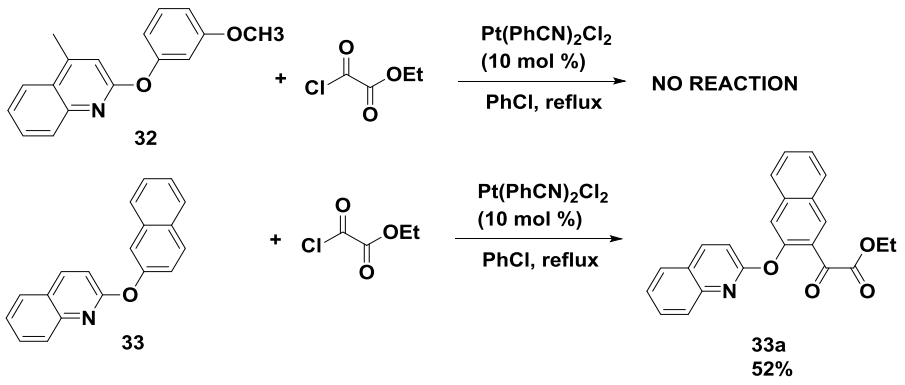
To further expand the scope of the acylation reaction, other heteroaryl aryl ethers, namely pyrimidine and quinoline were explored. The reaction proceeded smoothly in the first two hours, then became extremely sluggish. Despite the low yields, ligands **29-31** all proceeded to react with ethylchlorooxoacetate. (**Table 10**) As expected substrate **31** reacted to give a diacylated alpha-ketoester **31a.** It is possible that the low yield is due to presence of two coordinating nitrogen atoms on the substrate. According to GC analysis, no product formation was observed after 2 h. Since no change in the starting material peak was observed, it can be assumed that the platinum catalyst coordinated with the starting material, prohibiting the acylation reaction from proceeding.

Table 10 Acylation of substrates with pyrimidine moiety



Not all quinoline substrates successfully reacted with ethyl chlorooxoacetate. (**Scheme 21**) While ligand **33** reacted to give **33a** in poor yield of 52% ligand **32** showed no reaction at all. The failed reaction with ligand **32** can be attributed to the steric effects of the methyl and methoxy group on the substrate. Similarly the low yield of **33a** can be attributed to steric effects.

Scheme 21 Acylation reaction with quinoline substrates



4.6 Competing Reaction

A competing reaction was setup to determine the electronic effects of withdrawing groups and donating groups as substituents on phenoxypyridine. In order to directly compare their reactivity, equal molar amounts of **2b** (with a Me group) and **2f** (with a NO_2 group) were combined in the same reaction vessel and reacted with ethyl chlorooxoacetate in the presence of Pt catalyst and chlorobenzene as the solvent (**scheme 22**). As seen in **figure 4 2b** and **2f** were formed in 1.8:1 ratio with a combined yield of 40%. This data gathered clearly suggests that electron donating substituents accelerate the acylation reaction, while electron withdrawing substituents decelerate the reaction.

Scheme 22. Competing reaction of 2b (with a Me group) and 2f (with a NO_2 group)

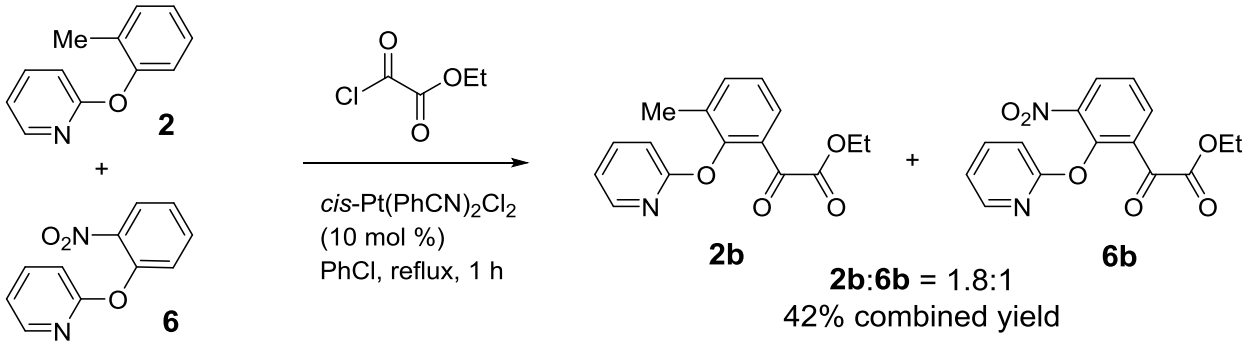
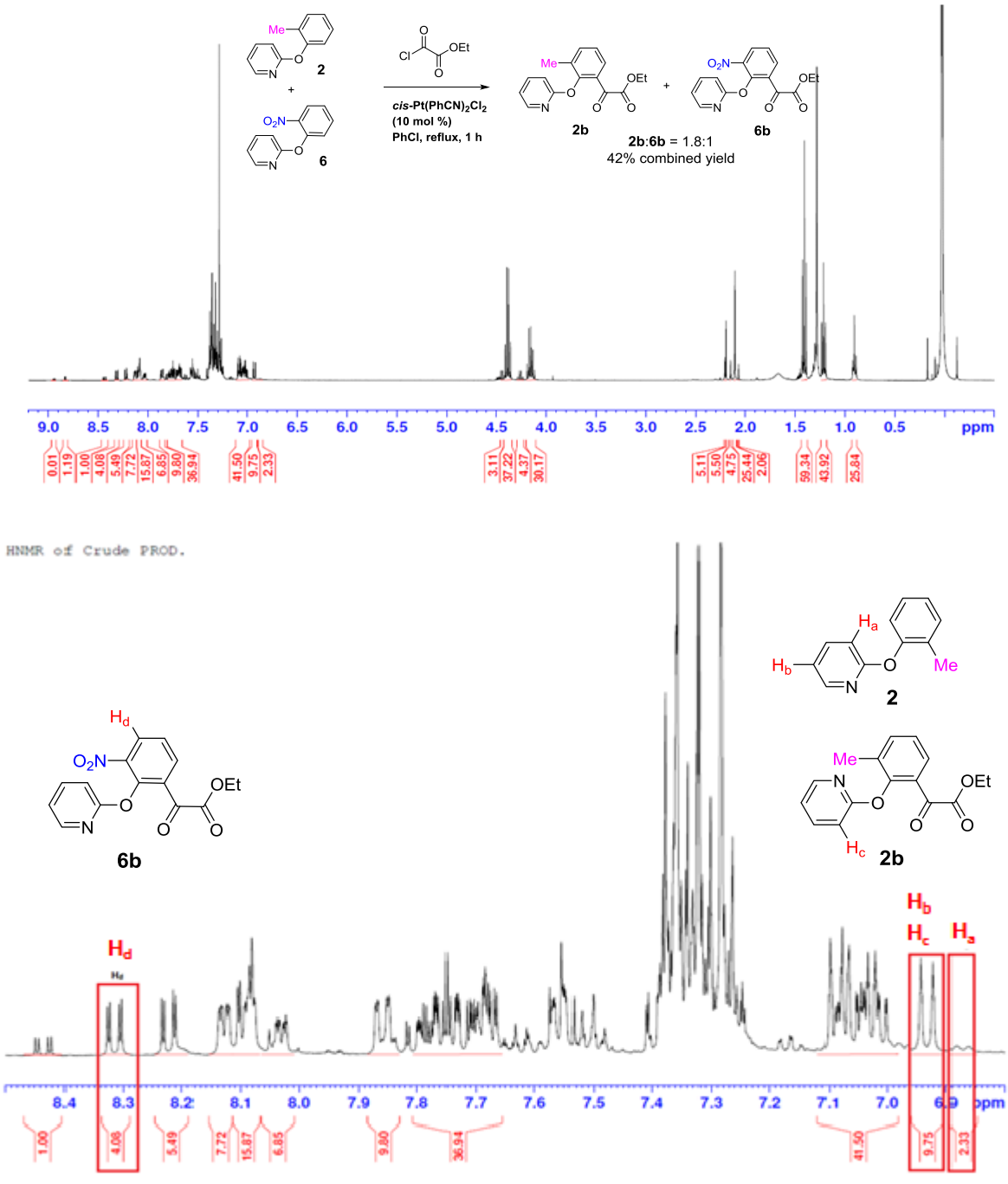


Fig. 4 ^{1}H NMR spectra of the competing reaction



4.7 Experimental

Condition optimization using 1 as the substrate

A 50 mL, three-necked round-bottom flask with a condenser was dried and purged with argon, and then charged with 2-(naphthalen-2-yloxy)pyridine (**1**, 111.0 mg, 0.5 mmol), cis-$Pt(PhCN)_2Cl_2$ (23.6 mg, 0.05 mmol), ethylchlorooxoacetate (0.17 ml, 1.5 mmol), tetradecane (65.0 μL) and anhydrous chlorobenzene (2 mL). A drying tube was placed on the top of the condenser and the mixture was stirred and heated at reflux. An aliquot of the reaction mixture was quenched with H_2O and extracted with dichloromethane for GC analysis. The conversion was calculated based on the ratio of **1** and the internal standard at the time the reaction mixture was analyzed and the ratio of **1** and internal standard measured before the reaction was started (zero time of the reaction). The results were summarized in **Table 5**.

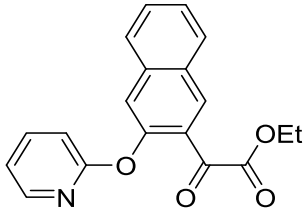
General Procedures for the Pt-catalyzed acylation reaction

General Procedure B: A 50 mL, three-necked round-bottom flask with a condenser was dried and purged with argon, and then charged with 2-(naphthalen-2-yloxy)pyridine (221.5 mg, 1 mmol), *cis*-$Pt(PhCN)_2Cl_2$ (47.3 mg, 0.1 mmol), ethylchlorooxoacetate (0.34 ml, 3 mmol), tetradecane (65.0 μL) and anhydrous chlorobenzene (4 mL). A drying tube was placed on the top of the condenser and the mixture was stirred and heated at reflux for 1 h. The mixture was cooled and quenched with H_2O (20 ml). In a separate 10 mL beaker sodium carbonate (423.9 mg, 4 mmol) was dissolved in H_2O (6 ml) and added drop wise to the reaction mixture. The mixture was stirred for 1 hour. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic phase was separated, dried under Na_2SO_4, filtered, and concentrated via rotary evaporator. The product

was isolated and purified via column chromatography on silica gel with hexanes-ethyl acetate (3:1) as the eluting solvent, yellow solid, 180.2 mg, 56%.

General Procedure C: A 50 mL, three-necked round-bottom flask with a condenser was dried and purged with argon, and then charged with 2-(naphthalen-2-yloxy)pyridine (221.5 mg, 1 mmol), *cis*-$Pt(PhCN)_2Cl_2$ (47.4 mg, 0.1 mmol), ethylchlorooxoacetate (0.34 ml, 3 mmol), tetradecane (65.0 μL) and anhydrous chlorobenzene (4 mL). A drying tube was placed on the top of the condenser and the mixture was stirred and heated at reflux for 1 h. The temperature was lowered to 100 °C and pyridine (1.0 ml) was added dropwise to the reaction mixture. After being stirred for 1 hour, the mixture was filtered through a pad of celite. The filtrate was transferred to a 250 ml separatory funnel, H_2O (20 ml) was added, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The organic layers were combined, dried over Na_2SO_4, filtered, and concentrated via rotary evaporator. The product was isolated and purified via column chromatography on silica gel with hexanes-ethyl acetate (3:1) as the eluting solvent, yellow solid, 245.5 mg, 76.4%.

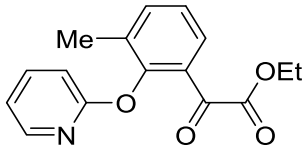
The following compounds were prepared according to General Procedure C.



1a

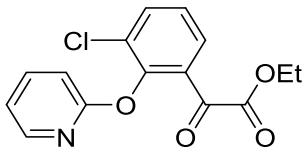
*Synthesis of **1a.*** Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 3:1): yellow solid, 76.4% yield. Melting point: 76-77.0 °C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.57

(s, 1H), 8.22 (dd, *J* = 5.0, 1.7 Hz, 1H), 8.00 (d, *J* = 8.1, 1H), 7.82-7.75 (m, 2H), 7.64-7.59 (m, 2H), 7.56-7.50 (m, 1H), 7.12-7.07 (m, 1H), 7.01(d, *J* = 8.2, 1H), 4.19(q, *J* = 7.1 Hz, 2H), 1.21 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 186.1, 164.2, 162.9, 149.9, 147.7, 139.8, 136.8, 133.4, 130.1, 129.7, 129.5, 127.4, 126.4, 126.3, 119.4, 118.9, 112.0, 62.2, 13.9. **MS** Calculated for $C_{19}H_{16}NO_4$ ($M+H^+$) 322.1; Found: 322.3. **Anal**. Calculated for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found C, 71.08; H, 4.87; N, 4.32.



2a

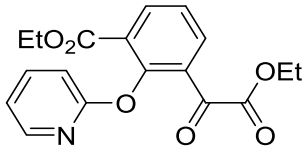
*Synthesis of **2a***. Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow oil, 74.5% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.13 (dd, *J* = 6.3, 2.5 Hz, 1H), 7.86 (dd, *J* = 6.8, 4.0 Hz, 1H), 7.77-7.71 (m, 1H), 7.56 (dd, *J* = 6.6, 1.0 Hz, 1H), 7.36-7.29 (m, 1H), 7.04-6.99 (m, 1H), 6.93 (d, *J* = 9.0 Hz, 1H), 4.16 (q, *J* = 7.8 Hz, 2H), 2.1 (s, 3H), 1.21 (t, *J* = 8.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 164.5, 162.7, 152.1, 147.6, 139.7, 137.6, 132.6, 128.7, 127.92, 125.8, 118.7, 110.6, 62.0, 16.6, 13.9. **MS** Calculated for $C_{16}H_{16}NO_4$ ($M+H^+$) 286.1; Found: 286.1. **Anal.** Calculated for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found C, 67.08; H, 5.31; N, 4.83.



3a

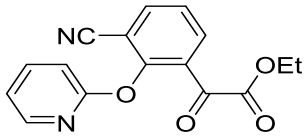
*Synthesis of **3a***. Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 3:1): yellow oil, 87.0% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.01 (dd, *J* = 5.0, 2.0 Hz, 3H),

7.83 (dd, *J* = 7.9, 1.5 Hz, 2H), 7.70-7.61 (m, 2H), 7.28 (t, *J* = 8.0 Hz, 1H), 6.98-6.89 (m, 2H), 4.06 (q, *J* = 7.2 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 1H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.1, 162.8, 161.2, 149.0, 146.3, 138.8, 135.8, 128.8, 128.2, 128.1, 125.5, 118.3, 109.9, 61.2, 12.8. **MS** Calculated for $C_{15}H_{12}ClNO_4$ ($M+H^+$) 306.1; Found: 306.0. **Anal.** Calculated for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; N, 4.58. Found C, 58.94; H, 4.11; N, 4.51.



4a

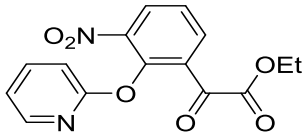
*Synthesis of **4a***. Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 2:1): clear oil, 74.8% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.26 (dd, *J* = 8.0, 4.0 Hz, 1H), 8.15 (dd, *J* = 6.4, 2.56 Hz, 1H), 8.08-8.08 (m, 1H), 7.79-7.73 (m, 1H), 7.48 (t, *J* = 7.7 Hz, 1H), 7.05-6.98 (m, 2H), 4.14-4.02 (m, 4H), 1.19 (t, *J* = 7.4 Hz, 3H), 1.06 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.0, 164.5, 163.8, 163.0, 152.5, 147.0, 139.6, 137.3, 134.5, 129.3, 126.2, 125.5, 118.9, 111.1, 62.1, 61.3, 13.8. **MS** Calculated for $C_{18}H_{18}NO_6$ ($M+H^+$) 344.1; Found: 344.1. **Anal.** Calculated for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found C, 62.73; H, 5.17; N, 4.22.



5a

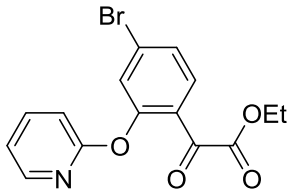
*Synthesis of **5a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 2:1): yellow solid, 84.2% yield. Melting point: 71-73°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.21 (dd, *J* = 6.5, 3.5 Hz, 1H), 8.12 (dd, *J* = 7.2, 3.2Hz, 1H), 7.95 (dd, *J* = 7.9, 4.0 Hz, 1H), 7.81 (td, *J*

= 7.0, 3.2 Hz, 1H), 7.51 (t, *J* = 8.5 Hz, 1H), 7.16-7.09 (m, 2H), 4.17 (q, *J* = 7.9 Hz, 2H), 1.22 (t, *J* = 7.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.6, 163.1, 161.9, 155.2, 147.1, 140.4, 138.7, 135.0, 129.4, 126.0, 120.3, 114.6, 111.5, 109.5, 62.5, 13.9. **MS** Calculated for $C_{16}H_{13}N_2O_4$ ($M+H^+$) 297.1; Found: 297.1. **Anal.** Calculated for $C_{16}H_{12}N_2O_4$: C, 64.86; H, 4.08; N, 9.46. Found C, 64.56; H, 4.29; N, 9.36.



6a

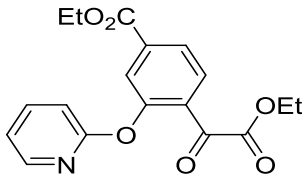
*Synthesis of **6a.*** Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): white solid, 79.5% yield. Melting point: 75-77°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.31 (dd, *J* = 9.2, 1.0 Hz, 1H), 8.22 (dd, *J* = 7.5 Hz, 0.4 Hz, 1H), 8.03 (dd, *J* = 6.7 , 1.5 Hz, 1H), 7.83-7.76 (m, 1H), 7.55 (t, *J* = 8.6 Hz, 1H), 7.11-7.03 (m, 2H), 4.13 (q, *J* = 7.8 Hz, 2H), 1.21 (t, *J* = 7.9 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.7, 163.0, 161.1, 147.0, 146.4, 143.2, 140.3, 135.5, 130.8, 130.6, 125.7, 120.0, 111.1, 62.5, 13.9. MS Calculated for $C_{15}H_{12}N_2O_6$ ($M+H^+$) 317.1; Found: 317.2. **Anal**. Calculated for $C_{15}H_{12}N_2O_6$: C, 56.97; H, 3.82; N, 8.86. Found C, 56.78; H, 3.82; N, 8.86.



10a

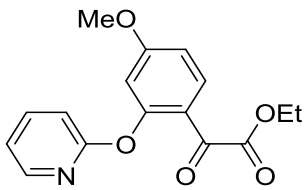
*Synthesis of **10a.*** Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): white solid, 86.1 % yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (s, 1H), 7.88 (d, *J* =

8.1 Hz, 1H), 7.79 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 6.8, 1.8 Hz, 1H), 7.39 (d, *J* = 1.2 Hz, 1H), 7.13 (t, *J* = 6.1 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 4.13 (q, *J* = 7.2 Hz, 2H), 1.17 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.1, 164.0, 161.5, 154.7, 147.7, 140.1, 131.6, 129.6, 128.4, 125.1, 125.3, 120.2, 112.1, 62.1, 13.7. **MS** Calculated for $C_{15}H_{13}BrNO_4$ ($M+H^+$) 350.0, 352.0; Found: 350.1; 352.1. **Anal.** Calculated for $C_{15}H_{12}BrNO_4$: C, 51.45; H, 3.45; N, 4.00. Found C, 51.71; H, 3.42; N, 4.11.



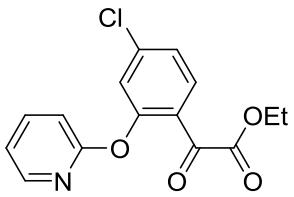
11a

*Synthesis of **11a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): light orange oil, 47.4% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.25 (dd, *J* = 5.2, 3.6 Hz, 1H), 8.05-7.96 (m, 2H), 7.89-7.87 (m, 1H), 7.79 (dd, *J* = 8.7, 3.1 Hz, 1H), 7.12 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 1H) ,4.41 (q, *J* = 7.3, 2H), 4.16 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.3 Hz, 3H), 1.14 (t, *J* = 7.5 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 185.6, 164.5, 163.7, 162.1, 154.2, 147.7, 140.0, 136.6, 130.7, 129.9, 125.6, 123.5, 119.9, 112.0, 62.2, 61.8, 14.3, 13.8. **MS** Calculated for $C_{18}H_{18}NO_6$ ($M+H^+$) 344.1; Found: 344.1. **Anal**. Calculated for $C_{18}H_{17}NO_6$: C, 62.97; H, 4.99; N, 4.08. Found C, 63.16; H, 5.16; N, 4.02.



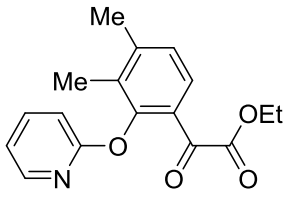
13a

*Synthesis of **13a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 2:1): brown oil, 83.8% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.24 (dd, J = 3.2, 1.8 Hz, 1H), 8.02 (d, J = 8.8 Hz, 1H), 7.80-7.73 (m, 1H), 7.12-7.07 (m, 1H), 6.99 (d, J = 8.3 Hz, 1H), 6.87 (dd, J = 6.5, 2.0 Hz, 1H), 6.65 (d, J = 2.4 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.85 (s, 3H), 1.17 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 184.7, 165.8, 165.3, 162.4, 156.8, 147.9, 139.9, 132.6, 119.7, 119.2, 112.2, 111.7, 107.0, 61.8, 55.8, 13.9. **MS** Calculated for $C_{16}H_{16}NO_5$ ($M+H^+$) 302.1; Found: 302.1. **Anal**. Calculated for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found C, 63.66; H, 5.15; N, 4.68.



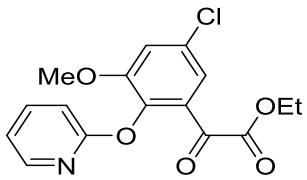
14a

*Synthesis of **14a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): white solid, 76.7% yield. Melting point: 51-53°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.25 (dd, J = 5.0, 2.0 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.83-7.77 (m, 1H), 7.33 (dd, J = 8.6, 1.9 Hz, 1H), 7.24 (d, J = 1.9 Hz, 1H), 7.17-7.12 (m, 1H), 7.00 (d, J = 8.4 Hz, 1H), 4.16 (q, J = 7.2 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 185.0, 164.2, 161.8, 154.9, 147.9, 141.4, 140.2, 131.7, 125.6, 124.8, 122.5, 120.3, 112.0, 62.1, 13.90. **MS** Calculated for $C_{15}H_{13}ClNO_4$ ($M+H^+$) 306.1; Found: 306.0. **Anal**. Calculated for $C_{15}H_{12}ClNO_4$: C, 58.93; H, 3.96; N, 4.58. Found C, 58.82; H, 4.10; N, 4.52.



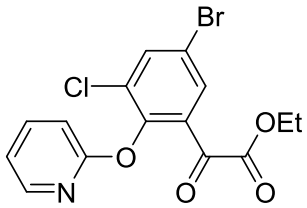
15a

*Synthesis of **15a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 3:1): clear oil, 70.8% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23-8.20 (m, 1H), 7.79-7.72 (m, 2H), 7.08-7.04 (m, 1H), 6.97-6.93 (m, 2H), 4.13 (q, *J* = 7.5 Hz, 2H), 2.32 (s, 6H), 1.16 (t, *J* = 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 185.9, 165.0, 162.7, 152.6, 147.8, 146.3, 139.7, 134.0, 131.2, 123.8, 123.3, 119.4, 111.8, 61.8, 20.6, 19.1, 13.9. **MS** Calculated for $C_{17}H_{18}NO_4$ ($M+H^+$) 300.1; Found: 300.3. **Anal**. Calculated for $C_{17}H_{17}NO_4$: C, 68.22; H, 5.72; N, 4.68. Found C, 68.29; H, 5.68; N, 4.68.



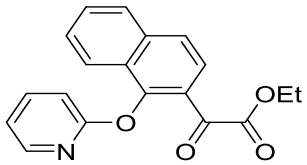
19a

*Synthesis of **19a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 2:1): brown oil, 83.8% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.14-8.10 (m, 1H), 7.76-7.70 (m, 1H), 7.56 (d, *J* = 5.3 Hz, 1H), 7.20 (d, *J* = 5.1 Hz, 1H), 7.06-7.02 (m, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 185.0, 163.8, 162.4, 152.8, 147.3, 142.3, 139.5, 131.7, 129.0, 121.0, 119.1, 118.6, 110.5, 62.2, 56.5, 13.8. **MS** Calculated for $C_{16}H_{15}ClNO_5$ ($M+H^+$) 336.1; Found: 336.0. **Anal**. Calculated for $C_{16}H_{14}ClNO_5$: C, 57.24; H, 4.20; N, 4.17. Found C, 57.26; H, 4.38; N, 4.15.



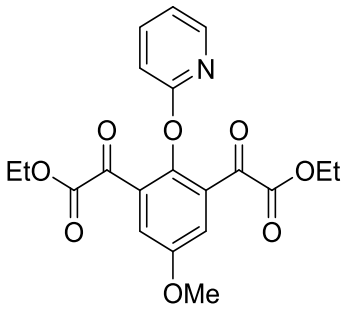
20a

*Synthesis of **20a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow solid, 75.1% yield. Melting point: 74-76°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.13-8.07 (m, 1H), 8.02 (d, J = 2.4 Hz, 1H) 7.86 (d, J = 1.0 Hz, 1H), 7.81-7.75 (m, 1H), 7.11-7.00 (m, 2H), 4.17 (q, J = 7.2 Hz, 2H), 1.21 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 183.8, 163.1, 161.8, 149.1, 147.3, 140.0, 138.3, 131.8, 131.0, 130.4, 119.6, 119.0, 110.9, 62.4, 14.0. **MS** Calculated for $C_{15}H_{12}BrClNO_4$ ($M+H^+$) 384.0, 386.0; Found: 384.2, 386.2. **Anal.** Calculated for $C_{15}H_{11}BrClNO_4$: C, 46.84; H, 2.88; N, 3.64. Found C, 47.10; H, 2.84; N, 3.68.



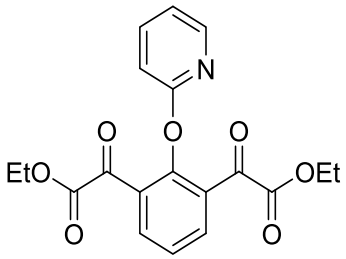
21a

*Synthesis of **21a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow solid, 78.0% yield. Melting point: 120-122°C. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.09-8.02 (m, 2H), 7.93 (d, J = 4.2 Hz, 1H), 7.89-7.80 (m, 2H), 7.79-7.74 (m, 1H), 7.66-7.60 (m,1H), 7.46 (td, J = 7.2, 1.1 Hz, 1H), 7.07-7.01 (m, 2H), 4.22 (q, J = 7.1 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 186.3, 164.7, 169.0, 152.4, 147.8, 139.8, 137.0, 129.4, 128.4, 127.3, 127.1, 126.3, 124.6, 124.0, 123.7, 119.1, 110.5, 62.1, 13.9. **MS** Calculated for $C_{19}H_{16}NO_4$ ($M+H^+$) 322.2; Found: 322.1. **Anal.** Calculated for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found C, 70.58; H, 4.69; N, 4.33.



23a

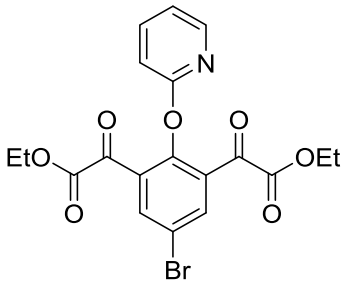
*Synthesis of **23a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow oil, 69.9% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 5.2, 1.8 Hz, 1H), 7.77-7.71 (m, 1H), 7.67 (s, 2H), 7.06-7.02 (m, 1H), 6.92 (d, *J* = 8.3 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 4H), 3.94 (s, 3H), 1.23 (t, J = 7.2, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 184.6, 162.8, 162.4 156.7, 146.8, 145.6, 140.0, 130.0, 120.8, 119.7, 111.1, 62.5, 56.2, 13.9. **MS** Calculated for $C_{20}H_{20}NO_8$ ($M+H^+$) 402.1; Found: 402.2. **Anal.** Calculated for $C_{20}H_{19}NO_8$: C, 59.85; H, 4.77; N, 3.49. Found C, 60.11; H, 5.03; N, 3.43.



24a

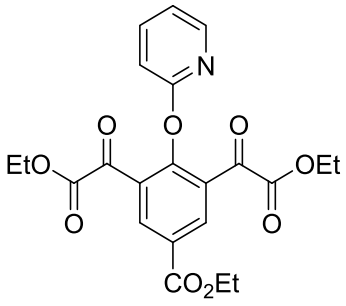
*Synthesis of **24a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow oil, 86.6% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 7.7 Hz, 2H), 8.04 (dd, *J* = 5.1, 2.2 Hz, 1H),7.80-7.73 (m, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.09-7.04 (m, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 4.17 (q, *J* = 7.2, 4H), 1.23 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 184.6, 162.7, 161.9, 152.0, 149.8, 146.9, 140.2, 136.0, 129.1, 125.7, 123.9, 114.9, 111.2, 62.5, 13.8. MS

Calculated for $C_{19}H_{18}NO_7$ ($M+H^+$) 372.1; Found: 372.1. **Anal**. Calculated for $C_{19}H_{17}NO_7$: C, 61.45; H, 4.61; N, 3.77. Found C, 61.31; H, 4.67; N, 3.68.



26a

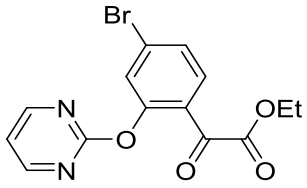
*Synthesis of **26a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1): yellow oil, 86.6% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.23 (s, 2H), 8.03 (d, *J* = 5.08 Hz, 1H), 7.77 (t, *J* = 7.1 Hz, 1H), 7.09 (t, *J* = 6.1 Hz, 1H), 6.94 (d, J = 8.3, 1H), 4.18 (q, J = 7.1 Hz, 4H), 1.21 (t, J = 7.1 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 183.1, 162.1, 161.3, 150.4, 146.7, 140.4, 138.1, 130.8, 120.1, 118.9, 111.1, 62.6, 13.9. **MS** Calculated for $C_{19}H_{17}BrNO_7$ ($M+H^+$) 450.0, 452.0; Found: 450.0, 452.0. **Anal**. Calculated for $C_{19}H_{16}BrNO_7$: C, 50.69; H, 3.58; N, 3.11. Found C, 50.88; H, 3.65; N, 3.15.



27a

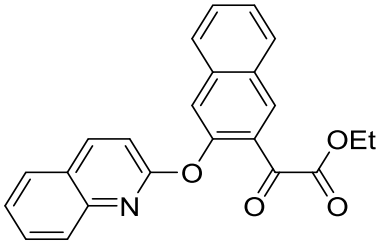
*Synthesis of **27a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 2:1): yellow oil, 65.0% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.81-8.74 (m, 2H), 8.02 (dd, *J* = 5.0, 1.9 Hz, 1H), 7.82-7.75 (m,1H), 7.12-7.07 (m, 1H), 6.98 (d, *J* = 8.3 Hz, 1H), 4.54-4.40 (m,

2H), 4.18 (q, *J* = 7.2 Hz, 4H), 1.50-1.40 (m, 4H), 1.24 (t, *J* = 7.2 Hz, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 183.8, 164.0, 162.2, 161.3, 154.5, 146.7, 140.5, 136.5, 129.5, 128.2, 120.3, 111.2, 62.6, 61.9, 14.3, 13.8. **MS** Calculated for $C_{22}H_{21}NO_9$: (M+H+): 443.12; Found: 444.13. **MS** Calculated for $C_{22}H_{22}NO_9$ ($M+H^+$) 444.1; Found: 444.1. **Anal**. Calculated for $C_{22}H_{21}NO_9$: C, 59.59; H, 4.77; N, 3.16. Found C, 58.74; H, 4.83; N, 3.18.



30a

*Synthesis of **30a**.* Purified via column chromatography on silica gel with DCM-hexanes (v/v = 10:1): yellow solid, 41.5% yield. Melting point: 56-58°C. **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* 8.61 (d, *J* = 4.8 Hz, 2H), 7.91 (d, *J* = 8.4 Hz, 1H), 7.60-7.55 (m, 1H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.15 (t, *J* = 4.8 Hz, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 184.7, 164.4, 163.8, 159.8, 153.2, 132.0, 129.9, 129.6, 127.0, 125.5, 117.4, 62.6, 14.0. **MS** Calculated for $C_{14}H_{12}BrN_2O_4$ ($M+H^+$) 351.0, 353.0; Found: 351.0, 353.0. **Anal.** Calculated for $C_{14}H_{11}BrN_2O_4$: C, 47.89; H, 3.16; N, 7.98. Found C, 48.12; H, 3.35; N, 7.81



32a

*Synthesis of **32a**.* Purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 2:1): yellow oil, 52.4% yield. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.58 (s, 1H), 8.21 (d, *J* = 8.6 Hz, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.86-7.74 (m, 4H), 7.68-7.61 (m, 2H), 7.60-7.54 (m, 1H), 7.50-7.45 (m, 1H), 7.19 (d, *J* = 8.8 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.15 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) *δ* 185.8, 163.9, 160.8, 149.3, 146.1, 140.2, 136.7, 133.2), 130.2, 130.1, 129.7, 129.4, 127.9, 127.5, 127.4, 126.8, 126.4, 126.0, 125.3, 119.4, 112.6, 62.2, 13.8. MS Calculated for $C_{23}H_{18}NO_4$ ($M+H^+$) 372.1; Found: 372.3. **Anal.** Calculated for $C_{23}H_{17}NO_4$: C, 74.38; H, 4.61; N, 3.77. Found C, 74.17; H, 4.69; N, 3.75.

Experimental for competing reaction

A 50 mL, three-necked round-bottom flask with a condenser was purged with $Ar_{(g)}$ and then charged with **2** (92.9 mg, 0.5 mmol), **6** (107.9 mg, 0.5 mmol), *cis*-$Pt(PhCN)_2Cl_2$ (48.0 mg, 0.1 mmol), ethyl chlorooxoacetate (0.34 ml, 3 mmol), tetradecane (65.0 μL) and anhydrous chlorobenzene (6.0 mL). A drying tube was placed on the top of the condenser and the mixture was then stirred and heated at reflux for 1 h. The temperature was lowered to 100 °C and pyridine (1.0 ml) was added dropwise. After stirring it for 30 min, the mixture was quenched with H_2O (30 ml) and extracted with ethyl acetate (3 x 20 mL). The combined organic solution was washed with water (3 x 20 mL) and brine (1 x 20 ml), dried over Na_2SO_4, and concentrated via rotary evaporator. The crude residue was analyzed by 1H NMR. Which indicated that the ratio of **2b**:**6b** is 1.8:1 (see **Figure S25**). The crude product was purified via column chromatography on silica gel with hexanes-ethyl acetate (v/v = 4:1). The fractions containing both products were combined and solvent was evaporated using rotary evaporator, yellow oil, 121.2 mg, with a combined isolated yield of 42%.

CHAPTER 5: MECHANISTIC INSIGHTS

5.1 Insights gathered from general reactions

During the determination of the scope of the acylation reaction several significant observations were notable. Acylation was consistently observed at the position ortho to the oxygen linker atom. As observed in the reaction of **22**, if the ortho position was occupied or sterically hindered, no acylation reaction was observed. The effect caused by electron-richness of the phenyl group on the acylation reaction was also noteworthy. The low conversion of **11** and failed acylation reaction with compounds **12** and **18** suggest the electron-withdrawing effect on the phenyl ring of 2-phenoxypyridine, particularly on the ortho carbons. Furthermore, the competing reaction of **2b** and **2f** clearly demonstrates that electron withdrawing group decelerates the acylation reaction.

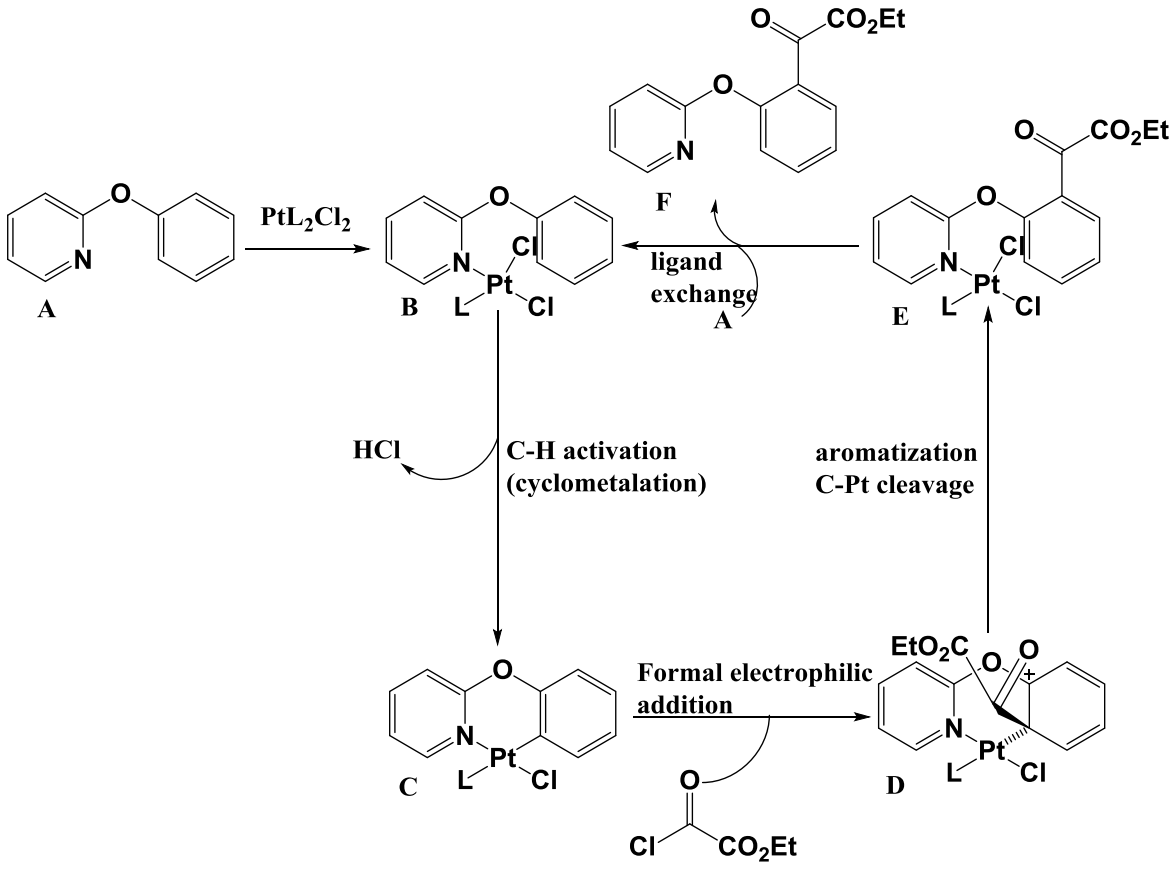
During reaction optimization, the reactions were stopped based on the consumption of 2-aryloxypyridine, which served as the limiting reagent. However, after the reaction was stopped a small amount of starting material remained detectable on GC, suggesting that the catalyst had undergone decomposition. There is also a likelihood that some of the starting material or product remains coordinated to catalyst even after the pyridine workup. The reaction yield are most likely consistent with these observations, as the highest yield of any reaction was 86%

5.2 Proposed Mechanism

The data gathered in this study helped understand some of the mechanistic insights gathered from experiments, as well as propose a possible mechanism, which is most likely similar to the mechanism of the Pt-catalyzed direct C-H acylation reaction reported at the end of chapter 1.Although the substituent, electronic and steric effects are understood to some extent, the reaction mechanism, especially the pathways for the acylation reaction need to be further elucidated. However, based the previous results in the Huo Lab, a possible mechanism has been proposed in

scheme 23. The reaction proceeds with platinum complex coordinating with the nitrogen on the pyridyl group to form **B**, which then undergoes cyclometalation to give **C**. Formal electrophilic addition of ethyl chlorooxoacetate to **C** forms intermediate **D**. Re-aromatization of **D** through C-Pt cleavage forms **E**. which then goes through ligand exchange with **A** to produce **F**, releasing **A** to enter the next catalytic cycle.

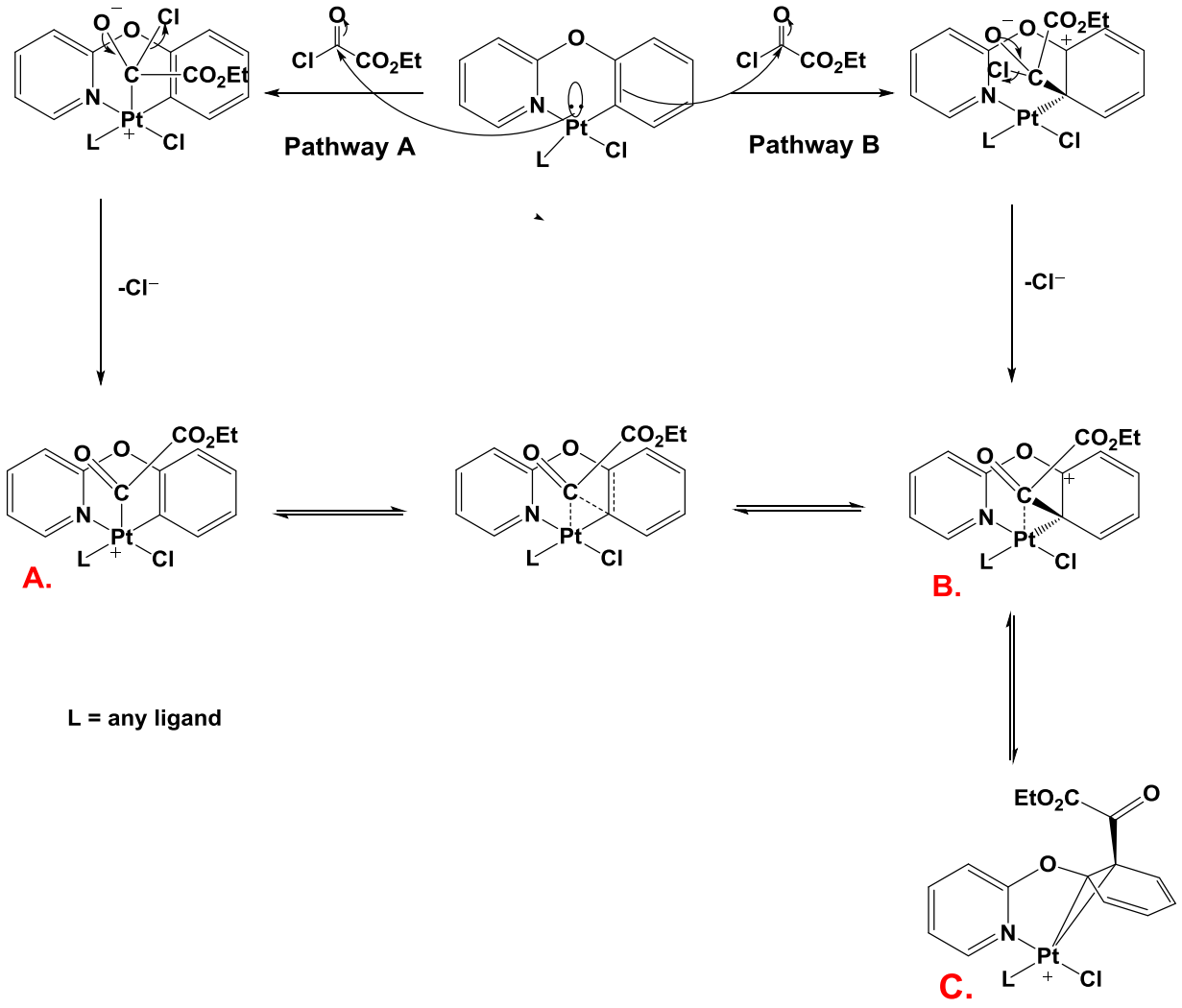
Scheme 23 Proposed Reaction Mechanisms



It is possible that the electrophilic addition of ethyl chlorooxoacetate may be triggered by nucleophilic attack of the platinum at the acyl chloride (**pathway A, scheme 24**). The five-coordinated Pt (IV) intermediate **A** then rearranges to form the arenium ion **B** through a bridged species. Alternatively, the arenium ion **B** can also be formed by a nucleophilic attack of the

metalated carbon at the acyl chloride (**Pathway B**). Arenium ion **B** may also get trapped by the platinum to form a metallacyclopropane or a π-complex, **C**. Further experiments and an extensive computational study is needed to clarify and gain insights into the details of the mechanism.

Scheme 24 Possible pathways for acylation



CHAPTER 6: CONCLUSION

This research accomplished the goal of developing a facile method for the synthesis of alpha-ketoester compounds. The optimal conditions for the reaction were established by screening a number of solvents. Though the best results were obtained when chlorobenzene was used, the acylation reaction proceeded in a number of solvents including benzonitrile, toluene, and m-xylene. Both cis and trans isomers of the platinum catalyst were tested in the acylation reaction and the cis isomer proved to be significantly more effective than its counterpart. The acylation reaction proceeded with a number of electron-donating and electron-withdrawing substituents; however the former seemed to accelerate the reaction. It was observed that when para-substituted ligands were used, both positions ortho to the linker atom were acylated. Similarly, monoacylated were synthesized when positions ortho or meta to the linker atom were substituted. In all cases acylation was observed only at the carbon ortho to the linker atom.

The acylation reaction was proposed to proceed via electrophilic aromatic substitution, which was consistent with the results as electron withdrawing group decelerated the reaction and in some cases didn't proceed at all. Although the substituent, electronic and steric effects are understood to some extent, the reaction mechanism need to be further elucidated. It was proposed that the reaction most likely proceeds via coordination of phenoxy pyridine to the platinum catalyst forming a cyclometalated complex followed by the electrophilic addition of the acyl chloride. Finally the desired compound is formed through re-aromatization and ligand exchange of the acylated cycloplatinum complex.

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