Copper-catalyzed condensation reactions for the synthesis of multisubstituted heteroarenes

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**COPPER-CATALYZED CONDENSATION REACTIONS
FOR THE SYNTHESIS OF MULTISUBSTITUTED
HETEROARENES**

TAN WEI WEN SIMON

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

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A thesis submitted to the Nanyang Technological University

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List of Abbreviations

δ	chemical shift (ppm)
$^{\circ}\text{C}$	degree centigrade
$\text{\AA}$	angstrom
Ac	acetyl
acac	acetylacetonate
Ar	aryl (substituted aromatic ring)
app.	apparent
aq	aqueous
br	broad
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
cod	1,5-cyclooctadiene
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
Cy	cyclohexyl
d	doublet
DCE	1,2-dichloroethane
dd	doublet of doublet
dt	doublet of triplet
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
eq/ equiv	equivalent

ESI	electrospray ionization
Et	ethyl
EWG	electron-withdrawing group
FID	flame ionization detector
GC	gas chromatography
h	hour
H	hydrogen
hfacac	hexafluoroacetylacetonate
HMBC	heteronuclear multiple bond correlation
HMQC	heteronuclear multiple quantum coherence
HRMS	high resolution mass spectrometry
<i>J</i>	coupling constants
LDA	lithium diisopropylamide
m	multiplet
m/z	mass per charge ratio
M ⁺	parent ion peak (mass spectrum)
Me	methyl
Mp	melting point
MS	molecular sieves
NBS	<i>N</i> -bromosuccinimide
NMR	nuclear magnetic resonance
Ph	phenyl
Phen	1,10-phenanthroline
PMB	<i>p</i> -methoxybenzyl
PMP	<i>p</i> -methoxyphenyl
ppm	parts per million

<i>i</i> -Pr	<i>iso</i> -propyl
q	quartet
s	singlet
sat	saturated
sept	septet
rt/r.t.	room temperature
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBS	<i>tert</i> -butyldimethylsilyl
td	triplet of doublet
TEA	triethylamine
temp	temperature
TEMPO	(2,2,6,6-tetramethyl-piperidin-1-yl)oxyl
tfacac	trifluoroacetylacetate
TLC	thin layer chromatography
TMS	trimethylsilyl
<i>p</i> -Tol	<i>p</i> -toluene
Ts	<i>p</i> -toluenesulfonyl
<i>p</i> -TsOH	<i>p</i> -toluenesulfonic acid
vol	volume

Abstract

Heteroarenes are ubiquitously found in many biologically active natural and man-made products such as pharmaceuticals, polymeric materials, and are also essential building blocks for the synthesis of complex molecules. Thus, the efficient and regioselective synthesis of heteroaromatic compounds has been one of the main topics of interest for organic, medicinal and material chemists. Over the past decades, transition metal catalysts have emerged to be attractive and powerful tools to enable heteroarene synthesis with a broad functional group compatibility and unique reaction patterns, thus complementing the limitations of classical synthetic methods.

This thesis describes the development of new copper-catalyzed condensation methods for the synthesis of highly substituted heteroarenes such as pyrroles, furans, thiophenes, and pyridines. Following the general introduction described in Chapter 1, Chapter 2 describes a copper-catalyzed condensation of imines and diazocarbonyl compounds to afford highly substituted pyrroles, which is also applicable to the synthesis of lamellarin family of natural products. Chapter 3 describes an extension of the method developed in Chapter 2, that is, a copper-catalyzed condensation of 2-siloxy-1-alkenes and diazocarbonyl compounds into highly substituted 2-siloxy-2,3-dihydrofurans. The 2-siloxy-2,3-dihydrofurans serve as versatile surrogates for the preparation of furans, pyrroles and thiophenes in one-pot. In Chapter 4, we have established a copper-catalyzed condensation of *O*-acetyl oximes and α,β -unsaturated imines to afford highly substituted pyridines. The reactions developed herein commonly feature simple and low cost catalytic systems, broad functional group tolerance, regioselective formation of highly substituted heteroarenes starting from readily available starting materials.

Chapter 1. General Introduction

1.1 Brief introduction to heteroarenes

Heteroarenes are a subset of heterocycles that belong to one of the largest and most diverse families of organic compounds (Figure 1.1). Heteroarene motifs are ubiquitously found in many biologically active natural and non-natural products such as pharmaceuticals, agrochemicals, and polymeric materials.¹ Thus, for many decades, the synthesis and application of heteroaromatic compounds have been one of the main topics of interest for organic, medicinal and material chemists. Classically, many of heteroaromatic compounds have been synthesized by way of condensation of carbonyl compounds. For illustrative purpose and in light of the scope of this thesis study, some of the most classical synthetic methods for three representative heteroarenes, namely, pyrroles, furans, and pyridines are discussed below.

Figure 1.1. Examples of monocyclic heteroarenes

In 1884, Carl Paal and Ludwig Knorr disclosed the so-called Paal–Knorr synthesis, which is one of the first classical methods for the synthesis of pyrroles and furans (Scheme 1.1).² 1,4-Diketones undergo condensation with amines to afford pyrroles, while they also undergo condensation by themselves under acidic conditions to afford furans. These reactions and their variants have been among the most heavily

utilized methods for the synthesis of pyrroles and furans. However, the Paal–Knorr synthesis is also known for some major limitations, which have thus far stimulated synthetic chemists to develop alternative methods. For example, the scope of the reaction is limited by the availability of the 1,4-diketones as precursors. In addition, the requirement for harsh reaction conditions would limit the functional group tolerance in some cases.

Scheme 1.1. Classical pyrrole and furan synthesis

(a) Paal-Knorr pyrrole synthesis

(b) Paal-Knorr furan synthesis

Another class of heteroarenes that have attracted considerable attention is pyridine. Three decades after the discovery of pyridine by Anderson in 1849, Hantzsch described the first major synthesis to access substituted pyridine derivatives in 1881 (Scheme 1.2a).³ The Hantzsch pyridine synthesis is a straightforward multicomponent condensation of aldehyde, two molecules of β -ketoester and a nitrogen source, such as ammonium acetate to afford a substituted dihydropyridine, which can be subsequently oxidized to a pyridine derivative. Since the discovery of the Hantzsch synthesis, many classical methods for pyridine synthesis, including the Bohlmann–Rahtz⁴ (Scheme 1.2b) and Kröhnke pyridine synthesis⁵ (Scheme 1.2c) have been developed based on carbonyl–amine condensation, which have collectively and significantly improved the ability of synthetic chemists to access substituted pyridines.

Scheme 1.2. Classical pyridine synthesis

(a) Hantzsch pyridine synthesis

(b) Bohlmann-Rahtz pyridine synthesis

(c) Kröhnke pyridine synthesis

1.2 Transition metal-catalyzed synthesis of heteroarenes

Over the past decades, numerous methods for the synthesis of heterocycles, including the privileged five- and six-membered heteroarenes, via transition metal catalysis have been developed.⁶ Transition metal catalysts often exhibit good level of functional group compatibility and unique reaction patterns, and hence can allow access to heterocycles with substitution patterns that are not readily synthesized by classical methods. In this context, copper is one of the most extensively studied transition metals in the development of heterocycle-forming reactions due to its unique redox and coordination ability as well as its relatively low cost and toxicity.⁷ Indeed, as examples discussed below illustrate, a number of copper-catalyzed reactions have been developed for the synthesis of highly substituted pyrroles and pyridine, among other heterocycles.

In 2007, Buchwald *et al.* reported on a copper-catalyzed vinylation of 1,2-bis-Boc-hydrazides with vinyl iodides to afford bis-Boc intermediates, which undergo [3,3]-rearrangement and cyclization to afford pentasubstituted pyrroles (Scheme 1.3a).⁸ In

2008, Narasaka *et al.* reported on a copper-catalyzed [3+2]-type cycloaddition of vinyl azides and ethyl acetoacetate to access tetrasubstituted N-H pyrroles (Scheme 1.3b).⁹ The reaction is proposed to proceed via a 1,4-addition of a copper enolate derived from ethyl acetoacetate to vinyl azide, followed by elimination of dinitrogen and cyclocondensation to the pyrrole product. In 2010, Park *et al.* reported on a copper-catalyzed [3+2]-type cycloaddition of β -dimethylamino acrylates with diazocarbonyl compounds, which affords, upon elimination of dimethylamine under acidic conditions, various pentasubstituted pyrroles (Scheme 1.3c).¹⁰ Liang *et al.* reported on a copper-catalyzed reaction of β -enamino ketones and activated alkynes to afford pentasubstituted pyrroles (Scheme 1.3d).¹¹ The reaction likely proceeds via Michael addition of β -enamino ketones to alkynes, then subsequent hydride abstraction and radical cyclization to afford pyrroles. Recently, Jiang *et al.* developed a [3+2]-type condensation of *O*-acetyl oximes and dialkyl acetylenedicarboxylates to access highly substituted N-H pyrroles (Scheme 1.3e).¹² They propose that a nucleophilic copper enamide generated through N–O reduction of the oxime reacts with the dialkyl acetylenedicarboxylate, which is followed by a single electron transfer, radical cyclization, and dehydrogenation to give the pyrrole product.

Scheme 1.3. Synthesis of highly substituted pyrroles via copper-catalyzed [3+2]-type cycloaddition reactions

(a) Buchwald

(b) Chiba and Narasaka

(c) Park

(d) Huang and Liang

(e) Jiang

Interestingly, many of the recently developed copper-catalyzed reactions to access highly substituted pyridines involve the use of oxime derivatives, presumably due to their ability to undergo N–O bond reduction with copper(I).¹³ In 2008, Liebeskind *et al.* reported a copper-catalyzed coupling of alkenylboronic acid and α,β -unsaturated ketoxime to afford highly substituted pyridines (Scheme 1.4a).¹⁴ The reaction is proposed

to proceed through N–O bond reduction of the oxime, cross-coupling with the boronic acid, and electrocyclization and oxidative aromatization in the presence of air. In 2011, Guan *et al.* reported a copper-catalyzed condensation of an aldehyde and two molecules of oxime acetate to afford symmetrical cyclic pyridines (Scheme 1.4b).¹⁵ They propose a copper-catalyzed N–O reduction of oxime to generate a copper-enamide which undergoes nucleophilic addition to aldehyde, then, condensation with another molecule of oxime, electrocyclization, and oxidation to furnish the desired pyridine. In 2013, our group reported on a [3+3]-type condensation of enals and *O*-acetyl oximes synergistically catalyzed by copper(I) salt and secondary amine to afford highly substituted pyridines (Scheme 1.4c).¹⁶ In 2015, Jiang *et al.* reported the three-component coupling of oximes, aldehydes and β -ketoesters to afford highly substituted pyridines (Scheme 1.4d).¹⁷ The latter two reactions are considered to involve the reaction of a nucleophilic enamide (generated via N–O reduction of the oxime with the copper catalyst) and activated Michael acceptor (iminium species generated from enal-amine condensation, or activated enones formed via Knoevenagel condensation) to afford an N–H imine intermediate that would undergo cyclocondensation to the pyridine product. Interestingly, Nakamura *et al.* reported a copper-catalyzed tandem [2,3]-rearrangement and 6π -3-azatriene electrocyclization of (*E*)-*O*-propargylic α,β -unsaturated oximes to afford polysubstituted pyridine *N*-oxides (Scheme 1.4e).¹⁸ They propose the nucleophilic attack by the oxime nitrogen to the activated carbon–carbon triple bond, ionic cleavage of the C–O bond, 6π -3-azatriene electrocyclization and isomerization to afford the desired product.

Scheme 1.4. Synthesis of highly substituted pyridines via copper-catalyzed condensation reactions

(a) Liebeskind

(b) Guan

(c) Yoshikai

(d) Jiang

(e) Nakamura

Despite these numerous reports, novel methodologies to access heteroarenes are still in constant demand. Ideally, organic chemists would like to develop an atom-economic yet simple catalytic system to access heteroarenes with high functional group tolerance and molecular complexity starting from readily available starting materials.

1.3 Design and summary of thesis research

The purpose of this research is to develop new efficient and selective synthetic methods for some of the privileged heteroarenes from readily available starting materials, which enable access to diverse substitution patterns. Our group has been actively utilizing imines as versatile substrates for various cobalt-catalyzed C–H functionalization reactions¹⁹ as well as palladium catalysis for the synthesis of various heterocycles such as indoles²⁰ and furans²¹. In this connection, we thus seek to combine the advantages of copper catalysis and imines to explore the possibility of developing novel methods to access highly substituted heteroarenes in a regiocontrolled manner.

In Chapter 2, we report a novel copper-catalyzed [3+2]-type condensation of enolizable ketimines and α -diazo- β -ketoesters to afford multisubstituted pyrroles (Scheme 1.5). The reaction likely proceeds via a nucleophilic addition of the imine to a copper carbenoid to give rise to an α -enaminoketone, which would undergo enamine–ketone cyclocondensation afford the pyrrole product. With the use of a unique co-catalyst Yb(OTf)₃, α -diazo- β -diketones could also participate in this reaction to afford pyrrole derivatives in a regioselective manner. The reaction features a simple catalytic system and is applicable to acyclic, exocyclic, and endocyclic imines with various functional groups. Furthermore, the present reaction opens an alternative route for the synthesis of lamellarin family of natural products.

Scheme 1.5. Copper-catalyzed condensation of imines and diazocarbonyl compounds for the synthesis of highly substituted pyrroles

In Chapter 3, we report a copper-catalyzed cyclization of 2-siloxy-1-alkenes and diazocarbonyl compounds to afford 2-siloxy-2,3-dihydrofurans, which represents an extension of the work reported in Chapter 2 (Scheme 1.6). The reaction likely proceeds via a nucleophilic addition of the silyl enol ether to the copper carbenoid to generate an enolate/oxonium species, which would then cyclize to give the 2-siloxy-2,3-dihydrofuran derivative. The reaction tolerates a wide variety of functional groups, and the thus-synthesized dihydrofurans serve as 1,4-diketone surrogates for the facile preparation of various trisubstituted furans, pyrroles, and thiophenes in one-pot.

Scheme 1.6. Copper-catalyzed condensation of 2-siloxy-1-alkenes and diazocarbonyl compounds for the synthesis of multisubstituted furans, pyrroles and thiophenes

In Chapter 4, we report a copper-catalyzed [3+3]-type cyclocondensation of *O*-acetyl oximes and α,β -unsaturated ketimines to access highly substituted pyridines (Scheme 1.7). The reaction allows for rapid access to polysubstituted pyridines under mild reaction conditions with broad functional group compatibility, and in addition, exhibits excellent regioselectivity when unsymmetrical alkyl oxime acetates are employed. In this context, the present reaction represents a useful addition to the synthetic repertoire for pyridines, because the substitution patterns of the synthesized pyridines are otherwise not readily accessible.

Scheme 1.7. Copper-catalyzed condensation of *O*-acetyl oximes and α,β -unsaturated imines for the synthesis of highly substituted pyridines

To summarize, we have developed a series of new copper-catalyzed reactions for the synthesis of highly substituted pyrroles, furans, thiophenes and pyridines. It is noteworthy that the reactions reported herein feature a simple and inexpensive catalytic system and allow rapid access to highly functionalized heteroarenes starting from readily available starting materials, many of which are not easily accessible by existing synthetic methods. These methods would therefore serve to be useful addition to the repertoire for heteroarene synthesis.

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Chapter 2. Copper-Catalyzed Condensation of Imines and α -Diazo- β -dicarbonyl Compounds: Modular and Regiocontrolled Synthesis of Multisubstituted Pyrroles

2.1 Introduction

2.1.1 Multisubstituted pyrroles and recent methods for their synthesis

Multisubstituted pyrrole moieties are present in many biologically active natural products and man-made pharmaceuticals. To name a few, the pyrrole core is common to lamellarin D (HIV-1 integrase inhibitor), atorvastatin (HMG-CoA reductase inhibitor), kendine 91 (HDAC inhibitor) and BM212 (antimycobacterial properties) as illustrated in Figure 2.1.¹ Consequently, the development of efficient and regioselective methods for the synthesis of multisubstituted pyrroles has been one of the most important subjects in heterocyclic chemistry. While there have been many reports on the synthesis of pyrroles, especially those catalyzed by transition metals reported in the last decade,^{2,3} there is still a continuous demand for a simple and robust catalytic method to access these privileged heterocycles in a regioselective manner. Notably, in quite a few of the transition metal-catalyzed methods, the catalyst plays an important role in the formation of linear intermediates such as α -enaminoketone,⁴ 1,4-diimine,⁵ and γ -ketoimine (or its enamine tautomer),⁶ which could undergo classical cyclocondensation to afford the desired pyrrole products.

Figure 2.1. Biologically active compounds containing pyrrole motifs

Some of the recent illustrative examples for accessing the α -enaminoketone or the γ -ketoimine intermediate are shown in Scheme 2.1. In 2013, Kempe *et al.* reported an iridium-catalyzed reaction of β -aminoalcohols and alcohols to give pyrroles, while Beller *et al.* reported a ruthenium-catalyzed three-component reaction of ketones, amines and diols to give pyrroles. Both the methods utilize the “hydrogen autotransfer” strategy to access the α -enaminoketone intermediate.^{4b,4d} On the other hand, in 2008, Narasaka and Chiba *et al.* reported a copper-catalyzed coupling reaction of vinyl azides with 1,3-dicarbonyl compounds to afford pyrroles via γ -ketoimine intermediate as described also in Chapter 1 (Scheme 1.3b).^{6b} A ruthenium-catalyzed coupling of unmasked amino alcohols and ketones utilizing the “hydrogen autotransfer” strategy, reported by Saito *et al.* also involves γ -ketoimine intermediates.^{6g} In light of these successful examples, any catalytic process that allows for the efficient and regioselective formation of the key linear intermediates starting from simple and readily available starting materials would serve to be a useful method for pyrrole synthesis.

Scheme 2.1. Recent metal-catalyzed pyrrole synthesis via α -enaminoketone or γ -ketoimine intermediates

2.1.2 Reaction of transition metal carbenoids with imines

Transition metal carbenoids generated *in situ* through the decomposition of diazo precursors have proven to serve as extremely versatile electrophilic intermediates for organic synthesis.⁷ Metal carbenoids are intermediates capable of many C–H, N–H, and O–H insertions, cyclopropanation, and other coupling reactions. Among these transformations, reactions utilizing *N*-aryl or *N*-alkyl aldimines as nucleophilic partners have been widely reported as they offer convenient methods to access nitrogen-containing heterocycles. The most common pathway of the reaction is illustrated in Scheme 2.2. Nucleophilic attack of the aldimine nitrogen onto the metal carbenoid generates an azomethine ylide,⁸ which can then undergo cyclization to afford an aziridine. The azomethine ylide intermediate can also be trapped by various dipolarophiles, thus affording a pyrrolidine or other related nitrogen-containing heterocycles.⁹

Scheme 2.2. Transition metal-catalyzed reaction of aldimines with diazocarbonyl compounds

Despite the numerous reports on reactions of aldimines with metal carbenoids, it is surprising that reactions between ketimines and metal carbenoids have rarely been reported. In 2013, Reddy *et al.* reported a reaction of isatin-derived ketimines with a rhodium carbenoid generated from dimethyl diazomalonate to afford an azomethine ylide (Scheme 2.3).¹⁰ The ylide generated *in situ* was subsequently trapped by a dipolarophile such as dimethyl acetylenedicarboxylate for [3+2]-type cycloaddition reactions.

Scheme 2.3. [3+2]-Type cycloaddition of ketimines, carbenoids and dipolarophile

While some other carbenoid transformations involving ketimines as reactants have been reported, none of them involves a direct reaction between the metal carbenoid and the ketimine. For example, Doyle *et al.* reported a rhodium-catalyzed reaction between diazoketoester and a ketimine to afford a β -lactam product, which involves Wolff rearrangement of the initially formed rhodium carbenoid and [2+2] cycloaddition of the resulting ketene with the ketimine (Scheme 2.4).¹¹

Scheme 2.4. [2+2]-Type cycloaddition of ketimines and diazocarbonyl compounds **2.1.3 Hypothesis**

With the above understanding, we wondered if an enolizable ketimine bearing α -protons could undergo nucleophilic addition towards a metal carbenoid (Scheme 2.5). The addition of the nitrogen atom of the ketimine or its enamine tautomer to the carbenoid carbon would give rise to an α -enaminoketone intermediate, which could then undergo cyclocondensation to produce a pyrrole derivative. On the other hand, the addition of the enamine carbon to the carbenoid would generate a γ -ketoimine intermediate, which would lead to a regioisomeric pyrrole product.

Scheme 2.5. [3+2]-Type cycloaddition of enolizable ketimines with diazocarbonyl compounds

This idea led us to develop an operationally simple pyrrole synthesis from enolizable ketimines and α -diazo- β -ketoesters under copper catalysis, which affords highly substituted pyrroles with the concomitant loss of dinitrogen and water (Scheme 2.6). The reaction is considered to proceed via nucleophilic addition of the imine nitrogen

to a copper carbenoid and tautomerization of the resulting azomethine ylide to an α -enamino- β -dicarbonyl intermediate. This intermediate can then readily undergo dehydrative cyclocondensation to afford the pyrrole product. This method enables expedient synthesis of various functionalized pyrroles that are not readily accessible by previous methods,¹² starting from simple and easily accessible starting materials.

Scheme 2.6. Copper-catalyzed condensation of imines and diazocarbonyl compounds

2.2 Results and discussion

Based on the above hypothesis, I commenced the study on the condensation of ketimine **1a** derived from *p*-anisidine and acetophenone with α -diazo- β -ketoester **2a** derived from ethyl isobutyrylacetate as summarized in Table 2.1. After extensive screening of the reaction conditions, I discovered a catalytic system consisting of copper(II) trifluoroacetylacetonate (10 mol%) and 4Å molecular sieves in toluene at 110 °C could afford the desired tetrasubstituted pyrrole **3aa** as the exclusive regioisomer in 88% isolated yield. Subsequent two-dimensional NMR analysis, such as the heteronuclear multiple bond correlation (HMBC) and heteronuclear multiple quantum coherence (HMQC), confirmed the regiochemistry of **3aa**. Using a more electron-deficient copper catalyst such as copper(II) hexafluoroacetylacetonate gave a comparable yield of 87% while the use of other copper salts such as copper(II) acetylacetonate and copper(II) acetate only gave low yields of the desired product (entries 2-4). The use of rhodium(II) acetate dimer, which is the most routinely used catalyst for metal carbenoid chemistry, failed to afford any desired product while giving a complex mixture (entry 5). In the

absence of 4Å molecular sieves, the yield was substantially decreased to 52% (entry 6). This observation can be ascribed to hydrolysis of ketimine **1a** by water generated by the condensation reaction. The reaction tolerated a lower catalyst loading (5 mol%) or a lower reaction temperature (90 °C) with slight decrease in the yield (entries 7 and 8). The use of non-coordinating solvents such as 1,2-dichloroethane (DCE) afforded a slightly lower yield of the desired pyrrole, while polar coordinating solvents such as dimethyl sulfoxide (DMSO) completely shut down the reaction (entries 9 and 10).

Table 2.1. Screening of reaction conditions

Entry	Deviation from the standard conditions ^a	Yield (%) ^b
1	none	88 ^c
2	$\text{Cu}(\text{hfacac})_2$ instead of $\text{Cu}(\text{tfacac})_2$	87
3	$\text{Cu}(\text{acac})_2$ instead of $\text{Cu}(\text{tfacac})_2$	7
4	$\text{Cu}(\text{OAc})_2$ instead of $\text{Cu}(\text{tfacac})_2$	21
5	$\text{Rh}_2(\text{OAc})_4$ instead of $\text{Cu}(\text{tfacac})_2$	0
6	Without 4Å MS	52
7	5 mol% of $\text{Cu}(\text{tfacac})_2$	76
8	T = 90 °C	82
9	DCE instead of toluene	81
10	DMSO instead of toluene	0

^a PMP = *p*-methoxyphenyl. $\text{Cu}(\text{tfacac})_2$ = copper(II) trifluoroacetylacetonate.

$\text{Cu}(\text{hfacac})_2$ = copper (II) hexafluoroacetylacetonate

^b Determined by GC using tridecane as internal standard.

^c Isolated yield.

With the optimized conditions in hand, I began to scope the condensation reaction starting from different *N*-PMP ketimines **1a-1t** and α -diazo- β -ketoester **2a** as shown in Scheme 2.7. Ketimines **1a-1o** derived from (hetero)aryl methyl ketones all participated in

the reaction to give moderate to good yields (52-92%) of the desired tetrasubstituted pyrroles. In order to demonstrate the practicality of the reaction, the model reaction was performed on a gram scale (5 mmol), which afforded the product **3aa** in an excellent yield. By X-ray diffraction analysis of a single crystal of pyrrole **3ja**, I could again confirm the regiochemistry of the pyrrole products. Various functional groups such as electron-donating methoxy group, electron-withdrawing halogen (F, Cl, Br, I), trifluoromethyl, cyano, and nitro groups, and naphthyl group could be well tolerated (**3ba-3ka**). Heteroaryl groups such as furyl, benzofuryl, thienyl and methyl-protected indolyl groups were also well tolerated (**3ia-3oa**). Ketimines **1p** and **1q** derived from propiophenone and deoxybenzoin, respectively, also participated in the reaction to afford the corresponding pentasubstituted pyrroles in good yields. Alkyl *N*-PMP ketimines **1r-1t** derived from acetyl cyclopropane and cycloalkanones also participated in the reaction to afford the desired tetra- or pentasubstituted pyrroles in good yields.

Scheme 2.7. Condensation of various *N*-PMP imines with α -diazo- β -ketoester **2a**^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 2.1.

I then moved on to study the scope of this condensation reaction using ketimines **1u-1ab** bearing different *N*-substituents other than the *p*-methoxyphenyl group (Scheme 2.8). Ketimine **1u**, derived from acetophenone and *p*-chloro aniline, participated in the reaction to give the desired pyrrole **3ua** in 42% yield,

which marks a significant drop in the yield as compared to the reaction of *N*-PMP ketimine **1a**. This result was not unexpected, as the electron richness on the nitrogen would significantly influence the nucleophilicity of the imine towards a copper carbenoid. Ketimines **1v-1z** afforded pyrroles bearing benzyl, *p*-methoxybenzyl and allyl groups, which could potentially be removed in an additional step to allow for the preparation of free N-H pyrroles. Indeed, by taking pyrrole **3ya** in the presence of trifluoroacetic anhydride and anisole, the *p*-methoxybenzyl group could be cleaved to afford N-H pyrrole **3ya'** in 90% yield. Notably, methyl-substituted dihydroisoquinoline **1aa**, easily prepared by Bischler-Napieralski reaction, also participated in the reaction to afford 5,6-dihydropyrrolo[2,1-*a*]isoquinoline **3aaa** in 73% yield. This skeletal framework implied that the present reaction could potentially be applied for the synthesis of lamellarin family of natural products.^{1b,1c} Interestingly, the reaction of benzyl-substituted dihydroisoquinoline **1ab** proceeded smoothly to afford a mixture of the desired product **3aba** and an unexpected dihydrobenz[*g*]indolizinone derivative **3aba'**.¹³

Scheme 2.8. Condensation of other imines with α -diazo- β -ketoester **2a**^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 2.1. ^b Performed on a 0.5 mmol scale. ^c TFA, anisole, CH₂Cl₂, 37 °C, 40 h.

As the ratio of **3aba** and **3aba'** remained unchanged over the course of reaction, we consider that **3aba'** forms from an intermediate on the pathway leading to **3aba** rather than from **3aba**. A plausible mechanism for the formation **3aba'** is proposed in Scheme 2.9. First, nucleophilic attack of dihydroisoquinoline **1ab** to diazoketoester **2a** under the standard conditions affords an ylide **I**. Tautomerization of the ylide **I** via proton transfer is followed by cyclization of the resulting α -enaminoketone intermediate **II**. Subsequent proton transfer and loss of a water molecule from the intermediate **III** could afford **3aba**. On the other hand, we proposed that the intermediate **IV** could also undergo oxidation, phenyl transfer and loss of a water molecule to afford **3aba'**.

Scheme 2.9. Plausible mechanism for the formation of **3aba'**

I next explored the reaction of some unstable imines with diazoketoester **2a** as shown in Scheme 2.10. First, N-H imine **1ac** freshly prepared from benzonitrile and methyllithium with minimal workup was utilized as the reactant for the present reaction. I could obtain a modest yield of the desired pyrrole **3acb** accompanied by the formation of a 2*H*-1,4-oxazine **4** as a byproduct. Next, condensation of (*p*-methoxyphenyl)acetaldehyde and *p*-anisidine was followed by treatment of the reaction mixture with **2b** under the standard conditions to afford pyrrole **3adb** in a modest yield. The low yield of this reaction may be ascribed to the complexity of the first condensation step, wherein many side reactions such as enamine aldol reaction can compete with the formation of the desired aldimine **1ad**.

Scheme 2.10. Condensation of unstable imines with α -diazo- β -ketoester **2b**^a

(a) N-H Imine

(b) Aldimine (one-pot)

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 2.1.

In the course of exploration of the scope of ketimines, I also discovered some unexpected cyclization modes by the use of pinacolone- and trifluoroacetone-derived ketimines **1ae** and **1af** (Scheme 2.11). Thus, the reaction of these ketimines with **2a** afforded 2,3-dihydrooxazole derivatives **5a** and **5b**, respectively, instead of affording the corresponding pyrrole products.

Scheme 2.11. Unexpected formation of 2,3-dihydrooxazole derivatives^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 2.1.

Next, I explored the scope of various α -diazo- β -ketoesters **2b-2p** with ketimine **1a** as listed in Table 2.2. Various alkyl- (**2b-2d**), benzyl- (**2e**) or (hetero)aryl-substituted (**2f-2m**) diazoketoesters participated in the reaction to give tetrasubstituted pyrroles in moderate to good yields (entries 1-12). Electron-donating methoxy group and electron-withdrawing bromo and nitro groups were tolerated on the aryl group of diazoketoester (entries 6-8 and 10). Sterically hindered diazoketoesters **2j** and **2k** bearing 2-bromo or 2-methyl groups could be employed, affording the desired pyrroles in moderate yields (entries 9 and 10). In addition, diazoketoesters **2n** and **2o** derived from diethyl 2-oxosuccinate and ethyl 4,4,4-trifluoroacetoacetate also participated in the reaction to afford pyrroles bearing an ester or trifluoromethyl functionality on the C-3 position (entries 13 and 14). Formyl diazoacetate **2p** also afforded the desired 1,2,5-trisubstituted pyrrole **3ap** in moderate yield (entry 15).

Table 2.2. Condensation of imine **1a** with various α -diazo- β -ketoester^a

Entry	R ¹	R ²	Product	Yield (%)
1	Me	Et	3ab	81
2	<i>c</i> -C ₃ H ₅	Et	3ac	80
3	<i>c</i> -C ₆ H ₁₁	Me	3ad	88
4	Bn	Me	3ae	94
5	Ph	Et	3af	77
6	4-MeOC ₆ H ₄	Et	3ag	77
7	4-BrC ₆ H ₄	Et	3ah	86
8	4-NO ₂ C ₆ H ₄	Et	3ai	80
9	2-MeC ₆ H ₄	Et	3aj	67
10	2-BrC ₆ H ₄	Et	3ak	60
11	1-Naphthyl	Me	3al	74
12	2-Furyl	Me	3am	70
13	CO ₂ Et	Et	3an	79
14	CF ₃	Et	3ao	41
15	H	Et	3ap	47

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 2.1.

In an attempt to expand the substrate scope with respect to diazocarbonyl compounds, I explored the reaction of ketimine **1a** with 3-diazopentane-2,4-dione **2q** (Table 2.3). Even using the more electrophilic copper(II) hexafluoroacetylacetonate, I could only obtain a *ca.* 1:1 mixture of the desired pyrrole **3aq** and its positional isomer **3aq'** in a low overall yield of 23% (entry 1). The formation of the positional isomer **3aq'** could be explained by formal C–H insertion of the copper carbenoid into the α -position of the ketimine **1a**. By a series of screening experiments, I was delighted to find that the addition of a co-catalyst Yb(OTf)₃ (10 mol%) afforded the desired product **3aq** in 36% yield while reducing the yield of its positional isomer **3aq'** to 5% (entry 2). The use of

other Lewis acid catalysts such as $\text{Gd}(\text{OTf})_3$, $\text{La}(\text{OTf})_3$, and $\text{In}(\text{OTf})_3$ also regioselectively produced **3aq** albeit in lower yields (entries 3-5). By reducing the reaction temperature to 80 °C, I could improve the yield of **3aq** while suppressing the formation of **3aq'** (entry 6). Increasing the amount of the Lewis acid co-catalyst to 20 mol% only resulted in a lower yield (entry 7).

Table 2.3. Screening of conditions of reaction of imine **1a** with diazo diketone **2q**

Entry	cocatalyst	temp (°C)	Yield (%) ^a	
			3aq	3aq'
1	none	110	11 ^b	12 ^b
2	$\text{Yb}(\text{OTf})_3$ (10 mol%)	110	36	5
3	$\text{Gd}(\text{OTf})_3$ (10 mol%)	110	23	trace
4	$\text{La}(\text{OTf})_3$ (10 mol%)	110	22	trace
5	$\text{In}(\text{OTf})_3$ (10 mol%)	110	23	trace
6	$\text{Yb}(\text{OTf})_3$ (10 mol%)	80	57^b	trace
7	$\text{Yb}(\text{OTf})_3$ (20 mol%)	80	21	trace

^a Determined by GC using tridecane as internal standard. ^b Isolated yield.

The application of the above Cu/Yb catalytic system to the reaction of **1a** with 1-diazo-1-benzoyl acetone **2r** resulted in two isomeric products, in favor of the benzoyl pyrrole isomer **3ar** over the acetyl pyrrole isomer **3ar'** (Scheme 2.12). Note that, without the addition of $\text{Yb}(\text{OTf})_3$, I observed only low yields of four different isomers by gas-chromatographic analysis. While we cannot be sure of the role of the Lewis acid, we speculate that $\text{Yb}(\text{OTf})_3$ enhances the electrophilicity of the copper carbenoid by coordinating to the diketo-moiety of the dione **2q** or **2r**, thus improving the reaction yield and selectivity.

Scheme 2.12. Condensation of imine **1a** with diazo diketone **2r**

Unfortunately, I was unable to obtain any desired pyrrole by employing more reactive α -diazoketones such as 2-diazo-1,2-diphenylethanone. I observed rapid decomposition of these diazo compounds under the standard conditions. Even employing a less reactive catalyst such as copper(II) acetylacetonate and milder reaction temperature, I was still unable to obtain any of the desired pyrrole.

With the substrate scope and limitations of the present reaction established, we then explored the possibility of applying the reaction to the synthesis of bioactive natural products. We were intrigued by the formation of 5,6-dihydropyrrolo[2,1-*a*]isoquinoline **3aaa** with its relevance to the skeletal framework of the lamellarin family of natural products, and hence wondered if the present reaction system is applicable to the synthesis of lamellarin. Lamellarins are a large family of more than 30 marine alkaloids that possess interesting bioactive properties such as the inhibition of topoisomerase I and HIV-1 integrase (Figure 2.2).¹⁴ Such features have stimulated many researchers including Steglich, Ishibashi/Iwao, Ruchirawat, and Banwell to develop new methodologies to access these privileged heterocycles.^{15,16} In some of the total syntheses reported, 3-alkoxycarbonyl-5,6-dihydropyrrolo[2,1-*a*]isoquinone derivatives serve as key intermediates. Thus, if our reaction allowed access to these intermediates with ease, it could potentially open an efficient and alternative route to the synthesis of lamellarin.

Figure 2.2. Outline of lamellarin scaffold

With the above conjecture, I tested two model reactions of methyl and benzyl-dihydroisoquinoline **1aa** and **1ab** with ethyl benzoyldiazoacetate **2f** (Scheme 2.13). The reaction of methyl dihydroisoquinoline **1aa** gave the desired product **3aaf** in 62% yield. However, the latter reaction using benzyl dihydroisoquinone **1ab** only afforded the dihydrobenz[*g*]indolizinone derivative **6**, as confirmed by X-ray crystallographic analysis. The formation of **6** presumably goes through the same mechanism as described in Scheme 2.9.

Scheme 2.13. Model condensation reaction of the dihydroisoquinolines **1aa** and **1ab** with ethyl benzoyldiazoacetate **2f**^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 2.1.

The failure of **1ab** seems to simply that a direct assembly of the tetrasubstituted pyrrole moiety of lamellarin by the present reaction may not be feasible. After screening of various substrates, I decided to utilize simple ethyl formyl diazoacetate **2p** as the reaction partner instead of **2f** (Scheme 2.14). To our satisfaction, the reaction of methyl dihydroisoquinone **1ag** bearing two methoxy groups with **2p** afforded the desired product in 68% yield. This bears resemblance to an analogous compound previously synthesized by Álvarez *et al.* and later utilized to access Lamellarin D and its analogues.^{16b,17} In the Álvarez total synthesis, the analogous compound was synthesized from an alkyl tosylate, which was prepared in multiple steps, and pyrrole 2-carboxylate through *N*-alkylation and intermolecular Heck reaction.

Scheme 2.14. Condensation of dihydroisoquinoline **1ag** with diazoketoester **2p** to access lamellarin scaffold

(a) 3-Alkoxy carbonyl derivative

(b) Alvarez et al. lamellarin synthesis

In addition, the reaction of benzyl dihydroisoquinoline **1ah** bearing four methoxy groups with diazoketoester **2p** afforded pyrrole **3ahp** in a modest yield (Scheme 2.15). This compound was previously synthesized by Handy *et al.* through a six-step manipulation of pyrrole **7**.^{16a} First, Boc protection of **7** was followed by Suzuki coupling with 3,4-methoxyphenylboronic acid to afford **9**. Subsequent bromination and Suzuki

coupling afforded pyrrole **11**. Lastly, a two-step protocol, involving formation of a tosylate and intramolecular alkylation of the pyrrole nitrogen afforded the intermediate **3ahp**, which was eventually converted to lamellarin G trimethyl ether in another two steps utilizing Suzuki coupling and cyclization. It is noteworthy to mention that **1ag** and **1ah** is commercially available or easily synthesized by condensation of corresponding acid and amine and subjecting the product to Bichler-Napieralski reaction in the presence of trichlorophosphate.¹⁸

Scheme 2.15. Condensation of dihydroisoquinoline **1ah** with diazoketoester **2p** to access lamellarin scaffold

(a) 1-Aryl-3-alkoxycarbonyl derivative

(b) Handy et al. lamellarin synthesis

In light of the regiochemistry of the pyrrole product and the common understanding of reaction patterns of metal carbenoids, the reaction is considered to involve a nucleophilic attack of the imine nitrogen to a copper carbenoid. To probe the

nature of this step, we designed some competition experiments using imines bearing different electron-withdrawing and electron-donating substituents (Scheme 2.16). In the first competition reaction, I subjected ketimines **1b** and **1h** derived from *p*-methoxy acetophenone and *p*-cyano acetophenone, respectively, to the reaction with diazoketoester **2a**, which afforded 63% of pyrrole **3ba** derived from the former ketimine as the major product. In the second competition reaction I subjected ketimine **1a** and **1u** derived from *p*-methoxy aniline and *p*-chloro aniline, respectively, to the reaction with diazoketoester **2a**, which resulted in the preferential reaction of the former ketimine to afford pyrrole **3aa** as the major product. From these competition experiments, it is evident that the electron richness of the imine nitrogen significantly affects the reaction.

Scheme 2.16. Competition experiments

We propose a plausible reaction mechanism for the present condensation reaction as illustrated in Scheme 2.17. First, the decomposition of α -diazo- β -ketoester **2** with the copper catalyst generates an electrophilic copper carbenoid. Subsequent nucleophilic attack of the imine nitrogen of **1** to the copper carbenoid generates the azomethine ylide **I** and regenerates the copper catalyst. The azomethine ylide **I** then tautomerizes to α -enaminoketone **II** via proton transfer, which is followed by cyclocondensation to afford the desired pyrrole **3**. Although we are unable to trap the azomethine ylide with dipolarophiles such as dimethyl maleate, dimethyl acetylenedicarboxylate or *N*-phenylphthalimide by [3+2] cycloaddition, the observation of other by-products would support the presence of the ylide intermediate. In the reaction of N-H imine, we observed the formation of 2*H*-1,4-oxazine **4** (Scheme 2.10).¹⁹ The formation of **4** may be rationalized by oxidation of **II** to 1-acyl-2-azadiene **III** and its 6 π electrocyclization. The azomethine ylide **I** can also function as an enolate/iminium species **I'** and undergo nucleophilic attack of the enolate oxygen onto the iminium to afford 2,3-dihydrooxazole **5** as observed in the reactions of pinacolone- and trifluoroacetone- derived imines **1ae** and **1af** (Scheme 2.11). The lower acidity of the α -proton (**1ae**) or the increased electrophilicity of the iminium moiety (**1af**) could be possible reason for the formation of **5**.

Scheme 2.17. Plausible mechanism leading to pyrrole and other by-products

2.3 Conclusion

In summary, we have developed a scalable and modular copper-catalyzed condensation reaction of imines and α -diazo- β -dicarbonyl compounds to afford multisubstituted pyrroles in a regiocontrolled manner. This reaction features a broad substrate scope, simple reaction setup and workup procedures, and readily available starting materials and thus allows for the synthesis of highly functionalized pyrroles, many of which may not be readily accessed by existing synthetic methods. In addition, the present condensation reaction would serve as a useful method for the synthesis of lamellarins and other natural products bearing the pyrrole scaffold. Last but not least, it is somewhat surprising this simple and powerful reaction of enolizable imines has not been reported regardless of the extensive studies on the reaction between imines and diazocarbonyl compounds over the past decades.

2.4 Experimental

Materials and Methods

General. All reactions dealing with air- and moisture-sensitive compounds were carried out in oven dried reaction vessels under a nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker 400 MHz NMR spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0.00 ppm) and CHCl_3 (77.26 ppm), respectively. Chemical shifts are reported in ppm and the multiplicities are reflected by s (singlet), d (doublet), q (quartet), sept (septet) and m (multiplet). Coupling constants are represented by J in hertz (Hz). Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-Tof Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected.

Materials. Unless otherwise noted, materials were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received. Copper(II) trifluoroacetylacetonate and copper(II) hexafluoroacetylacetonate were purchased from Alfa Aesar and Strem Chemicals, respectively, and were used as received. Anhydrous toluene used was distilled over calcium hydride (CaH_2) and stored under N_2 .

Synthesis of Imines

All imines except for **1aa**, **1ab**, **1ac**, **1ag**, **1ah**, were synthesized by condensation of the corresponding anilines and ketones according to the literature procedures,²⁰ and purified by recrystallization from EtOAc/hexane or distillation under reduced pressure. Below is

the summarized characterization data for newly synthesized imine. ^1H and ^{13}C NMR spectral data for the rest of the imines showed good agreement with literature data.²¹ Imines **1aa**, **1ab**, **1ac**, **1ad**, **1ag**, **1ah** were prepared according to the literature procedures.^{22,23}

4-Methoxy-*N*-(1-(*o*-tolyl)ethylidene)aniline (1j): Red oil (68% yield, *E/Z* = 3:2); ^1H NMR (400 MHz, CDCl_3 , *E*-isomer): δ 7.37–7.35 (m, 1H), 7.26–7.22 (m, 2H), 7.06–6.99 (m, 1H), 6.91 (d, J = 8.9 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 3.80 (s, 3H), 2.48 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3 , *E*-isomer): δ 170.3, 156.2, 144.5, 142.0, 135.0, 131.2, 128.7, 127.3, 125.95, 120.8, 114.5, 55.6, 21.3, 20.3; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{18}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 240.1388, found 240.1383.

***N*-Cycloheptylidene-4-methoxyaniline (1t):** Orange oil (66% yield); ^1H NMR (400 MHz, CDCl_3) δ 6.84 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 2.63–2.60 (m, 2H), 2.39–2.23 (m, 2H), 1.78–1.74 (m, 2H), 1.67–1.54 (m, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 178.5, 155.6, 144.7, 120.4, 114.3, 55.5, 40.7, 33.4, 30.3, 30.0, 26.9, 25.5; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{20}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 218.1545, found 218.1544.

Synthesis of Diazocarbonyl Compounds

General Method. To a 100 mL round bottom flask charged with ketoester (10 mmol) and 4-acetamidobenzenesulfonyl azide (2.64 g, 11 mmol) in acetonitrile (40 mL) was added triethylamine (4.2 mL, 30 mmol) dropwise at 0 °C. Upon stirring at room temperature for 14 h, the reaction mixture was concentrated under reduced pressure. The residual solid was triturated with ether/light petroleum ether. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification by flash chromatography afforded the corresponding diazocarbonyl compound.

Below are summarized characterization data for newly synthesized diazocarbonyl compounds. ^1H and ^{13}C NMR spectral data for the rest of the diazocarbonyl compound showed good agreement with literature data.²⁴

Ethyl 2-diazo-4-methyl-3-oxopentanoate (2a): Yellow oil (96% yield, eluent = hexane/EtOAc (90:10)); ^1H NMR (400 MHz, CDCl_3) δ 4.30 (q, J = 7.1 Hz, 2H), 3.58 (sept, J = 6.8 Hz, 1H), 1.34 (t, J = 7.1 Hz, 3H), 1.13 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 197.2, 161.4, 61.5, 37.0, 18.7, 14.5; **HRMS** (ESI) Calcd for $\text{C}_8\text{H}_{13}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 185.0926, found 185.0924.

Ethyl 3-cyclopropyl-2-diazo-3-oxopropanoate (2c): Yellow oil (95% yield, eluent = hexane/EtOAc (90:10)); ^1H NMR (400 MHz, CDCl_3) δ 4.33 (q, J = 7.1 Hz, 2H), 3.10 (tt, J = 7.9, 4.6 Hz, 1H), 1.35 (t, J = 7.1 Hz, 3H), 1.25–1.14 (m, 2H), 1.08–0.92 (m, 2H); ^{13}C

NMR (100 MHz, CDCl₃) δ 192.6, 162.0, 61.6, 17.9, 14.5, 12.0; **HRMS** (ESI) Calcd for C₈H₁₁N₂O₃ [M + H]⁺ 183.0770, found 183.0772.

Ethyl 2-diazo-3-oxo-3-(*o*-tolyl)propanoate (2j): Yellow oil (64% yield, eluent = hexane/EtOAc (90:10)); **¹H NMR** (400 MHz, CDCl₃): δ 7.39–7.29 (m, 1H), 7.28–7.18 (m, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.35 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 188.9, 160.6, 138.0, 135.1, 130.5, 130.3, 126.6, 125.3, 61.6, 19.2, 14.1; **HRMS** (ESI) Calcd for C₁₂H₁₃N₂O₃ [M + H]⁺ 233.0926, found 233.0921.

Ethyl 3-(2-bromophenyl)-2-diazo-3-oxopropanoate (2k): Yellow oil (72% yield, eluent = hexane/EtOAc (90:10)); **¹H NMR** (400 MHz, CDCl₃): δ 7.58 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.39 (td, *J* = 7.5, 1.1 Hz, 1H), 7.32 (td, *J* = 7.7, 1.8 Hz, 1H), 7.27 (dd, *J* = 7.5, 1.7 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 1.16 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 186.7, 160.32, 140.0, 132.5, 131.2, 127.8, 127.3, 119.0, 61.7, 14.0; **HRMS** (ESI) Calcd for C₁₁H₁₀BrN₂O₃ [M + H]⁺ 296.9875, found 296.9877.

Methyl 2-diazo-3-(naphthalen-1-yl)-3-oxopropanoate (2l): Yellow oil (74% yield, eluent = hexane/EtOAc (90:10)); **¹H NMR** (400 MHz, CDCl₃): δ 8.06–7.98 (m, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.85 (dd, *J* = 6.7, 2.6 Hz, 1H), 7.57–7.38 (m, 4H), 3.63 (s, 3H); **¹³C**

NMR (100 MHz, CDCl₃): δ 187.7, 160.9, 135.2, 133.5, 131.3, 129.9, 128.6, 127.4, 126.4, 125.8, 124.5, 124.4, 52.4; **HRMS** (ESI) Calcd for C₁₄H₁₁N₂O₃ [M + H]⁺ 255.0770, found 255.0764.

Copper-Catalyzed Condensation of Imines and Diazocarbonyl Compounds

General Procedure: A 10 mL Schlenk tube equipped with a stirrer bar was charged with imine (0.20 mmol), Cu(tfacac)₂ (7.4 mg, 0.020 mmol, 10 mol%), 4Å molecular sieves (300 mg), and diazocarbonyl compound (0.30 mmol), followed by the addition of toluene (0.5 mL). The resulting mixture was stirred at 110 °C for 12 h. Upon cooling to room temperature, the reaction mixture was diluted by ethyl acetate (5 mL), followed by filtration through a pad of silica gel with ethyl acetate (20 mL) as an eluent. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to afford the pyrrole product.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3aa):

The reaction was performed on a 5 mmol scale in a 100 mL 2-necked flask, following the same reaction stoichiometry and conditions as that of the general procedure. Yellow solid (92% yield, eluent = hexane/EtOAc (95:5)); Mp = 108–109 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.16–7.14 (m, 3H), 7.11–7.06 (m, 4H), 6.83–6.78 (m, 2H), 6.35 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.61 (sept, J = 6.8 Hz, 1H), 1.30 (d, J = 6.9 Hz, 6H), 1.12 (t, J = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 161.7, 159.0, 141.9, 140.1, 133.2, 132.7,

129.8, 129.1, 128.2, 127.3, 121.4, 113.6, 108.5, 59.7, 55.6, 26.4, 24.2, 14.3; **HRMS** (ESI)

Calcd for $C_{23}H_{26}NO_3$ $[M + H]^+$ 364.1913, found 364.1908.

Ethyl 3-isopropyl-1,5-bis(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3ba): Brown solid (84% yield, eluent = hexane/EtOAc (95:5)); Mp = 95–97 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.12–7.04 (m, 2H), 7.04–6.99 (m, 2H), 6.85–6.78 (m, 2H), 6.73–6.66 (m, 2H), 6.29 (s, 1H), 4.10 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.74 (s, 3H), 3.61 (sept, J = 6.8 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.7, 158.9, 141.9, 140.1, 133.4, 130.4, 129.9, 125.2, 121.0, 113.7, 113.6, 107.9, 59.7, 55.6, 55.4, 26.4, 24.2, 14.3; **HRMS** (ESI) Calcd for $C_{24}H_{28}NO_4$ $[M + H]^+$ 394.2018, found 394.2015.

Ethyl 5-(4-fluorophenyl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3ca): Yellow solid (85% yield, eluent = hexane/EtOAc (95:5)); Mp = 117–118 °C; 1H NMR (400 MHz, $CDCl_3$): δ 7.12–6.99 (m, 4H), 6.95–6.76 (m, 4H), 6.31 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 3.61 (sept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1 (d, J_{C-F} = 245.8 Hz), 161.6, 159.0,

141.8, 139.1, 133.0, 130.8 (d, $J_{C-F} = 8.0$ Hz), 129.8, 128.8 (d, $J_{C-F} = 3.4$ Hz), 121.4, 115.2 (d, $J_{C-F} = 21.5$ Hz), 113.7, 108.4, 59.8, 55.6, 26.3, 24.1, 14.3; **HRMS** (ESI) Calcd for $C_{23}H_{25}FNO_3$ $[M + H]^+$ 382.1818, found 382.1815.

Ethyl 5-(4-chlorophenyl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3da): Yellow solid (80% yield, eluent = hexane/EtOAc (95:5)); Mp = 119–120 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 7.13 (d, $J = 8.6$ Hz, 2H), 7.07 (d, $J = 8.8$ Hz, 2H), 7.01 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.34 (s, 1H), 4.11 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 3.60 (sept, $J = 6.9$ Hz, 1H), 1.29 (d, $J = 6.9$ Hz, 6H), 1.12 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.6, 159.1, 141.8, 138.8, 133.3, 132.9, 131.1, 130.3, 129.8, 128.4, 121.8, 113.7, 108.6, 59.8, 55.6, 26.3, 24.2, 14.3; **HRMS** (ESI) Calcd for $C_{23}H_{25}ClNO_3$ $[M + H]^+$ 398.1523, found 398.1526.

Ethyl 5-(4-bromophenyl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3ea): Yellow solid (72% yield, eluent = hexane/EtOAc (95:5)); Mp = 115–117 °C; **1H NMR** (400 MHz, $CDCl_3$): δ 7.28 (d, $J = 8.5$ Hz, 2H), 7.06 (d, $J = 8.8$ Hz, 2H), 6.95 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 6.34 (s, 1H), 4.10 (q, $J = 7.1$ Hz, 2H),

3.80 (s, 3H), 3.60 (sept, $J = 6.8$ Hz, 1H), 1.29 (d, $J = 6.9$ Hz, 6H), 1.12 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.6, 159.1, 141.8, 138.7, 132.9, 131.6, 131.4, 130.5, 129.8, 121.8, 121.5, 113.7, 108.6, 59.8, 55.6, 26.3, 24.1, 14.3; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{25}\text{BrNO}_3$ $[\text{M} + \text{H}]^+$ 442.1018, found 442.1023.

Ethyl 5-(4-iodophenyl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3fa): Yellow solid (71% yield, eluent = hexane/EtOAc (95:5)); Mp = 103–104 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.48 (d, $J = 8.0$ Hz, 2H), 7.07 (d, $J = 8.3$ Hz, 2H), 6.83–6.81 (m, 4H), 6.34 (s, 1H), 4.10 (q, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 3.59 (sept, $J = 6.5$ Hz, 1H), 1.29 (d, $J = 6.8$ Hz, 6H), 1.12 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.6, 159.1, 141.8, 138.8, 137.3, 132.9, 132.2, 130.7, 129.8, 121.9, 113.8, 108.6, 93.2, 59.9, 55.6, 26.3, 24.2, 14.3; HRMS (ESI) Calcd for $\text{C}_{23}\text{H}_{25}\text{INO}_3$ $[\text{M} + \text{H}]^+$ 490.0879, found 490.0877.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-(4-(trifluoromethyl)phenyl)-1H-pyrrole-2-carboxylate (3ga): Yellow solid (72% yield, eluent = hexane/EtOAc (97:3)); Mp = 94–95 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.41 (d, $J = 8.3$ Hz, 2H), 7.19 (d, $J = 8.2$ Hz, 2H),

7.08 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 6.41 (s, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 3.60 (sept, $J = 6.8$ Hz, 1H), 1.30 (d, $J = 6.9$ Hz, 6H), 1.13 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.6, 159.2, 141.8, 138.2, 136.2, 132.7, 129.8, 129.02, 129.02 (q, $J_{\text{C-F}} = 33.0$ Hz), 125.1 (q, $J_{\text{C-F}} = 4.0$ Hz), 124.3 (q, $J_{\text{C-F}} = 270.0$ Hz), 122.4, 113.8, 109.3, 60.0, 55.6, 26.3, 24.1, 14.3; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{25}\text{F}_3\text{NO}_3$ $[\text{M} + \text{H}]^+$ 432.1787, found 432.1782.

Ethyl 5-(4-cyanophenyl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate

(3ha): White solid (74% yield, eluent = hexane/EtOAc (90:10)); Mp = 121–123 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.44 (d, $J = 8.4$ Hz, 2H), 7.17 (d, $J = 8.4$ Hz, 2H), 7.08 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 6.45 (s, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.82 (s, 3H), 3.59 (sept, $J = 6.8$ Hz, 1H), 1.30 (d, $J = 6.9$ Hz, 6H), 1.13 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.5, 159.4, 141.7, 137.6, 137.1, 132.5, 132.0, 129.7, 129.1, 122.9, 119.0, 113.9, 110.5, 109.8, 60.1, 55.6, 26.3, 24.1, 14.2; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{25}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 389.1865, found 389.1861.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-(4-nitrophenyl)-1H-pyrrole-2-carboxylate

(3ia): Orange solid (52% yield, eluent = hexane/EtOAc (95:5)); Mp = 106–107 °C; **¹H NMR** (400 MHz, CDCl₃): δ 8.02 (d, *J* = 8.8 Hz, 2H), 7.23 (d, *J* = 8.8 Hz, 2H), 7.09 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.50 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.82 (s, 3H), 3.60 (sept, *J* = 6.8 Hz, 1H), 1.30 (d, *J* = 6.8 Hz, 6H), 1.14 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.5, 159.5, 146.5, 141.8, 139.1, 137.2, 132.5, 129.8, 129.1, 123.6, 123.3, 114.0, 110.2, 60.2, 55.7, 26.3, 24.1, 14.3; **HRMS** (ESI) Calcd for C₂₃H₂₅N₂O₅ [M + H]⁺ 409.1763, found 409.1767.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-(*o*-tolyl)-1H-pyrrole-2-carboxylate (3ja):

Orange solid (88% yield, eluent = hexane/EtOAc (95:5)); Mp = 98–99 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.15–7.03 (m, 2H), 7.03–6.87 (m, 4H), 6.69 (d, *J* = 8.8 Hz, 2H), 6.17 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 3.63 (sept, *J* = 6.8 Hz, 1H), 2.09 (s, 3H), 1.29 (d, *J* = 6.9 Hz, 6H), 1.11 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.8, 158.5, 141.7, 139.6, 137.9, 133.1, 132.6, 131.7, 129.9, 129.1, 128.2, 125.1, 120.0, 113.3, 108.8, 59.7, 55.5, 26.4, 24.2, 20.6, 14.3; **HRMS** (ESI) Calcd for C₂₄H₂₈NO₃ [M + H]⁺ 378.2069, found 378.2072. Recrystallization from EtOAc/hexane afforded single crystals suitable for X-ray diffraction analysis, which unambiguously confirmed the substitution pattern of **3ja** (see below).²⁵

Figure S1. ORTEP diagram of **3ja**. Thermal ellipsoids drawn at 50% probability.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-(naphthalen-2-yl)-1H-pyrrole-2-carboxylate (3ka): Yellow solid (87% yield, eluent = hexane/EtOAc (95:5)); Mp = 130–132 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.73–7.70 (m, 1H), 7.68–7.64 (m, 1H), 7.64–7.54 (m, 2H), 7.44–7.34 (m, 2H), 7.17–7.09 (m, 3H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.47 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.77 (s, 3H), 3.64 (sept, *J* = 6.8 Hz, 1H), 1.33 (d, *J* = 6.9 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.7, 159.0, 142.0, 140.0, 133.3, 133.2, 132.4, 130.2, 129.9, 128.3, 128.2, 127.7, 127.6, 126.9, 126.34, 126.28, 121.6, 113.7, 108.9, 59.8, 55.6, 26.4, 24.2, 14.3; **HRMS** (ESI) Calcd for C₂₇H₂₈NO₃ [*M* + *H*]⁺ 414.2069, found 414.2072.

Ethyl 5-(furan-2-yl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate

(3la): Yellow solid (83% yield, eluent = hexane/EtOAc (95:5)); Mp = 80–82 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.30 (d, J = 1.3 Hz, 1H), 7.19 (d, J = 8.8 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 6.61 (s, 1H), 6.16 (dd, J = 3.4, 1.8 Hz, 1H), 5.13 (d, J = 3.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.87 (s, 3H), 3.60 (sept, J = 6.8 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H), 1.10 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.5, 159.7, 147.0, 142.0, 141.6, 133.5, 131.4, 129.6, 121.5, 114.1, 111.4, 106.6, 106.4, 59.7, 55.7, 26.3, 24.1, 14.2; HRMS (ESI) Calcd for $\text{C}_{21}\text{H}_{24}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 354.1705, found 354.1706.

Ethyl 5-(benzofuran-2-yl)-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (3ma):

Yellow solid (87% yield, eluent = hexane/EtOAc (95:5)); Mp = 85–86 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.41 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 7.5 Hz, 1H), 7.27–7.23 (m, 2H), 7.23–7.17 (m, 1H), 7.11 (t, J = 7.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 2H), 6.86 (s, 1H), 5.43 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 3.62 (sept, J = 6.8 Hz, 1H), 1.33 (d, J = 6.9 Hz, 6H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.4, 159.9, 154.1, 148.6, 141.9, 133.2, 130.6, 129.7, 129.0, 124.6, 123.1, 122.9, 121.2,

114.3, 110.9, 108.4, 102.5, 59.9, 55.7, 26.4, 24.1, 14.2; **HRMS** (ESI) Calcd for $C_{25}H_{26}NO_4$ $[M + H]^+$ 404.1862, found 404.1862.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-(thiophen-2-yl)-1H-pyrrole-2-carboxylate

(3na): Yellow solid (73% yield, eluent = hexane/EtOAc (95:5)); Mp = 73–75 °C; **¹H NMR** (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 5.1 Hz, 1H), 6.91 (d, J = 8.8 Hz, 2H), 6.84–6.80 (m, 1H), 6.65 (d, J = 3.7 Hz, 1H), 6.46 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.60 (sept, J = 6.9 Hz, 1H), 1.29 (d, J = 6.9 Hz, 6H), 1.11 (t, J = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, $CDCl_3$): δ 161.4, 159.8, 142.0, 134.4, 134.0, 132.9, 130.3, 127.1, 125.7, 125.4, 121.7, 114.0, 107.9, 59.7, 55.7, 26.3, 24.1, 14.3; **HRMS** (ESI) Calcd for $C_{21}H_{24}NO_3S$ $[M + H]^+$ 370.1477, found 370.1476.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-5-(1-methyl-1H-indol-3-yl)-1H-pyrrole-2-

carboxylate (3oa): Yellow solid (70% yield, eluent = hexane/EtOAc (95:5)); Mp = 134–135 °C; **¹H NMR** (400 MHz, $CDCl_3$): δ 7.83 (d, J = 7.9 Hz, 1H), 7.23 (dd, J = 3.4, 1.0 Hz, 2H), 7.21–7.04 (m, 3H), 6.85 (d, J = 8.9 Hz, 2H), 6.55 (s, 1H), 6.15 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.81 (s, 3H), 3.67 (sept, J = 6.8 Hz, 1H), 3.56 (s, 3H), 1.35 (d, J = 6.9 Hz,

6H), 1.12 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.7, 159.1, 142.4, 136.5, 134.7, 134.0, 129.9, 127.8, 127.5, 122.3, 120.4, 120.2, 120.0, 113.7, 109.5, 107.6, 107.0, 59.5, 55.6, 33.0, 26.5, 24.2, 14.3; **HRMS** (ESI) Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_2\text{O}_3$ $[\text{M} + \text{H}]^+$ 417.2178, found 417.2177.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-4-methyl-5-phenyl-1H-pyrrole-2-carboxylate (3pa): Orange solid (77% yield, eluent = hexane/EtOAc (95:5)); Mp = 88–89 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.22–7.14 (m, 3H), 7.03 (dd, $J = 7.6, 1.9$ Hz, 2H), 6.95 (d, $J = 8.9$ Hz, 2H), 6.70 (d, $J = 8.9$ Hz, 2H), 4.03 (q, $J = 7.1$ Hz, 2H), 3.76 (sept, $J = 6.8$ Hz, 1H), 3.74 (s, 3H), 2.07 (s, 3H), 1.38 (d, $J = 7.2$ Hz, 6H), 0.99 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.3, 158.5, 138.2, 137.7, 133.6, 132.2, 131.2, 129.5, 127.9, 127.3, 121.0, 116.9, 113.3, 59.8, 55.5, 26.1, 22.2, 14.1, 11.8; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 378.2069, found 378.2069.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-4,5-diphenyl-1H-pyrrole-2-carboxylate (3qa): Brown solid (76% yield, eluent = hexane/EtOAc (95:5)); Mp = 126–128 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.25–7.13 (m, 5H), 7.07 (d, $J = 8.8$ Hz, 2H), 6.97 (d, $J = 6.9$

Hz, 3H), 6.87 (dd, $J = 7.4, 1.8$ Hz, 2H), 6.73 (d, $J = 8.8$ Hz, 2H), 4.08 (q, $J = 7.1$ Hz, 2H), 3.74 (s, 3H), 3.43 (sept, $J = 7.1$ Hz, 1H), 1.26 (d, $J = 7.1$ Hz, 6H), 1.06 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.3, 158.7, 137.6, 137.5, 136.4, 133.2, 131.78, 131.76, 131.3, 129.8, 127.8, 127.5, 127.0, 126.5, 125.0, 121.6, 113.4, 60.1, 55.5, 26.5, 22.9, 14.2; **HRMS** (ESI) Calcd for $\text{C}_{29}\text{H}_{30}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 440.2226, found 440.2221.

Ethyl 5-cyclopropyl-3-isopropyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate

(3ra): Yellow solid (84% yield, eluent = hexane/EtOAc (95:5)); Mp = 72–73 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.18 (d, $J = 8.8$ Hz, 2H), 6.93 (d, $J = 8.8$ Hz, 2H), 5.75 (s, 1H), 4.05 (q, $J = 7.1$ Hz, 2H), 3.84 (s, 3H), 3.56 (sept, $J = 6.8$ Hz, 1H), 1.40–1.31 (m, 1H), 1.22 (d, $J = 6.9$ Hz, 6H), 1.07 (t, $J = 7.1$ Hz, 3H), 0.76–0.66 (m, 2H), 0.66–0.55 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.4, 159.0, 143.3, 141.9, 133.5, 129.2, 119.7, 113.8, 102.3, 59.3, 55.6, 26.3, 24.1, 14.2, 8.3, 8.0; **HRMS** (ESI) Calcd for $\text{C}_{20}\text{H}_{26}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 328.1913, found 328.1909.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-4,5,6,7-tetrahydro-1H-indole-2-carboxylate

(3sa): Yellow oil (73% yield, eluent = hexane/EtOAc (95:5)); ^1H NMR (400 MHz,

CDCl₃): δ 7.08 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 4.00 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.79 (sept, J = 6.8 Hz, 1H), 2.64 (t, J = 5.4 Hz, 2H), 2.23 (t, J = 5.6 Hz, 2H), 1.74–1.69 (m, 4H), 1.30 (d, J = 7.1 Hz, 6H), 0.97 (t, J = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 162.0, 158.8, 137.7, 136.5, 133.5, 128.7, 119.3, 117.5, 113.8, 59.3, 55.6, 26.1, 23.8, 23.7, 23.4, 22.9, 22.4, 14.1; **HRMS** (ESI) Calcd for C₂₁H₂₈NO₃ [M + H]⁺ 342.2069, found 342.2068.

Ethyl 3-isopropyl-1-(4-methoxyphenyl)-1,4,5,6,7,8-hexahydrocyclohepta[b]pyrrole-2-carboxylate (3ta): Yellow solid (68% yield, eluent = hexane/EtOAc (95:5)); Mp = 85–87 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.06 (d, J = 8.7 Hz, 2H), 6.89 (d, J = 8.7 Hz, 2H), 3.97 (q, J = 7.1 Hz, 2H), 3.83 (s, 3H), 3.82 (sept, J = 7.1 Hz, 1H), 2.71–2.68 (m, 2H), 2.40–2.25 (m, 2H), 1.80–1.76 (m, 2H), 1.71–1.60 (m, 2H), 1.53–1.57 (m, 2H), 1.32 (d, J = 7.2 Hz, 6H), 0.95 (t, J = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.9, 158.7, 140.8, 137.4, 133.5, 129.1, 122.7, 118.3, 113.5, 59.1, 55.4, 32.3, 28.2, 26.9, 26.5, 26.2, 25.1, 22.5, 13.9; **HRMS** (ESI) Calcd for C₂₂H₃₀NO₃ [M + H]⁺ 356.2226, found 356.2227.

Ethyl 1-(4-chlorophenyl)-3-isopropyl-5-phenyl-1H-pyrrole-2-carboxylate (3ua):

Orange solid (42% yield, eluent = hexane/EtOAc (95:5)); Mp = 90–91 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.29–7.23 (m, 2H), 7.19–7.17 (m, 3H), 7.12–7.03 (m, 4H), 6.36 (s, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.61 (sept, *J* = 6.8 Hz, 1H), 1.30 (d, *J* = 6.9 Hz, 6H), 1.13 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 161.3, 142.2, 139.9, 138.8, 133.4, 132.0, 130.0, 129.0, 128.4, 128.1, 127.4, 121.0, 108.8, 59.7, 26.1, 23.9, 14.0; HRMS (ESI) Calcd for C₂₂H₂₃ClNO₂ [M + H]⁺ 368.1417, found 368.1417.

Ethyl 1-benzyl-3-isopropyl-5-phenyl-1H-pyrrole-2-carboxylate (3va):

Yellow oil (72% yield, eluent = hexane/EtOAc (97:3)); ¹H NMR (400 MHz, CDCl₃): δ 7.31 (s, 5H), 7.26–7.20 (m, 2H), 7.16 (t, *J* = 7.2 Hz, 1H), 6.84 (d, *J* = 7.2 Hz, 2H), 6.25 (s, 1H), 5.53 (s, 2H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.60 (sept, *J* = 6.8 Hz, 1H), 1.26 (d, *J* = 6.8 Hz, 6H), 1.21 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.0, 142.7, 141.2, 140.3, 132.8, 129.6, 128.64, 128.60, 128.3, 126.8, 125.8, 119.4, 108.5, 59.8, 50.0, 26.6, 24.2, 14.4; HRMS (ESI) Calcd for C₂₃H₂₆NO₂ [M + H]⁺ 348.1964, found 348.1961.

Ethyl 1-benzyl-5-(4-fluorophenyl)-3-isopropyl-1H-pyrrole-2-carboxylate (3wa):

Yellow oil (68% yield, eluent = hexane/EtOAc (97:3)); ¹H NMR (400 MHz, CDCl₃): δ

7.72–7.15 (m, 5H), 7.00 (t, $J = 8.6$ Hz, 2H), 6.82 (d, $J = 7.4$ Hz, 2H), 6.21 (s, 1H), 5.49 (s, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.60 (sept, $J = 6.8$ Hz, 1H), 1.26 (d, $J = 6.8$ Hz, 6H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.85 (d, $J_{\text{C-F}} = 248.1$ Hz), 162.0, 142.5, 140.1, 140.0, 131.39 (d, $J_{\text{C-F}} = 8.2$ Hz), 128.82 (d, $J_{\text{C-F}} = 3.3$ Hz), 128.7, 126.9, 125.7, 119.5, 115.64 (d, $J_{\text{C-F}} = 21.5$ Hz), 108.5, 59.9, 49.9, 26.5, 24.1, 14.4; **HRMS** (ESI) Calcd for $\text{C}_{23}\text{H}_{25}\text{FNO}_2$ $[\text{M} + \text{H}]^+$ 366.1869, found 366.1866.

Ethyl 1-benzyl-5-(4-chlorophenyl)-3-isopropyl-1H-pyrrole-2-carboxylate (3xa):

Yellow oil (72% yield, eluent = hexane/EtOAc (97:3)); ^1H NMR (400 MHz, CDCl_3): δ 7.35 – 7.12 (m, 7H), 6.83 (d, $J = 7.5$ Hz, 2H), 6.23 (s, 1H), 5.50 (s, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 3.60 (sept, $J = 6.7$ Hz, 1H), 1.26 (d, $J = 6.9$ Hz, 6H), 1.22 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.0, 142.6, 140.0, 139.8, 134.4, 131.2, 130.8, 128.9, 128.7, 127.0, 125.7, 119.8, 108.6, 59.9, 50.0, 26.5, 24.1, 14.4; **HRMS** (ESI) Calcd for $\text{C}_{23}\text{H}_{25}\text{ClNO}_2$ $[\text{M} + \text{H}]^+$ 382.1574, found 382.1569.

Ethyl 3-isopropyl-1-(4-methoxybenzyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ya):

Yellow oil (73% yield, eluent = hexane/EtOAc (97:3)); ^1H NMR (400 MHz, CDCl_3): δ 7.32 (s, 5H), 6.76 (s, 4H), 6.22 (s, 1H), 5.47 (s, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.74 (s,

3H), 3.59 (sept, $J = 6.8$ Hz, 1H), 1.25 (d, $J = 6.8$ Hz, 6H). 1.25 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.1, 158.5, 142.6, 141.1, 132.8, 132.3, 129.6, 128.6, 128.2, 127.1, 119.3, 114.0, 108.4, 59.8, 55.4, 49.3, 26.5, 24.2, 14.5; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{28}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 378.2069, found 378.2068.

General Protocol for Deprotection of PMB: To a 50 mL oven dried Schlenk tube was added **3ya** (56.6 mg, 0.15 mmol), anisole (152 mg, 1.35 mmol) and trifluoroacetic acid (1.5 mL) in dichloromethane (6.0 mL) and stirred at 37 °C for 40 h. The reaction mixture was concentrated under reduced pressure, and the residue purified by flash chromatography on silica gel to afford the desired N-H pyrrole.

Ethyl 3-isopropyl-5-phenyl-1H-pyrrole-2-carboxylate (3ya'): White solid (90% yield, eluent = hexane/EtOAc (90:10)); Mp = 104-106 °C; ^1H NMR (400 MHz, Acetone) δ 10.62 (s, 1H), 7.79 (d, $J = 7.4$ Hz, 2H), 7.39 (t, $J = 7.7$ Hz, 2H), 7.28 (d, $J = 7.4$ Hz, 1H), 6.63 (d, $J = 2.8$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.61 (hept, $J = 6.9$ Hz, 1H), 1.32 (t, $J = 7.1$ Hz, 3H), 1.25 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, Acetone) δ 160.7, 140.9, 135.4, 131.9, 128.7, 127.2, 124.9, 118.7, 105.7, 59.2, 25.4, 23.2, 13.9; HRMS (ESI) Calcd for $\text{C}_{16}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 258.1494, found 258.1498.

Ethyl 1-allyl-3-isopropyl-5-phenyl-1H-pyrrole-2-carboxylate (3za): Yellow oil (57% yield, eluent = hexane/EtOAc (97:3)); ^1H NMR (400 MHz, CDCl_3): δ 7.48–7.32 (m, 5H),

6.17 (s, 1H), 6.04–5.84 (m, 1H), 5.06 (dd, $J = 10.4, 1.3$ Hz, 1H), 4.92–4.87 (m, 2H), 4.76 (dd, $J = 17.2, 1.3$ Hz, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 3.58 (sept, $J = 6.8$ Hz, 1H), 1.36 (t, $J = 7.1$ Hz, 3H), 1.24 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.2, 142.1, 140.7, 136.4, 132.9, 129.7, 128.5, 128.3, 119.0, 115.2, 108.2, 59.9, 48.7, 26.6, 24.2, 14.6; **HRMS** (ESI) Calcd for $\text{C}_{19}\text{H}_{24}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 298.1807, found 298.1805.

Ethyl 2-isopropyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3aaa):

Yellow oil (73%, eluent = hexane/EtOAc (95:5)); ^1H NMR (400 MHz, CDCl_3) δ 7.55 (d, $J = 7.6$ Hz, 1H), 7.28–7.19 (m, 1H), 7.20–7.09 (m, 2H), 6.50 (s, 1H), 4.63–4.52 (m, 2H), 4.35 (d, $J = 7.1$ Hz, 2H), 3.56 (hept, $J = 6.8$ Hz, 1H), 3.04 (t, $J = 6.8$ Hz, 2H), 1.38 (t, $J = 7.1$ Hz, 3H), 1.27 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.4, 142.5, 135.1, 132.1, 128.6, 127.9, 127.4, 127.2, 123.8, 118.5, 103.0, 59.9, 42.8, 29.3, 26.5, 24.2, 14.6. **HRMS** (ESI) Calcd for $\text{C}_{18}\text{H}_{22}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 284.1651, found 284.1652.

Ethyl 2-isopropyl-1-phenyl-5,6-dihydropyrrolo[2,1-a]isoquinoline-3-carboxylate

(3aba): White solid (48%, eluent = hexane/EtOAc (98:2)); Mp = 135–136 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.42–7.36 (m, 3H), 7.33–7.27 (m, 2H), 7.15 (d, $J = 7.5$ Hz, 1H), 7.04 (t, $J = 7.4$ Hz, 1H), 6.85 (t, $J = 7.7$ Hz, 1H), 6.68 (d, $J = 7.9$ Hz, 1H), 4.54 (t, $J = 6.6$ Hz, 2H), 4.37 (q, $J = 7.1$ Hz, 2H), 3.33 (sept, $J = 7.1$ Hz, 1H), 3.05 (t, $J = 6.6$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H), 1.16 (d, $J = 7.2$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 162.7,

138.2, 137.5, 133.5, 131.6, 131.1, 128.9, 128.7, 127.8, 127.3, 126.8, 126.7, 125.3, 123.1, 118.7, 60.3, 43.0, 29.9, 26.5, 22.8, 14.6; **HRMS** (ESI) Calcd for $C_{24}H_{26}NO_2$ $[M + H]^+$ 360.1964, found 360.1960.

Ethyl 2-isopropyl-1-oxo-10b-phenyl-1,5,6,10b-tetrahydropyrrolo[2,1-a]isoquinoline-3-carboxylate (3aba'): Orange oil (50%, eluent = hexane/EtOAc (96:4)); **1H NMR** (400 MHz, $CDCl_3$) δ 7.88 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.38–7.25 (m, 5H), 7.20–7.18 (m, 1H), 7.12–6.91 (m, 2H), 4.47 (q, $J = 6.9$ Hz, 2H), 3.73–3.67 (m, 1H), 3.58–3.43 (m, 1H), 3.02–3.98 (m, 1H), 2.89–2.66 (m, 2H), 1.45 (t, $J = 7.1$ Hz, 3H), 1.22 (d, $J = 10.8$, 3H), 1.21 (d, $J = 10.8$, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 201.5, 163.1, 162.0, 140.9, 134.3, 133.1, 128.48, 128.45, 128.4, 127.8, 127.7, 127.4, 126.6, 120.1, 73.3, 62.4, 41.6, 29.5, 24.2, 21.21, 21.15, 14.2; **HRMS** (ESI) Calcd for $C_{24}H_{26}NO_3$ $[M + H]^+$ 376.1913, found 376.1908.

Ethyl 3-methyl-5-phenyl-1H-pyrrole-2-carboxylate (3acb): White solid (35%, eluent = hexane/EtOAc (96:4)); Mp = 114–116 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 9.15 (s, 1H), 7.59 – 7.54 (m, 2H), 7.42 (t, $J = 7.7$ Hz, 2H), 7.34 – 7.27 (m, 1H), 6.41 (d, $J = 3.0$ Hz, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 2.41 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.8, 135.1, 131.4, 129.4, 129.0, 127.6, 124.6, 119.9, 110.2, 60.1, 14.6, 13.0; **HRMS** (ESI) Calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$ 230.1181, found 230.1183

Ethyl 6-methyl-3-phenyl-2H-1,4-oxazine-5-carboxylate (4): Yellow oil (22%, eluent = hexane/EtOAc (96:4)); **¹H NMR** (400 MHz, CDCl₃) δ 7.97–7.76 (m, 2H), 7.51–7.39 (m, 3H), 4.82 (s, 2H), 4.37 (q, *J* = 7.1 Hz, 2H), 2.41 (s, 3H), 1.42 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 165.8, 157.6, 148.3, 135.0, 130.6, 128.7, 126.6, 120.7, 62.0, 60.6, 17.9, 14.4; **HRMS** (ESI) Calcd for C₁₄H₁₆NO₃ [*M* + *H*]⁺ 246.1130, found 246.1136

Ethyl 1,4-bis(4-methoxyphenyl)-3-methyl-1H-pyrrole-2-carboxylate (3adb): Yellow oil (32%, eluent = hexane/EtOAc (98:2)); **¹H NMR** (400 MHz, CDCl₃) δ 7.34 (d, *J* = 8.5 Hz, 2H), 7.25 (d, *J* = 8.7 Hz, 2H), 6.98–6.94 (m, 4H), 6.89 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.868 (s, 3H), 3.866 (s, 3H), 2.47 (s, 3H), 1.17 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 161.5, 158.8, 158.3, 134.5, 129.7, 127.5, 127.32, 127.28, 126.8, 125.8, 121.6, 113.9, 113.6, 59.7, 55.5, 55.3, 14.2, 12.2; **HRMS** (ESI) Calcd for C₂₂H₂₄NO₄ [*M* + *H*]⁺ 366.1705, found 366.1701

Ethyl 2-(*t*-butyl)-5-isopropyl-3-(4-methoxyphenyl)-2-methyl-2,3-dihydrooxazole-4-carboxylate (5a): Orange oil (95% yield, eluent = hexane/EtOAc (95:5)); ^1H NMR (400 MHz, CDCl_3): δ 7.07 (s, 2H), 6.80 (d, $J = 9.1$ Hz, 2H), 4.09 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.94 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.79 (s, 3H), 3.64 (sept, $J = 7.0$ Hz, 1H), 1.28 (d, $J = 7.0$ Hz, 3H), 1.24 (d, $J = 6.9$ Hz, 3H), 1.11 (s, 9H), 1.10 (s, 3H), 1.01 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.0, 163.0, 156.7, 140.7, 116.3, 113.6, 108.7, 59.3, 55.3, 41.4, 26.0, 25.0, 20.1, 19.8, 19.7, 14.1; **HRMS** (ESI) Calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 362.2331, found 362.2327.

Ethyl 5-isopropyl-3-(4-methoxyphenyl)-2-methyl-2-(trifluoromethyl)-2,3-dihydrooxazole-4-carboxylate (5b): Yellow oil (70% yield, eluent = hexane/EtOAc (95:5)); ^1H NMR (400 MHz, CDCl_3): δ 7.13 (s, 1H), 6.95 (s, 1H), 6.85 (s, 2H), 4.14 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.96 (dq, $J = 10.8, 7.1$ Hz, 1H), 3.81 (s, 3H), 3.64 (sept, $J = 7.0$ Hz, 1H), 1.31 (s, 3H), 1.27 (d, $J = 7.0$ Hz, 3H), 1.22 (d, $J = 6.9$ Hz, 3H), 1.02 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.1, 162.1, 157.9, 137.2, 129.4, 125.9, 123.3 (q, $J_{\text{C-F}} = 287.4$ Hz), 115.9, 114.3, 114.0, 98.6 (q, $J_{\text{C-F}} = 31.4$ Hz), 60.2, 55.6, 26.0, 20.3, 19.2, 17.5, 14.1; **HRMS** (ESI) Calcd for $\text{C}_{18}\text{H}_{23}\text{F}_3\text{NO}_4$ $[\text{M} + \text{H}]^+$ 374.1579, found 374.1578.

Ethyl 1-(4-methoxyphenyl)-3-methyl-5-phenyl-1H-pyrrole-2-carboxylate (3ab):

Yellow solid (81% yield, eluent = hexane/EtOAc (95:5)); Mp = 104–105 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.17–7.15 (m, 3H), 7.12–7.01 (m, 4H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.26 (s, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.44 (s, 3H), 1.16 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.7, 159.0, 140.1, 133.1, 132.4, 130.3, 129.9, 129.1, 128.2, 127.4, 122.6, 113.6, 112.9, 59.7, 55.6, 14.5, 14.4; **HRMS** (ESI) Calcd for C₂₁H₂₂NO₃ [*M* + *H*]⁺ 336.1600, found 336.1599.

Ethyl 3-cyclopropyl-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ac):

Yellow solid (80% yield, eluent = hexane/EtOAc (95:5)); Mp = 108–109 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.19–7.10 (m, 3H), 7.10–7.00 (m, 4H), 6.80 (d, *J* = 8.8 Hz, 2H), 5.95 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.78 (s, 3H), 2.60 (tt, *J* = 8.5, 5.2 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.05–0.90 (m, 2H), 0.75–0.59 (m, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.9, 159.0, 140.5, 137.4, 133.1, 132.4, 129.9, 129.1, 128.2, 127.4, 123.1, 113.6, 106.7, 59.8, 55.5, 14.4, 9.3, 8.7; **HRMS** (ESI) Calcd for C₂₃H₂₄NO₃ [*M* + *H*]⁺ 362.1756, found 362.1754.

Methyl 3-cyclohexyl-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ad):

Yellow solid (88% yield, eluent = hexane/EtOAc (95:5)); Mp = 128–130 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.18–7.13 (m, 3H), 7.11–7.06 (m, 4H), 6.81 (d, *J* = 8.9 Hz, 2H), 6.33 (s, 1H), 3.79 (s, 3H), 3.64 (s, 3H), 3.23–3.17 (m, 1H), 1.99–1.97 (m, 2H), 1.89–1.71 (m, 3H), 1.50–1.37 (m, 4H), 1.32–1.25 (m, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 162.2, 158.9, 141.1, 140.4, 133.1, 132.6, 129.8, 129.1, 128.1, 127.3, 121.2, 113.6, 109.1, 55.5, 51.0, 36.7, 34.7, 27.2, 26.6; HRMS (ESI) Calcd for C₂₅H₂₈NO₃ [M + H]⁺ 390.2069, found 390.2066.

Methyl 3-benzyl-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ae):

Yellow solid (94% yield, eluent = hexane/EtOAc (95:5)); Mp = 139–141 °C; ¹H NMR (400 MHz, CDCl₃): δ 7.35–7.27 (m, 4H), 7.24–7.16 (m, 1H), 7.16–7.01 (m, 7H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.14 (s, 1H), 4.22 (s, 2H), 3.79 (s, 3H), 3.65 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ 162.0, 159.1, 141.5, 140.5, 133.5, 132.8, 132.2, 129.8, 129.2, 129.1, 128.6, 128.2, 127.4, 126.1, 121.9, 113.7, 112.3, 55.5, 51.0, 34.4; HRMS (ESI) Calcd for C₂₆H₂₄NO₃ [M + H]⁺ 398.1756, found 398.1757.

Ethyl 1-(4-methoxyphenyl)-3,5-diphenyl-1H-pyrrole-2-carboxylate (3af): Yellow solid (77% yield, eluent = hexane/EtOAc (95:5)); Mp = 125–127 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.52 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.4 Hz, 2H), 7.30 (t, J = 7.3 Hz, 1H), 7.20 – 7.08 (m, 7H), 6.84 (d, J = 8.8 Hz, 2H), 6.46 (s, 1H), 3.97 (q, J = 7.1 Hz, 2H), 3.79 (s, 3H), 0.90 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.4, 159.0, 139.6, 136.2, 133.2, 132.3, 132.0, 129.6, 129.5, 129.0, 128.1, 127.7, 127.3, 126.8, 121.9, 113.6, 111.9, 60.0, 55.4, 13.7; **HRMS** (ESI) Calcd for $\text{C}_{26}\text{H}_{24}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 398.1756, found 398.1752.

Ethyl 1,3-bis(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ag): Yellow solid (77% yield, eluent = hexane/EtOAc (95:5)); Mp = 107–108 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.47 (d, J = 8.7 Hz, 2H), 7.23–7.06 (m, 7H), 6.93 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 6.43 (s, 1H), 3.98 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 0.93 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.6, 159.2, 158.9, 139.8, 133.3, 132.7, 132.3, 130.8, 129.8, 129.2, 128.8, 128.3, 127.5, 121.9, 113.8, 113.4, 112.1,

60.1, 55.6, 55.5, 14.0; **HRMS** (ESI) Calcd for $C_{27}H_{26}NO_4$ $[M + H]^+$ 428.1862, found 428.1857.

Ethyl 3-(4-bromophenyl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate

(3ah): Orange solid (86% yield, eluent = hexane/EtOAc (95:5)); Mp = 109–110 °C; **¹H NMR** (400 MHz, $CDCl_3$): δ 7.50 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.5 Hz, 2H), 7.23–7.10 (m, 7H), 6.84 (d, J = 8.9 Hz, 2H), 6.42 (s, 1H), 3.98 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 0.93 (t, J = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, $CDCl_3$): δ 161.3, 159.3, 140.0, 135.4, 132.4, 132.2, 132.0, 131.4, 131.0, 129.7, 129.2, 128.3, 127.7, 122.0, 121.1, 113.8, 111.9, 60.3, 55.6, 13.9; **HRMS** (ESI) Calcd for $C_{26}H_{23}BrNO_3$ $[M + H]^+$ 470.0861, found 476.0860.

Ethyl 1-(4-methoxyphenyl)-3-(4-nitrophenyl)-5-phenyl-1H-pyrrole-2-carboxylate

(3ai): Orange solid (80% yield, eluent = hexane/EtOAc (95:5)); Mp = 122–123 °C; **¹H NMR** (400 MHz, $CDCl_3$): δ 8.25 (d, J = 8.8 Hz, 2H), 7.70 (d, J = 8.7 Hz, 2H), 7.24–7.19 (m, 3H), 7.17–7.10 (m, 4H), 6.86 (d, J = 8.8 Hz, 2H), 6.48 (s, 1H), 3.99 (q, J = 7.1 Hz,

2H), 3.82 (s, 3H), 0.92 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.1, 159.5, 146.9, 143.50, 140.4, 132.1, 131.7, 130.9, 130.4, 129.7, 129.2, 128.4, 127.9, 123.2, 122.4, 113.9, 111.8, 60.5, 55.6, 13.9; **HRMS** (ESI) Calcd for $\text{C}_{26}\text{H}_{23}\text{N}_2\text{O}_5$ $[\text{M} + \text{H}]^+$ 443.1607, found 443.1611.

Ethyl 1-(4-methoxyphenyl)-5-phenyl-3-(*o*-tolyl)-1H-pyrrole-2-carboxylate (3aj):

Yellow solid (67% yield, eluent = hexane/EtOAc (95:5)); Mp = 114–116 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.33–7.12 (m, 11H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.35 (s, 1H), 3.87 (q, $J = 7.1$ Hz, 2H), 3.81 (s, 3H), 2.28 (s, 3H), 0.76 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.3, 159.2, 140.0, 137.1, 136.9, 133.4, 132.6, 132.2, 130.2, 129.9, 129.5, 129.1, 128.3, 127.5, 127.2, 125.2, 122.6, 113.8, 112.3, 59.8, 55.0, 20.6, 13.6; **HRMS** (ESI) Calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 412.1913, found 412.1908.

Ethyl 3-(2-bromophenyl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ak):

Orange solid (60% yield, eluent = hexane/EtOAc (95:5)); Mp = 117–119 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.63 (d, $J = 8.0$ Hz, 1H), 7.41 (dd, $J = 7.6, 1.6$ Hz, 1H), 7.32

(t, $J = 7.5$ Hz, 1H), 7.22–7.12 (m, 8H), 6.86 (d, $J = 8.8$ Hz, 2H), 6.40 (s, 1H), 3.91 (q, $J = 7.1$ Hz, 2H), 3.80 (s, 3H), 0.80 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.9, 159.3, 139.8, 138.5, 132.38, 132.35, 132.3, 132.1, 131.6, 129.9, 129.1, 128.5, 128.3, 127.5, 126.9, 124.7, 122.8, 113.8, 112.2, 60.0, 55.6, 13.6; **HRMS** (ESI) Calcd for $\text{C}_{26}\text{H}_{23}\text{BrNO}_3$ $[\text{M} + \text{H}]^+$ 476.0861, found 476.0864.

Methyl 1-(4-methoxyphenyl)-3-(naphthalen-1-yl)-5-phenyl-1H-pyrrole-2-carboxylate

(3al): Orange solid (74% yield, eluent = hexane/EtOAc (90:10)); Mp = 125–127 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.03–7.94 (m, 1H), 7.91–7.85 (m, 1H), 7.83 (dd, $J = 5.9, 3.6$ Hz, 1H), 7.55–7.47 (m, 2H), 7.44 (tt, $J = 12.6, 3.4$ Hz, 2H), 7.28–7.16 (m, 7H), 6.88 (d, $J = 9.0$ Hz, 2H), 6.52 (s, 1H), 3.80 (s, 3H), 3.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 161.8, 159.3, 140.2, 135.0, 133.7, 132.7, 132.4, 132.1, 131.6, 129.9, 129.1, 128.4, 128.3, 127.6, 127.5, 127.4, 126.5, 125.9, 125.7, 125.3, 123.2, 113.9, 113.5, 55.5, 50.9; **HRMS** (ESI) Calcd for $\text{C}_{29}\text{H}_{24}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 434.1756, found 434.1759.

Methyl 3-(furan-2-yl)-1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate

(3am): Orange solid (70% yield, eluent = hexane/EtOAc (95:5)); Mp = 140–141 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.47 (d, *J* = 1.2 Hz, 1H), 7.22–7.16 (m, 3H), 7.15–7.04 (m, 4H), 6.91 (d, *J* = 3.3 Hz, 1H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.76 (s, 1H), 6.49 (dd, *J* = 3.3, 1.8 Hz, 1H), 3.80 (s, 3H), 3.64 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 161.6, 159.2, 149.2, 141.7, 140.4, 132.4, 131.9, 129.6, 129.2, 128.3, 127.7, 122.9, 120.7, 113.8, 111.6, 110.0, 109.0, 55.6, 51.3; **HRMS** (ESI) Calcd for C₂₃H₂₀NO₄ [M + H]⁺ 374.1392, found 374.1395.

Diethyl 1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2,3-dicarboxylate (3an):

Yellow oil (79% yield, eluent = hexane/EtOAc (95:5)); **¹H NMR** (400 MHz, CDCl₃): δ 7.23–7.15 (m, 3H), 7.14–7.02 (m, 4H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.75 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 164.5, 161.9, 159.7, 137.3, 131.5, 130.8, 129.5, 129.3, 129.0, 128.4, 127.7, 118.5, 114.1, 110.5, 61.6, 60.7, 55.6, 14.5, 14.1; **HRMS** (ESI) Calcd for C₂₃H₂₄NO₅ [M + H]⁺ 394.1654, found 394.1658.

Ethyl 1-(4-methoxyphenyl)-5-phenyl-3-(trifluoromethyl)-1H-pyrrole-2-carboxylate (3ao): Yellow solid (41% yield, eluent = hexane/EtOAc (95:5)); Mp = 111–113 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.21–7.19 (m, 3H), 7.15–7.02 (m, 4H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.65 (s, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): 159.69, 159.66, 139.2, 131.2, 131.1, 129.6, 129.3, 128.4, 128.1, 126.2 (q, *J*_{C-F} = 3.3 Hz) 123.2 (q, *J*_{C-F} = 265.0 Hz), 120.5 (q, *J*_{C-F} = 37.2 Hz), 114.0, 109.3 (q, *J*_{C-F} = 4.2 Hz), 61.2, 55.6, 13.9; **HRMS** (ESI) Calcd for C₂₁H₁₉F₃NO₃ [M + H]⁺ 390.1317, found 390.1314.

Ethyl 1-(4-methoxyphenyl)-5-phenyl-1H-pyrrole-2-carboxylate (3ap): White solid (47% yield, eluent = hexane/EtOAc (95:5)); Mp = 132–133 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.23–7.08 (m, 8H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.40 (d, *J* = 4.0 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 160.8, 159.2, 141.6, 132.4, 132.2, 129.8, 129.1, 128.3, 127.5, 125.4, 118.4, 113.8, 109.9, 60.0, 55.6, 14.6; **HRMS** (ESI) Calcd for C₂₀H₂₀NO₃ [M + H]⁺ 322.1443, found 322.1444.

1-(1-(4-Methoxyphenyl)-3-methyl-5-phenyl-1H-pyrrol-2-yl)ethanone (3aq): Brown solid (11% yield, eluent = hexane/EtOAc (98:2)); Mp = 118–120 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.23–7.14 (m, 3H), 7.10–7.03 (m, 4H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.26 (s,

1H), 3.80 (s, 3H), 2.46 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 189.1, 159.2, 140.4, 133.1, 132.5, 132.2, 130.0, 129.8, 129.2, 128.2, 127.6, 114.0, 113.6, 55.6, 30.7, 15.3; **HRMS** (ESI) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 306.1494, found 306.1490.

1-(1-(4-Methoxyphenyl)-2-methyl-5-phenyl-1H-pyrrol-3-yl)ethanone (3aq'): Brown solid (12% yield, eluent = hexane/EtOAc (98:2)); Mp = 98–100 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.29–7.26 (m, 3H), 7.21–7.18 (m, 2H), 6.95 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 6.64 (s, 1H), 3.75 (s, 3H), 2.36 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 196.9, 158.7, 138.5, 133.0, 132.6, 131.5, 128.5, 128.4, 127.6, 124.2, 122.5, 121.4, 114.2, 55.6, 30.9, 12.8; **HRMS** (ESI) Calcd for $\text{C}_{20}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 306.1494, found 306.1490.

(1-(4-Methoxyphenyl)-3-methyl-5-phenyl-1H-pyrrol-2-yl)(phenyl)methanone (3ar): Yellow oil (50%, eluent = hexane/EtOAc (95:5)); ^1H NMR (400 MHz, CDCl_3): δ 7.76–7.72 (m, 2H), 7.50–7.45 (m, 1H), 7.38 (t, J = 7.5 Hz, 2H), 7.20–7.19 (m, 3H), 7.15–7.09 (m, 2H), 7.05 (d, J = 8.9 Hz, 2H), 6.73 (d, J = 8.9 Hz, 2H), 6.28 (s, 1H), 3.73 (s, 3H), 1.96 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 188.1, 158.7, 140.6, 140.3, 132.4, 132.2, 132.1,

129.6, 129.4, 129.0, 128.8, 128.4, 128.3, 127.5, 113.9, 113.0, 55.5, 14.0; **HRMS** (ESI)

Calcd for $C_{25}H_{22}NO_2$ $[M + H]^+$ 368.1651, found 368.1653.

1-(1-(4-Methoxyphenyl)-3,5-diphenyl-1H-pyrrol-2-yl)ethanone (3ar'): Yellow solid (13%, eluent = hexane/EtOAc (95:5)); Mp = 126-128 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 7.51–7.33 (m, 5H), 7.21–7.17 (m, 3H), 7.15–7.11 (m, 4H), 6.84 (d, J = 8.9 Hz, 2H), 6.42 (s, 1H), 3.81 (s, 3H), 1.98 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 190.5, 158.9, 140.0, 136.7, 135.7, 134.9, 133.8, 132.5, 131.7, 129.5, 129.0, 128.3, 128.1, 127.5, 127.4, 113.7, 112.3, 55.4, 30.6; **HRMS** (ESI) Calcd for $C_{25}H_{22}NO_2$ $[M + H]^+$ 368.1651, found 368.1653.

Application to Lamellarin Scaffolds

Ethyl 2-phenyl-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (3aaf): White solid (62% yield, eluent = hexane/EtOAc (95:5)); Mp = 119-121 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.57 (d, *J* = 7.5 Hz, 1H), 7.44-7.41 (m, 2H), 7.37-7.34 (m, 2H), 7.32-7.26 (m, 2H), 7.23-7.22 (m, 2H), 6.57 (s, 1H), 4.73-4.41 (m, 2H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.12 (t, *J* = 6.8 Hz, 2H), 1.06 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 161.9, 136.9, 134.7, 134.4, 132.0, 129.6, 128.1, 127.9, 127.51, 127.45, 127.2, 126.7, 123.6, 118.7, 106.9, 59.9, 42.7, 29.0, 13.8; **HRMS** (ESI) Calcd for C₂₁H₂₀NO₂ [M + H]⁺ 318.1494, found 318.1495.

Ethyl 1-oxo-2,10b-diphenyl-1,5,6,10b-tetrahydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (6): Yellow solid (63% yield, eluent = hexane/EtOAc (93:7)); Mp = 168-169 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.05-7.94 (m, 1H), 7.42-7.40 (m, 2H), 7.37-7.27 (m, 7H), 7.25-7.19 (m, 2H), 7.17-7.11 (m, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 3.86-3.80 (m, 1H), 3.64-3.57 (m, 1H), 3.08-3.04 (m, 1H), 2.88-2.83 (m, 1H), 1.23 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 199.2, 162.9, 162.4, 140.3, 134.0, 132.8, 130.2, 128.61, 128.55, 128.5, 128.2, 127.8, 127.72, 127.68, 126.8, 113.8, 74.2, 62.8, 41.6, 29.9, 13.8; **HRMS** (ESI) Calcd for C₂₇H₂₄NO₃ [M + H]⁺ 410.1756, found 410.1757. Recrystallization from EtOAc/hexane afforded single crystals suitable for X-ray diffraction analysis, which unambiguously confirmed structure of **6** (see below)²⁶

Figure S2. ORTEP diagram of **6**. Thermal ellipsoids drawn at 50% probability.

Ethyl 8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (3agp):

White solid (68% yield, eluent = hexane/EtOAc (95:5)); Mp = 134-136 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.12–6.94 (m, 2H), 6.73 (s, 1H), 6.42 (d, *J* = 4.1 Hz, 1H), 4.61 (t, *J* = 6.8 Hz, 2H), 4.29 (q, *J* = 7.1 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 3.00 (t, *J* = 6.8 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 161.6, 148.9, 148.5, 136.5, 124.8, 121.9, 121.3, 118.5, 111.2, 107.1, 103.5, 60.0, 56.3, 56.2, 42.5, 28.8, 14.7; HRMS (ESI) Calcd for C₁₇H₂₀NO₄ [M + H]⁺ 302.1392, found 302.1403.

Ethyl 1-(3,4-dimethoxyphenyl)-8,9-dimethoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinoline-3-carboxylate (3ahp): Pale yellow solid (48% yield, eluent = hexane/EtOAc (95:5)); Mp = 148-149 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.02-6.98 (m, 3H), 6.91-6.89 (m, 2H), 6.73 (s, 1H), 4.62 (t, *J* = 6.6 Hz, 2H), 4.32 (q, *J* = 7.1 Hz, 2H),

3.91 (s, 3H), 3.89 (s, 3H), 3.84 (s, 3H), 3.44 (s, 3H), 3.03 (t, $J = 6.5$ Hz, 2H), 1.37 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.6, 149.0, 148.4, 148.2, 147.5, 131.7, 129.5, 126.1, 121.9, 121.7, 121.3, 120.7, 119.3, 112.9, 111.5, 111.0, 108.9, 60.1, 56.2, 56.1, 56.1, 55.7, 42.7, 29.3, 14.7; HRMS (ESI) Calcd for $\text{C}_{25}\text{H}_{28}\text{NO}_6$ $[\text{M} + \text{H}]^+$ 438.1917, found 438.1918.

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²⁵ CCDC 1040843 contains the supplementary crystallographic data for this paper. www.ccdc.cam.ac.uk/data_request/cif.

²⁶ CCDC 1063222 contains the supplementary crystallographic data for this paper. www.ccdc.cam.ac.uk/data_request/cif.

Chapter 3: Copper-Catalyzed Coupling of 2-Siloxy-1-alkenes and Diazocarbonyl Compounds: Approach to Multisubstituted Furans, Pyrroles and Thiophenes

3.1 Introduction

Multisubstituted heterocycles such as furans, pyrroles and thiophenes are core motifs present in many biologically active natural and non-natural products including pharmaceuticals, organic light emitting materials, and agrochemicals as illustrated in Figure 3.1.¹ In addition, these heterocycles are also useful synthetic building blocks for the synthesis of complex molecules.²

Figure 3.1. Furans, pyrroles and thiophenes motifs in functional molecules

Over the decades, numerous classical and new methods, especially those catalyzed by transition metals, have been developed to access these privileged five-membered heterocycles.³ In many of the reported syntheses, different methods or starting materials

are required for the synthesis of each specific heterocycle. Thus, a single or one-pot method that could allow rapid access to any member of these heterocycles from common starting materials would be attractive.

Transition metal carbenoids have been widely utilized as electrophilic intermediates for numerous chemical transformations.⁴ In particular, the most frequently employed nucleophilic reactants towards carbenoids are olefins. Olefins typically participate in cyclopropanation reactions with metal carbenoids to give rise to cyclopropane adduct.⁵ Among various olefins, silyl enol ethers are known to react with copper or rhodium carbenoids generated *in situ* from α -diazoesters to give donor/acceptor-substituted cyclopropane derivatives,⁶ which have been employed as building blocks for natural product synthesis (Scheme 3.1).⁷

Scheme 3.1. Cyclopropanation reaction of silyl enol ether and diazocarbonyl compound

On the other hand, in rare cases, the condensation reaction between silyl enol ethers and diazocarbonyl compounds has been reported to afford 2-siloxy-2,3-dihydrofurans. In 2013, Kitamura *et al.* reported a rhodium-catalyzed reaction of silyl enol ether or ketene silyl acetal with diazonaphthoquinone to afford a dihydronaphthofuran derivative (Scheme 3.2).⁸ However, the reaction typically suffers from low yield when silyl enol ethers were used. Recently in 2015, Mead *et. al.* reported a rhodium-catalyzed reaction of silyl vinyl ether with diazocarbonyl compound leading to the formation of dihydrofuran in low yields but the reaction was largely focused on the formation of cyclopropanes⁹. In addition, Kitamura's study was mainly focused on the reaction of diazonaphthoquinone derivatives and ketene silyl acetals, this [3+2]-type cycloaddition

reaction remains largely unexplored with respect to both diazocarbonyl compound and silyl enol ether regardless of its possible utility for the synthesis of other five-membered heterocycles.¹⁰

Scheme 3.2. [3+2]-Type cycloaddition of silyl enol ether and diazonaphthoquinone

Kitamura M. et al. *Eur. J. Org. Chem.* **2013**, 5045.

Mead, K. T. et al. *Synthesis* **2015**, 47, 3020.

As described in Chapter 2, we have developed a reaction between enolizable ketimines and α -diazo- β -ketoesters under copper catalysis to afford highly substituted pyrroles. The proposed mechanism of this reaction involves nucleophilic addition of the ketimine nitrogen to a copper carbenoid to generate an azomethine ylide, which tautomerizes and undergoes cyclocondensation to furnish the pyrrole product. In this same connection and based on the understanding of the reactivity of silyl enol ethers, I conjectured that silyl enol ethers and copper carbenoids could react in a similar mechanistic fashion to undergo cyclization to 2-siloxy-2,3-dihydrofurans. Herein, we report a copper-catalyzed coupling reaction of 2-siloxy-1-alkenes and diazocarbonyl compounds to afford 2-siloxy-2,3-dihydrofurans which could subsequently be converted to access highly substituted furans, pyrroles and thiophenes in a one-pot procedure (Scheme 3.3). This method would serve as a useful addition to the synthetic repertoire for the synthesis of such five-membered heterocycles.

Scheme 3.3. Copper-catalyzed reaction of 2-siloxy-1-alkenes and diazocarbonyl compounds

3.2 Results and Discussion

Based on the above hypothesis, I commenced the study of the reaction between silyl enol ether **1a** derived from acetophenone and α -diazo- β -ketoester **2a** derived from ethyl acetoacetate as summarized in Table 3.1. The denitrogenative coupling reaction of these starting materials proceeded smoothly by using copper(II) hexafluoroacetylacetonate (10 mol%) as a catalyst in dichloromethane at 40 °C, affording 2-siloxy-2,3-dihydrofuran **3aa** in 84% yield (entry 1).¹¹ When the same reaction was followed by a treatment with *p*-toluenesulfonic acid at reflux (one-pot), trisubstituted furan **4aa** was obtained in 86% isolated yield. Attempts to use a less Lewis acidic catalyst such as copper(II) trifluoroacetylacetonate which was the optimum catalyst for the pyrrole-forming reaction in Chapter 2, failed to afford any desired product (entry 2). Not surprisingly, using less Lewis acidic catalysts such as copper(II) acetylacetonate and copper(II) acetate failed to afford any desired product (entries 3 and 4). The use of rhodium(II) acetate dimer afforded the desired product in only 12% yield (entry 5). The reaction with a lower catalyst loading (5 mol%) resulted in a lower yield (entry 6). The silyl enol ether derived from *t*-butyldimethylsilyl chloride also participated in the reaction to afford **4aa** in a slightly lower yield (entry 7).

Table 3.1. Screening of reaction conditions

Entry	Deviation from the standard conditions	Yield (%) ^a
1	none	84 ^b (86) ^c
2	$\text{Cu}(\text{tfacac})_2$ instead of $\text{Cu}(\text{hfacac})_2$	0
3	$\text{Cu}(\text{acac})_2$ instead of $\text{Cu}(\text{hfacac})_2$	0
4	$\text{Cu}(\text{OAc})_2$ instead of $\text{Cu}(\text{hfacac})_2$	0
5	$\text{Rh}_2(\text{OAc})_4$ instead of $\text{Cu}(\text{hfacac})_2$	12
6	5 mol% of $\text{Cu}(\text{tfacac})_2$	65
7	none	(76) ^{c,d}

^a Determined by GC using tridecane as internal standard. ^b Isolated yield of **3aa**.

^c Isolated yield of **4aa** by directed treatment of reaction with $p\text{-TsOH}$ ^d (*t*-butyldimethylsiloxy)styrene was used instead of **1a**

With the optimized reaction conditions in hand, I explored the reaction of various α -diazo- β -ketoesters **2a-2n** with silyl enol ether **1a** (Scheme 3.4). Various primary and secondary alkyl diazoketoesters **2a-2e** bearing methyl, isopropyl, cyclopropyl, cyclohexyl, and adamantyl groups were well tolerated to afford trisubstituted furans **4aa-4ae** in moderate to good yields. The reaction also tolerated various aryl diazoketoesters **2f-2j** bearing substituents such as electron-donating methoxy groups and electron-withdrawing nitro or bromo groups to afford furans **4af-4aj** in good yields. Heteroaryl diazoketoesters **2k** and **2l** bearing furan and thiophene substituents, respectively, were well tolerated to afford the desired furans **4ak** and **4al** in good yields. The reaction also tolerated diazoketoester **2m** bearing a trifluoromethyl group to give 2-trifluoromethyl

substituted furan **4am** in moderate yield. Notably, I could also utilize α -diazo- β -ketosulfone **2n**, which afforded 3-sulfonyl furan **4an** in good yield.

Scheme 3.4. Reaction of silyl enol ether **1a** with various α -diazo- β -ketoesters^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions

Moving on, I investigated the reactivity of other diazocarbonyl compounds such as α -diazo- β -diketones, α -diazoketones and α -diazoesters (Scheme 3.5). Unfortunately, the reaction of the α -diazo- β -diketone derived from acetylacetone with **1a** only afforded a complex mixture of products with no furan formation detected by gas chromatographic analysis. This may be due to the rapid decomposition of the diazocarbonyl compound under the standard reaction conditions. On the other hand, various α -diazoketones **2o-2r**

bearing alkyl or aryl substituents participated well in the reaction to afford furans **4ao-4ar** in good to excellent yields. Note that the reaction of α -diazoketones directly afforded the furan products without the treatment of the reaction mixture with *p*-toluenesulfonic acid. This observation may be ascribed to the lack of electron-withdrawing ester group on the 4-position of the 2-siloxy-2,3-dihydrofuran intermediate as well as the coordination of the Lewis acid to the silanol, which would aid in the loss of silanol to directly afford the desired furan. The reaction of silyl enol ether **1a** with α -diazoester **2s** afforded the non-cyclized 1,4-ketoester derivative **5** in a good yield.

Scheme 3.5. Reaction of silyl enol ether **1a** with various α -diazoketone or α -diazoester^a

^a The reaction was performed using 0.2 mmol of silyl enol ether and 0.26 mmol of diazo

I also explored the reaction of various silyl enol ethers **1b-1n** derived from methyl ketones with α -diazo- β -ketoester **2a** (Scheme 3.6). Silyl enol ethers bearing various substituents such as electron-donating methoxy groups or electron-withdrawing fluoro, bromo, and nitro groups were well tolerated to afford furans **4ba-4ea** in moderate to good

yields. Sterically hindered silyl enol ether **1f** participated in the reaction to afford moderate yield of the desired furan **4fa**. The reaction also tolerated silyl enol ethers **1h** and **1i** derived from furanyl and thiophenyl methyl ketones, respectively, to afford furans **4ha** and **4ia** in good yields. Various alkyl silyl enol ethers **1j-1l** and even alkenyl silyl enol ether **1m** participated in the reaction to afford furans **4ja-4ma** in good yields. Notably, a two-fold coupling of bis-silyl enol ether **1n** derived from 1,4-diacetylbenzene with **2a** afforded a teraryl derivative **4na** in a modest yield. Unfortunately, when I screened the reaction of **2a** with trisubstituted silyl enol ethers derived from cyclohexanone, tetralone, and propiophenone, all failed to afford the desired furans and resulted in full recovery of the silyl enol ethers.

Scheme 3.6. Reaction of various silyl enol ethers with α -diazo- β -ketoester **2a**^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 3.1. ^b 0.2 mmol of bis-silyl enol ether and 0.48 mmol of diazo compound was used

The 2-siloxy-2,3-dihydrofuran formed *in situ* could serve as a 1,4-diketone surrogate that could be transformed into other five-membered heterocycles. Indeed, in a one pot fashion, 2-siloxy-2,3-dihydrofuran was desilylated with tetra-*n*-butyl ammonium fluoride (TBAF), and treated with ammonium acetate in acetic acid under heating, to afford various trisubstituted N-H pyrroles **6a-6f** in good yields (Scheme 3.7).

Scheme 3.7 Synthesis of multisubstituted pyrroles^a

^a The reaction was performed using 0.2 mmol of silyl enol ether and 0.24 mmol of diazo compound

Similarly, after fluoride-mediated desilylation of the 2-siloxy-2,3-dihydrofuran, treatment of the resulting mixture with Lawesson's reagent instead of ammonium acetate afforded various thiophenes **7a-7f** in moderate to good yields (Scheme 3.8). As demonstrated, the present reaction is applicable for the synthesis of various aryl, heteroaryl and alkyl functionalized pyrroles and thiophenes.

Scheme 3.8 Synthesis of multisubstituted thiophenes^a

^a The reaction was performed using 0.2 mmol of silyl enol ether and 0.24 mmol of diazo compound

We propose a plausible mechanistic pathway for the copper-catalyzed denitrogenative coupling reaction of silyl enol ether **1** and diazo carbonyl compound **2** as shown in Scheme 3.9. First, decomposition of the diazo compound **2** with the copper catalyst generates an electrophilic copper carbenoid **A**. Next, nucleophilic attack of silyl enol ether **1** to the copper carbenoid generates an intermediate **B** bearing both enolate and oxonium moieties. The enolate oxygen of **B** can directly attack the oxonium carbon to give dihydrofuran **3** while regenerating the copper catalyst. Alternatively, we may also propose an alternative pathway involving a siloxycyclopropane intermediate **C**, which would undergo ring opening and re-cyclization. When the R^3 substituent is not an electron-withdrawing group such as ester, the loss of the siloxy group may be facilitated by the Lewis acidic copper catalyst which results in direct formation of the furan product **4**.

Scheme 3.9 Plausible reaction pathways

3.3 Conclusion

In conclusion, we have demonstrated that 2-siloxy-1-alkenes could serve as excellent nucleophiles to participate in coupling with carbenoids generated from diazocarbonyl compounds under copper catalysis to afford 2-siloxy-2,3-dihydrofuran derivatives or 2,3,5-trisubstituted furans. In a simple one-pot procedure, the 2-siloxy-2,3-dihydrofuran derivatives can be converted to furans, pyrroles and thiophenes. Although there were previous reports on the synthesis of furans via transition metal-catalyzed coupling of α -diazoketoesters and terminal alkynes,¹² or other available methods,^{13,14} the accessibility to pyrroles¹⁵ and thiophenes could make the present reaction a useful synthetic method for five-membered heterocycles.^{3,16}

3.4 Experimental

Materials and Methods

General. All reactions dealing with air- and moisture-sensitive compounds were carried out in oven dried reaction vessels under a nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker 300, 400, 500 MHz NMR spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0.00 ppm) and CHCl_3 (77.26 ppm), respectively. Chemical shifts are reported in ppm and the multiplicities are reflected by s (singlet), d (doublet), q (quartet), and m (multiplet). Coupling constants are represented by J in hertz (Hz). Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected.

Materials. Unless otherwise noted, materials were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received.

Synthesis of Diazocarbonyl Compounds

All diazocarbonyl compounds were synthesized from the corresponding ketoester/ketone and 4-acetamidobenzenesulfonyl azide according to literature procedure,¹⁷ and was purified by flash column chromatography. ^1H and ^{13}C NMR spectral data for the diazocarbonyl compound showed good agreement with literature data.¹⁸

Synthesis of Silyl Enol Ethers

All silyl enol ethers were synthesized from the corresponding ketones and trimethylsilyl chloride according to the literature procedures,¹⁹ and purified by distillation under reduced pressure. ¹H and ¹³C NMR spectral data for the silyl enol ethers showed good agreement with literature data.²⁰

Copper-Catalyzed Condensation of Silyl Enol Ethers and Diazocarbonyl Compounds to Furans

Method A: A 10 mL Schlenk tube equipped with a stirrer bar was charged with silyl enol ether (0.20 mmol), Cu(hfacac)₂ (9.6 mg, 0.02 mmol, 10 mol%), and diazocarbonyl compound (0.24 mmol), followed by the addition of dichloromethane (1.0 mL). The resulting mixture was stirred at 40 °C for 6 h. Upon cooling to room temperature, *p*-Toluenesulfonic acid monohydrate (11.4 mg, 0.03 mmol, 30 mol%) was added, followed by addition of toluene (1.0 mL). The resulting mixture was stirred at 110 °C for 1.5 h. The reaction was cooled to room temperature then diluted with ethyl acetate (5 mL) and was purified by flash chromatography on silica gel to afford the furan product.

Method B: A 10 mL Schlenk tube equipped with a stirrer bar was charged with silyl enol ether (0.20 mmol), Cu(hfacac)₂ (9.6 mg, 0.02 mmol, 10 mol%) followed by the addition of dichloromethane (0.5 mL). Diazocarbonyl compound (0.26 mmol) in dichloromethane (0.5 mL) solution was added dropwise over 5 min at room temperature. The resulting mixture was then stirred at 40 °C for 6 h. Upon cooling to room temperature, the reaction mixture was diluted with ethyl acetate (5 mL) and was purified by flash chromatography on silica gel to afford the furan product.

Copper-Catalyzed Condensation of Silyl Enol Ethers and Diazocarbonyl Compounds to Pyrroles

Method C: A 10 mL Schlenk tube equipped with a stirrer bar was charged with silyl enol ether (0.20 mmol), Cu(hfacac)₂ (9.6 mg, 0.02 mmol, 10 mol%), and diazocarbonyl compound (0.24 mmol), followed by the addition of dichloromethane (1.0 mL). The resulting mixture was stirred at 40 °C for 6 h. The reaction mixture was then cooled to 0 °C, followed by addition of THF (1.0 mL). Tetrabutylammonium fluoride 1M in THF solution (0.24 mL, 0.24 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 15 min. The resulting solution was evacuated, followed by addition of ammonium acetate (123 mg, 1.6 mmol) and acetic acid (1.0 mL). The resulting mixture was stirred at 120 °C for 20 h. The reaction was cooled to room temperature and the solvents were concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to afford the pyrrole product.

Method D: A 10 mL Schlenk tube equipped with a stirrer bar was charged with silyl enol ether (0.20 mmol), Cu(hfacac)₂ (9.6 mg, 0.02 mmol, 10 mol%), and diazocarbonyl compound (0.24 mmol), followed by the addition of dichloromethane (1.0 mL). The resulting mixture was stirred at 40 °C for 6 h. The reaction mixture was then cooled to 0 °C, followed by addition of THF (1.0 mL). Tetrabutylammonium fluoride 1M in THF solution (0.24 mL, 0.24 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 15 min. The resulting solution was evacuated, followed by addition of ammonium acetate (616 mg, 8.0 mmol). The resulting mixture was stirred at 120 °C for 14 h. The reaction was cooled to room temperature and diluted with ethyl acetate (20.0 mL), followed by extraction with water. The organic phase was dried under magnesium sulphate, resulting solution concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to afford the pyrrole product.

Copper-Catalyzed Condensation of Silyl Enol Ethers and Diazocarbonyl Compounds to Thiophenes

Method E: A 10 mL Schlenk tube equipped with a stirrer bar was charged with silyl enol ether (0.20 mmol), Cu(hfacac)₂ (9.6 mg, 0.02 mmol, 10 mol%), and diazocarbonyl compound (0.24 mmol), followed by the addition of dichloromethane (1.0 mL). The resulting mixture was stirred at 40 °C for 6 h. The reaction mixture was then cooled to 0 °C, and followed by addition of THF (1.0 mL). Tetrabutylammonium fluoride 1M in THF solution (0.24 mL, 0.24 mmol) was added dropwise and the resulting mixture was stirred at 0 °C for 15 min. Lawesson's reagent (194 mg, 0.48 mmol) was added and the resulting mixture was stirred at 50 °C for 12 h. The reaction was cooled to room temperature and the solvents were concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel to afford the thiophene product.

Ethyl 2-methyl-5-phenyl-5-((trimethylsilyl)oxy)-4,5-dihydrofuran-3-carboxylate

(3aa): This compound was synthesized using Method A without the addition of *p*-toluenesulfonic acid monohydrate. Colourless oil (84% yield, eluent = hexane/EtOAc (98:2)); **¹H NMR** (400 MHz, CDCl₃): δ 7.46 (d, *J* = 7.3 Hz, 2H), 7.42–7.32 (m, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.18 (dd, *J* = 15.9, 1.1 Hz, 1H), 3.09 (dd, *J* = 15.9, 1.7 Hz, 1H), 2.38 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 0.09 (s, 9H); **¹³C NMR** (100 MHz, CDCl₃): δ 165.8, 165.0, 144.2, 128.12, 128.05, 124.8, 109.5, 102.0, 59.6, 47.2, 14.4, 14.3, 1.3; **HRMS** (ESI) Calcd for C₁₇H₂₅O₄Si [M + H]⁺ 321.1522, found 321.1524.

Ethyl 2-methyl-5-phenylfuran-3-carboxylate (4aa): This compound was synthesized using Method A. Colourless oil (86% yield, eluent = hexane/EtOAc (97:3)); **¹H**

NMR(400 MHz, CDCl₃): δ 7.65–7.63 (m, 2H), 7.38 (t, J = 7.7 Hz, 2H), 7.34–7.21 (m, 1H), 6.88 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 2.65 (s, 3H), 1.37 (t, J = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 164.1, 158.6, 151.7, 130.1, 128.7, 127.6, 123.6, 115.4, 105.5, 60.2, 14.4, 13.9; **HRMS** (ESI) Calcd for C₁₄H₁₅O₃ [M + H]⁺ 231.1021, found 231.1025.

Ethyl 2-isopropyl-5-phenylfuran-3-carboxylate (4ab): This compound was synthesized using Method A. Yellow oil (90% yield, eluent = hexane/EtOAc (97:3)); **¹H NMR** (400 MHz, CDCl₃): δ 7.58–7.51 (m, 2H), 7.29 (t, J = 7.7 Hz, 2H), 7.19–7.15 (m, 1H), 6.79 (s, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.72 (hept, J = 7.0 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H), 1.26 (d, J = 4.0 Hz, 6H); **¹³C NMR** (100 MHz, CDCl₃): δ 166.8, 164.1, 151.5, 130.5, 128.9, 127.8, 123.8, 113.7, 105.7, 60.3, 27.6, 21.1, 14.6; **HRMS** (ESI) Calcd for C₁₆H₁₉O₃ [M + H]⁺ 259.1334, found 259.1340.

Ethyl 2-cyclopropyl-5-phenylfuran-3-carboxylate (4ac): This compound was synthesized using Method A. Colourless oil (60% yield, eluent = hexane/EtOAc (97:3)); **¹H NMR** (400 MHz, CDCl₃): δ 7.59–7.53 (m, 2H), 7.36 (t, J = 7.7 Hz, 2H), 7.24 (t, J = 6.4 Hz, 1H), 6.87 (s, 1H), 4.33 (q, J = 7.1 Hz, 2H), 2.83 (tt, J = 8.4, 5.2 Hz, 1H), 1.38 (t, J = 7.1 Hz, 3H), 1.19–1.13 (m, 2H), 1.13–1.06 (m, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 164.6, 162.9, 150.5, 130.3, 128.9, 127.7, 123.7, 115.2, 106.1, 60.4, 14.7, 9.6, 9.2; **HRMS** (ESI) Calcd for C₁₆H₁₇O₃ [M + H]⁺ 257.1178, found 257.1170.

Methyl 2-cyclohexyl-5-phenylfuran-3-carboxylate (4ad): This compound was synthesized using Method A. Yellow oil (90% yield, eluent = hexane/EtOAc (97:3)); **¹H NMR** (400 MHz, CDCl₃): δ 7.65–7.62 (m, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.33–7.16 (m, 1H), 6.86 (s, 1H), 3.84 (s, 3H), 3.47 (tt, *J* = 11.9, 3.5 Hz, 1H), 1.97–1.78 (m, 4H), 1.79–1.62 (m, 3H), 1.53–1.19 (m, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 166.7, 164.6, 151.6, 130.4, 128.9, 127.8, 123.8, 113.4, 105.5, 51.5, 37.2, 31.2, 26.4, 26.1; **HRMS** (ESI) Calcd for C₁₈H₂₁O₃ [*M* + *H*]⁺ 285.1491, found 285.1501.

Ethyl 2-(adamantan-2-yl)-5-phenylfuran-3-carboxylate (4ae): This compound was synthesized using Method A. White solid (68% yield, eluent = hexane/EtOAc (97:3)), Mp = 135–137 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.64–7.62 (m, 2H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.28–7.11 (m, 1H), 6.93 (s, 1H), 4.31 (q, *J* = 7.1 Hz, 2H), 2.25 (d, *J* = 2.6 Hz, 6H), 2.09 (s, 3H), 1.89–1.74 (m, 6H), 1.39 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 167.9, 164.0, 149.9, 130.5, 128.9, 127.7, 123.8, 114.4, 107.7, 60.5, 39.2, 37.3, 36.9, 28.7, 14.7; **HRMS** (ESI) Calcd for C₂₃H₂₇O₃ [*M* + *H*]⁺ 351.1960, found 351.1956.

Ethyl 2,5-diphenylfuran-3-carboxylate (4af): This compound was synthesized using Method A. Colourless solid (70% yield, eluent = hexane/EtOAc (97:3)), Mp = 80–82 °C; **¹H NMR** (400 MHz, CDCl₃): δ 8.09–8.06 (m, 2H), 7.80–7.68 (m, 2H), 7.53–7.35 (m,

5H), 7.35–7.25 (m, 1H), 7.08 (s, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 1.36 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.8, 156.7, 152.6, 130.0, 129.6, 129.0, 128.6, 128.34, 128.28, 124.2, 116.0, 108.1, 60.9, 14.5; **HRMS** (ESI) Calcd for $\text{C}_{19}\text{H}_{17}\text{O}_3$ $[\text{M} + \text{H}]^+$ 293.1178, found 293.1180.

Ethyl 2-(4-methoxyphenyl)-5-phenylfuran-3-carboxylate (4ag): This compound was synthesized using Method A. White solid (68% yield, eluent = hexane/EtOAc (97:3)), Mp = 95–97 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.06 (d, $J = 8.9$ Hz, 2H), 7.78–7.65 (m, 2H), 7.41 (t, $J = 7.7$ Hz, 2H), 7.29 (t, $J = 7.4$ Hz, 1H), 7.06 (s, 1H), 6.98 (d, $J = 8.9$ Hz, 2H), 4.33 (q, $J = 7.1$ Hz, 2H), 3.86 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.9, 160.7, 157.1, 151.9, 130.20, 130.15, 129.0, 128.1, 124.1, 122.7, 114.7, 113.8, 108.1, 60.7, 55.6, 14.6; **HRMS** (ESI) Calcd for $\text{C}_{20}\text{H}_{19}\text{O}_4$ $[\text{M} + \text{H}]^+$ 323.1283, found 323.1296.

Ethyl 2-(4-nitrophenyl)-5-phenylfuran-3-carboxylate (4ah): This compound was synthesized using Method A. Yellow solid (79% yield, eluent = hexane/EtOAc (92:8)), Mp = 126–128 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.33 (d, $J = 9.2$ Hz, 2H), 8.28 (d, $J = 9.2$ Hz, 2H), 7.85 – 7.67 (m, 2H), 7.47–7.43 (m, 2H), 7.40–7.33 (m, 1H), 7.13 (s, 1H), 4.37 (q, $J = 7.1$ Hz, 2H), 1.40 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 163.3, 154.1, 153.3, 147.7, 135.6, 129.3, 129.2, 129.0, 128.8, 124.5, 123.7, 118.9, 108.9, 61.4, 14.5; **HRMS** (ESI) Calcd for $\text{C}_{19}\text{H}_{16}\text{NO}_5$ $[\text{M} + \text{H}]^+$ 338.1028, found 338.1025.

Ethyl 2-(2-bromophenyl)-5-phenylfuran-3-carboxylate (4ai): This compound was synthesized using Method A. Yellow oil (88% yield, eluent = hexane/EtOAc (97:3)); **¹H NMR** (400 MHz, CDCl₃): δ 7.75–7.70 (m, 2H), 7.68 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.54 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.42–7.37 (m, 3H), 7.34–7.27 (m, 2H), 7.09 (s, 1H), 4.21 (q, *J* = 7.1 Hz, 2H), 1.18 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.2, 155.7, 153.8, 133.1, 132.7, 132.0, 131.1, 130.0, 129.0, 128.4, 127.0, 124.3, 124.2, 118.4, 106.3, 60.7, 14.2; **HRMS** (ESI) Calcd for C₁₉H₁₆BrO₃ [M + H]⁺ 371.0283, found 371.0283.

Methyl 2-(naphthalen-1-yl)-5-phenylfuran-3-carboxylate (4aj): This compound was synthesized using Method A. White solid (74% yield, eluent = hexane/EtOAc (97:3)), Mp = 145–147 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.97 (d, *J* = 8.2 Hz, 1H), 7.93 – 7.89 (m, 1H), 7.87 (d, *J* = 7.6 Hz, 1H), 7.76–7.72 (m, 3H), 7.60–7.54 (m, 1H), 7.53–7.46 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.19 (s, 1H), 3.66 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.9, 156.9, 153.8, 133.8, 132.2, 130.5, 130.1, 129.7, 129.1, 128.6, 128.4, 127.8, 126.9, 126.3, 125.8, 125.1, 124.3, 118.1, 106.8, 51.7; **HRMS** (ESI) Calcd for C₂₂H₁₇O₃ [M + H]⁺ 329.1178, found 329.1184.

Methyl 5-phenyl-[2,2'-bifuran]-3-carboxylate (4ak): This compound was synthesized using Method A. Colourless solid (66% yield, eluent = hexane/EtOAc (97:3)), Mp = 93–95 °C; **¹H NMR** (400 MHz, CDCl₃): 7.74 (d, *J* = 7.3 Hz, 2H), 7.57 (dd, *J* = 7.0, 2.3 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.03 (s, 1H), 6.57 (dd, *J* = 3.5, 1.8 Hz, 1H), 3.89 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.5, 152.6, 148.4, 144.8, 143.7, 129.8, 129.0, 128.4, 124.3, 114.3, 113.7, 112.3, 107.3, 51.9; **HRMS** (ESI) Calcd for C₁₆H₁₃O₄ [M + H]⁺ 269.0814, found 269.0820.

Methyl 5-phenyl-2-(thiophen-2-yl)furan-3-carboxylate (4al): This compound was synthesized using Method A. White solid (71% yield, eluent = hexane/EtOAc (97:3)), Mp = 71–73 °C; **¹H NMR** (400 MHz, CDCl₃): δ 8.12 (dd, *J* = 3.8, 1.0 Hz, 1H), 7.74–7.68 (m, 2H), 7.46–7.37 (m, 3H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.13 (dd, *J* = 5.0, 3.9 Hz, 1H), 7.02 (s, 1H), 3.90 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 164.0, 152.4, 152.0, 131.8, 129.7, 129.0, 128.4, 128.2, 127.8, 124.2, 114.0, 107.6, 51.9; **HRMS** (ESI) Calcd for C₁₆H₁₃O₃S [M + H]⁺ 285.0585, found 284.0582.

Ethyl 5-phenyl-2-(trifluoromethyl)furan-3-carboxylate (4am): This compound was synthesized using Method A. Colourless solid (48% yield, eluent = hexane/EtOAc (95:5)), Mp = 38–41 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.77–7.69 (m, 2H), 7.52–7.37

(m, 3H), 7.08 (d, $J = 0.9$ Hz, 1H), 4.40 (q, $J = 7.1$ Hz, 2H), 1.41 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 160.9, 154.9, 142.2 (q, $J_{\text{C-F}} = 42$ Hz), 129.3, 128.9, 128.4, 121.4, 118.7 (q, $J_{\text{C-F}} = 267$ Hz), 106.9, 61.5, 13.9; HRMS (ESI) Calcd for $\text{C}_{14}\text{H}_{12}\text{F}_3\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 285.0739, found 285.0747.

2,5-Diphenyl-3-(phenylsulfonyl)furan (4an): This compound was synthesized using Method A with the addition of *p*-toluenesulfonic acid monohydrate (100 mol%). White solid (80% yield, eluent = hexane/EtOAc (95:5)), Mp = 148–150 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.96 (dd, $J = 6.7, 2.9$ Hz, 2H), 7.86 (d, $J = 8.1$ Hz, 2H), 7.76–7.70 (m, 2H), 7.56–7.52 (m, 1H), 7.50–7.40 (m, 7H), 7.36 (t, $J = 7.3$ Hz, 1H), 7.12 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 154.1, 152.8, 141.8, 133.3, 130.1, 129.0, 128.9, 128.72, 128.67, 128.4, 127.1, 125.7, 124.2, 107.3; HRMS (ESI) Calcd for $\text{C}_{22}\text{H}_{17}\text{O}_3\text{S}$ [$\text{M} + \text{H}$] $^+$ 361.0898, found 361.0895.

2-Methyl-3,5-diphenylfuran (4ao): This compound was synthesized using Method B. Brown oil (84% yield, eluent = hexane/EtOAc (97:3)); ^1H NMR (400 MHz, CDCl_3): δ 7.58 (dd, $J = 8.3, 1.1$ Hz, 2H), 7.36–7.23 (m, 6H), 7.22–7.09 (m, 2H), 6.68 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 151.9, 147.8, 134.3, 131.1, 128.89, 128.85, 127.7, 127.3, 126.7, 123.7, 123.3, 106.7, 13.4; HRMS (ESI) Calcd for $\text{C}_{17}\text{H}_{15}\text{O}$ [$\text{M} + \text{H}$] $^+$ 235.1123, found 235.1133.

2,3,5-Triphenylfuran (4ap): This compound was synthesized using Method B. White solid (83% yield, eluent = hexane/EtOAc (97:3)), Mp = 91–93 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.85–7.81 (m, 2H), 7.74–7.63 (m, 2H), 7.56–7.52 (m, 2H), 7.50–7.42 (m, 4H), 7.42–7.29 (m, 5H), 6.88 (s, 1H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 152.8, 148.1, 134.6, 131.3, 130.8, 129.0, 128.94, 128.91, 128.6, 127.8, 127.7, 127.5, 126.4, 124.8, 124.1, 109.7; **HRMS** (ESI) Calcd for $\text{C}_{22}\text{H}_{17}\text{O}$ $[\text{M} + \text{H}]^+$ 297.1279, found 297.1284.

3-(4-Fluorophenyl)-2-methyl-5-phenylfuran (4aq): This compound was synthesized using Method B. Brown oil (98% yield, eluent = hexane/EtOAc (97:3)); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.75–7.68 (m, 2H), 7.46–7.38 (m, 4H), 7.31–7.27 (m, 1H), 7.19–7.10 (m, 2H), 6.78 (s, 1H), 2.53 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 161.7 (d, $J_{\text{C-F}} = 244$ Hz), 151.7, 147.4, 130.7, 130.1 (d, $J_{\text{C-F}} = 4$ Hz), 129.0 (d, $J_{\text{C-F}} = 8$ Hz), 128.7, 127.1, 123.5, 122.2, 115.5 (d, $J_{\text{C-F}} = 21$ Hz), 106.4, 13.1; **HRMS** (ESI) Calcd for $\text{C}_{17}\text{H}_{14}\text{FO}$ $[\text{M} + \text{H}]^+$ 253.1029, found 253.1034.

2-Methyl-5-phenyl-3-(p-tolyl)furan (4ar): This compound was synthesized using Method B. Brown oil (71% yield, eluent = hexane/EtOAc (97:3)); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.63–7.54 (m, 2H), 7.32–7.20 (m, 4H), 7.14 (t, $J = 7.8$ Hz, 3H), 6.68 (s, 1H), 2.42 (s, 3H), 2.29 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 151.5, 147.3, 136.2, 131.2,

131.0, 129.3, 128.7, 127.4, 127.0, 123.4, 123.0, 106.6, 21.2, 13.2; **HRMS** (ESI) Calcd for $C_{18}H_{17}O$ $[M + H]^+$ 249.1279, found 249.1284.

Methyl 4-oxo-2,4-diphenylbutanoate (5): This compound was synthesized using Method A. Colourless solid (88% yield, eluent = hexane/EtOAc (95:5)), Mp = 100–102 °C; **1H NMR** (400 MHz, $CDCl_3$): δ 7.97 (d, J = 7.8 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 7.35 (d, J = 4.1 Hz, 4H), 7.33–7.22 (m, 1H), 4.30 (dd, J = 10.3, 3.9 Hz, 1H), 3.95 (dd, J = 18.0, 10.3 Hz, 1H), 3.69 (s, 3H), 3.27 (dd, J = 18.0, 4.0 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 197.6, 173.9, 138.4, 136.4, 133.3, 128.9, 128.6, 128.1, 127.8, 127.6, 52.4, 46.4, 42.8; **HRMS** (ESI) Calcd for $C_{17}H_{17}O_3$ $[M + H]^+$ 269.1178, found 269.1176.

Ethyl 5-(4-methoxyphenyl)-2-methylfuran-3-carboxylate (4ba): This compound was synthesized using Method A. Colourless solid (87% yield, eluent = hexane/EtOAc (97:3)), Mp = 62–64 °C; **1H NMR** (400 MHz, $CDCl_3$): δ 7.56 (d, J = 8.9 Hz, 2H), 6.91 (d, J = 8.9 Hz, 2H), 6.73 (s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 2.63 (s, 3H), 1.36 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.4, 159.5, 158.2, 152.0, 125.3, 123.4, 115.5, 114.4, 104.0, 60.3, 55.5, 14.6, 14.1; **HRMS** (ESI) Calcd for $C_{15}H_{17}O_4$ $[M + H]^+$ 261.1127, found 261.1134.

Ethyl 5-(4-fluorophenyl)-2-methylfuran-3-carboxylate (4ca): This compound was synthesized using Method A. White solid (70% yield, eluent = hexane/EtOAc (98:2)), Mp = 63–65 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): 7.82–7.40 (m, 2H), 7.07 (t, $J = 8.8$ Hz, 2H), 6.81 (s, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 2.63 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 164.2, 162.5 (d, $J_{\text{C-F}} = 246$ Hz), 158.8, 151.1, 126.7 (d, $J_{\text{C-F}} = 4$ Hz), 125.7 (d, $J_{\text{C-F}} = 8$ Hz), 116.0 (d, $J_{\text{C-F}} = 22$ Hz), 115.7, 105.4, 60.5, 14.6, 14.1; **HRMS** (ESI) Calcd for $\text{C}_{14}\text{H}_{14}\text{FO}_3$ $[\text{M} + \text{H}]^+$ 249.0927, found 249.0935.

Ethyl 5-(4-bromophenyl)-2-methylfuran-3-carboxylate (4da): This compound was synthesized using Method A. White solid (74% yield, eluent = hexane/EtOAc (97:3)), Mp = 75–77 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.48 (s, 4H), 6.87 (s, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 2.63 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 163.8, 158.9, 150.7, 131.9, 129.0, 125.1, 121.4, 115.6, 106.1, 60.3, 14.4, 13.9; **HRMS** (ESI) Calcd for $\text{C}_{14}\text{H}_{14}\text{BrO}_3$ $[\text{M} + \text{H}]^+$ 309.0126, found 309.0131.

Ethyl 2-methyl-5-(4-nitrophenyl)furan-3-carboxylate (4ea): This compound was synthesized using Method A. Yellow solid (38% yield, eluent = hexane/EtOAc (92:8)), Mp = 131–133 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.25 (d, $J = 9.0$ Hz, 2H), 7.77 (d, $J = 9.0$ Hz, 2H), 7.12 (s, 1H), 4.34 (q, $J = 7.1$ Hz, 2H), 2.69 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 163.4, 160.6, 149.4, 146.6, 135.7, 124.4, 123.8, 116.3,

109.6, 60.5, 14.4, 14.0; **HRMS** (ESI) Calcd for $C_{14}H_{14}NO_5$ $[M + H]^+$ 276.0872, found 276.0876.

Ethyl 2-methyl-5-(*o*-tolyl)furan-3-carboxylate (4fa): This compound was synthesized using Method A. Colourless oil (56% yield, eluent = hexane/EtOAc (97:3)); **1H NMR** (400 MHz, $CDCl_3$): 7.87–7.62 (m, 1H), 7.36–7.17 (m, 3H), 6.77 (s, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 2.65 (s, 3H), 2.49 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.2, 158.2, 151.2, 134.6, 131.2, 129.4, 127.7, 126.8, 126.0, 115.2, 109.1, 60.2, 21.9, 14.4, 13.9; **HRMS** (ESI) Calcd for $C_{15}H_{17}O_3$ $[M + H]^+$ 245.1178, found 245.1169.

Ethyl 2-methyl-5-(naphthalen-2-yl)furan-3-carboxylate (4ga): This compound was synthesized using Method A. White solid (87% yield, eluent = hexane/EtOAc (97:3)), Mp = 91–93 °C; **1H NMR** (400 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.80 (dd, $J = 17.4, 8.4$ Hz, 3H), 7.69 (dd, $J = 8.5, 1.6$ Hz, 1H), 7.52–7.38 (m, 2H), 6.98 (s, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 2.67 (s, 3H), 1.37 (t, $J = 7.1$ Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.2, 159.1, 152.0, 133.7, 133.0, 128.7, 128.4, 128.0, 127.6, 126.8, 126.3, 122.3, 122.2, 115.8, 106.3, 60.4, 14.6, 14.2; **HRMS** (ESI) Calcd for $C_{18}H_{17}O_3$ $[M + H]^+$ 281.1178, found 281.1183.

Ethyl 5-methyl-[2,2'-bifuran]-4-carboxylate (4ha): This compound was synthesized using Method A. Brown oil (86% yield, eluent = hexane/EtOAc (97:3)); **¹H NMR** (400 MHz, CDCl₃): δ 7.41 (dd, *J* = 1.7, 0.7 Hz, 1H), 6.77 (s, 1H), 6.54 (d, *J* = 3.3 Hz, 1H), 6.45 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 2.63 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.8, 158.4, 145.7, 144.3, 142.1, 115.1, 111.3, 105.5, 60.3, 14.3, 13.8; **HRMS** (ESI) Calcd for C₁₂H₁₃O₄ [M + H]⁺ 221.0814, found 221.0821.

Ethyl 2-methyl-5-(thiophen-2-yl)furan-3-carboxylate (4ia): This compound was synthesized using Method A. Colourless oil (78% yield, eluent = hexane/EtOAc (97:3)); **¹H NMR** (400 MHz, CDCl₃): δ 7.26-7.25 (m, 2H), 7.05 (dd, *J* = 5.0, 3.7 Hz, 1H), 6.75 (s, 1H), 4.33 (q, *J* = 7.1 Hz, 2H), 2.65 (s, 3H), 1.39 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.9, 158.3, 147.3, 132.8, 127.6, 124.4, 122.9, 115.4, 105.4, 60.3, 14.4, 13.8; **HRMS** (ESI) Calcd for C₁₂H₁₃O₃S [M + H]⁺ 237.0585, found 237.0596.

Ethyl 5-butyl-2-methylfuran-3-carboxylate (4ja): This compound was synthesized using Method A. Colourless oil (73% yield, eluent = hexane/EtOAc (98:2)); **¹H NMR** (400 MHz, CDCl₃): 6.24 (s, 1H), 4.29 (q, *J* = 7.1 Hz, 2H), 2.67–2.43 (m, 5H), 1.70–1.58 (m, 2H), 1.42-1.34 (m, 5H), 0.95 (t, *J* = 7.3 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 164.4, 157.5, 154.4, 113.8, 105.4, 59.9, 29.9, 27.3, 22.2, 14.4, 13.8, 13.7; **HRMS** (ESI) Calcd for C₁₂H₁₉O₃ [M + H]⁺ 211.1334, found 211.1324.

Ethyl 5-cyclopropyl-2-methylfuran-3-carboxylate (4ka): This compound was synthesized using Method A. Colourless oil (82% yield, eluent = hexane/EtOAc (97:3)); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.17 (s, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 2.51 (s, 3H), 1.90–1.71 (m, 1H), 1.33 (t, $J = 7.1$ Hz, 3H), 0.95–0.78 (m, 2H), 0.77–0.55 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 164.3, 157.2, 155.3, 113.9, 104.1, 59.9, 14.4, 13.7, 8.3, 6.4; **HRMS** (ESI) Calcd for $\text{C}_{11}\text{H}_{15}\text{O}_3$ $[\text{M} + \text{H}]^+$ 195.1021, found 195.1024.

Ethyl 5-cyclohexyl-2-methylfuran-3-carboxylate (4la): This compound was synthesized using Method A. Colourless oil (76% yield, eluent = hexane/EtOAc (97:3)); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 6.19 (d, $J = 0.7$ Hz, 1H), 4.26 (q, $J = 7.1$ Hz, 2H), 2.52 (s, 4H), 2.09–1.96 (m, 2H), 1.89–1.73 (m, 2H), 1.40–1.17 (m, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 164.5, 158.8, 157.2, 113.6, 103.5, 59.9, 36.9, 31.3, 26.0, 25.8, 14.4, 13.7; **HRMS** (ESI) Calcd for $\text{C}_{14}\text{H}_{21}\text{O}_3$ $[\text{M} + \text{H}]^+$ 237.1491, found 237.1488.

(E)-Ethyl 2-methyl-5-styrylfuran-3-carboxylate (4ma): This compound was synthesized using Method A. Yellow oil (91% yield, eluent = hexane/EtOAc (97:3)); $^1\text{H NMR}$ (400 MHz, CDCl_3): 7.44 (d, $J = 7.4$ Hz, 2H), 7.33 (t, $J = 7.6$ Hz, 2H), 7.24 (dd, $J = 8.6, 6.0$ Hz, 1H), 7.00 (d, $J = 16.3$ Hz, 1H), 6.78 (d, $J = 16.3$ Hz, 1H), 6.56 (s, 1H), 4.29

(q, $J = 7.1$ Hz, 2H), 2.62 (s, 3H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.1, 159.1, 151.2, 137.0, 128.2, 128.0, 127.7, 126.6, 116.0, 115.6, 109.1, 60.4, 14.6, 14.2; **HRMS** (ESI) Calcd for $\text{C}_{16}\text{H}_{17}\text{O}_3$ $[\text{M} + \text{H}]^+$ 257.1178, found 257.1185.

Diethyl 5,5'-(1,4-phenylene)bis(2-methylfuran-3-carboxylate) (4na): This compound was synthesized using Method A. White solid (44% yield, eluent = hexane/EtOAc (97:3)), Mp = 149–151 °C; ^1H NMR (400 MHz, CDCl_3): δ 7.66 (s, 4H), 6.92 (s, 2H), 4.34 (q, $J = 7.1$ Hz, 4H), 2.67 (s, 6H), 1.40 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (100 MHz, CDCl_3): δ 164.0, 158.8, 151.3, 129.1, 123.9, 115.6, 105.8, 60.2, 14.4, 13.9; **HRMS** (ESI) Calcd for $\text{C}_{22}\text{H}_{23}\text{O}_6$ $[\text{M} + \text{H}]^+$ 383.1495, found 383.1499.

Ethyl 2-methyl-5-phenyl-1H-pyrrole-3-carboxylate (6a): This compound was synthesized using Method C. Brown solid (83% yield, eluent = hexane/EtOAc (90:10)), Mp = 114–116 °C; ^1H NMR (400 MHz, CDCl_3): δ 8.71 (s, 1H), 7.53–7.45 (m, 2H), 7.42–7.34 (m, 2H), 7.24 (dt, $J = 9.0, 4.3$ Hz, 1H), 6.87 (d, $J = 2.9$ Hz, 1H), 4.32 (q, $J = 7.1$ Hz, 2H), 2.61 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3): δ 165.7, 136.2, 131.9, 130.0, 128.9, 126.6, 123.7, 113.4, 107.4, 59.6, 14.5, 13.4; **HRMS** (ESI) Calcd for $\text{C}_{14}\text{H}_{16}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 230.1181, found 230.1184.

Ethyl 5-(4-methoxyphenyl)-2-methyl-1H-pyrrole-3-carboxylate (6b): This compound was synthesized using Method D. Brown solid (74% yield, eluent = hexane/EtOAc (90:10)), Mp = 146–148 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.61 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 2.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 2.56 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 165.8, 158.5, 135.1, 130.1, 125.2, 124.9, 114.4, 113.1, 106.1, 59.5, 55.3, 14.5, 13.3; **HRMS** (ESI) Calcd for $\text{C}_{15}\text{H}_{18}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 260.1287, found 260.1300.

Ethyl 5-(furan-2-yl)-2-methyl-1H-pyrrole-3-carboxylate (6c): This compound was synthesized using Method D. Brown solid (44% yield, eluent = hexane/EtOAc (90:10)), Mp = 134–136 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.54 (s, 1H), 7.34 (d, J = 1.7 Hz, 1H), 6.73 (d, J = 2.8 Hz, 1H), 6.42 (dd, J = 3.4, 1.8 Hz, 1H), 6.36 (d, J = 3.3 Hz, 1H), 4.28 (q, J = 7.1 Hz, 2H), 2.57 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 165.4, 147.3, 140.6, 135.5, 121.9, 113.1, 111.6, 106.6, 102.8, 59.5, 14.5, 13.3; **HRMS** (ESI) Calcd for $\text{C}_{12}\text{H}_{14}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 220.0974, found 220.0985.

Ethyl 5-cyclopropyl-2-methyl-1H-pyrrole-3-carboxylate (6d): This compound was synthesized using Method C. Colourless solid (82% yield, eluent = hexane/EtOAc (90:10)), Mp = 55–57 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.35 (s, 1H), 6.14 (d, J = 2.8 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 2.47 (s, 3H), 1.79–1.64 (m, 1H), 1.32 (t, J = 7.1 Hz, 3H), 0.84–0.71 (m, 2H), 0.66–0.52 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 165.9,

134.9, 132.6, 111.2, 105.4, 59.3, 14.5, 13.2, 7.7, 6.4; **HRMS** (ESI) Calcd for $C_{11}H_{16}NO_2$ $[M + H]^+$ 194.1181, found 194.1184.

Ethyl 2,5-diphenyl-1H-pyrrole-3-carboxylate (6e): This compound was synthesized using Method C. Yellow solid (66% yield, eluent = hexane/EtOAc (90:10)), Mp = 149–151 °C; **1H NMR** (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.63–7.61 (m, 2H), 7.54–7.49 (m, 2H), 7.43–7.32 (m, 5H), 7.25 (dd, J = 8.8, 5.9 Hz, 1H), 7.00 (d, J = 3.0 Hz, 1H), 4.21 (q, J = 7.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 164.9, 137.8, 131.9, 131.8, 131.5, 129.04, 129.03, 128.4, 128.2, 127.0, 124.0, 113.8, 109.1, 59.8, 14.3; **HRMS** (ESI) Calcd for $C_{19}H_{18}NO_2$ $[M + H]^+$ 292.1338, found 292.1336.

Ethyl 2-isopropyl-5-phenyl-1H-pyrrole-3-carboxylate (6f): This compound was synthesized using Method C. Brown solid (92% yield, eluent = hexane/EtOAc (90:10)), Mp = 111–113 °C; **1H NMR** (400 MHz, $CDCl_3$): δ 8.46 (s, 1H), 7.54–7.42 (m, 2H), 7.37 (t, J = 7.8 Hz, 2H), 7.25–7.20 (m, 1H), 6.84 (d, J = 2.9 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.86 (sept, J = 7.0 Hz, 1H), 1.38–1.32 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 165.3, 146.0, 132.0, 129.7, 129.0, 126.6, 123.8, 112.0, 107.7, 59.5, 26.1, 22.0, 14.5; **HRMS** (ESI) Calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$ 258.1494, found 258.1502.

Ethyl 2-methyl-5-phenylthiophene-3-carboxylate (7a): This compound was synthesized using Method E. Colourless oil (74% yield, eluent = hexane/EtOAc (95:5)); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.59 (s, 1H), 7.58–7.53 (m, 2H), 7.37 (t, $J = 7.6$ Hz, 2H), 7.31–7.25 (m, 1H), 4.33 (q, $J = 7.1$ Hz, 2H), 2.75 (s, 3H), 1.39 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 163.7, 148.5, 139.3, 133.7, 129.2, 128.9, 127.6, 125.6, 124.6, 60.4, 15.6, 14.4; **HRMS** (ESI) Calcd for $\text{C}_{14}\text{H}_{15}\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 247.0793, found 247.0796.

Ethyl 5-(4-methoxyphenyl)-2-methylthiophene-3-carboxylate (7b): This compound was synthesized using Method E. Yellow solid (64% yield, eluent = hexane/EtOAc (95:5)), Mp = 84–86 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.54–7.45 (m, 3H), 6.92 (d, $J = 8.8$ Hz, 2H), 4.35 (q, $J = 7.1$ Hz, 2H), 3.85 (s, 3H), 2.76 (s, 3H), 1.41 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 163.7, 159.3, 147.6, 139.2, 129.1, 126.9, 126.5, 123.5, 114.3, 60.3, 55.4, 15.6, 14.4; **HRMS** (ESI) Calcd for $\text{C}_{15}\text{H}_{17}\text{O}_3\text{S}$ $[\text{M} + \text{H}]^+$ 277.0898, found 277.0889.

Ethyl 5-(furan-2-yl)-2-methylthiophene-3-carboxylate (7c): This compound was synthesized using Method E. Red oil (47% yield, eluent = hexane/EtOAc (95:5)); $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 7.50 (s, 1H), 7.39 (dd, $J = 1.8, 0.7$ Hz, 1H), 6.50–6.35 (m, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 2.73 (s, 3H), 1.38 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3): δ 163.4, 148.6, 147.9, 141.8, 129.0, 128.8, 124.0, 111.7, 105.1, 60.4, 15.4, 14.4; **HRMS** (ESI) Calcd for $\text{C}_{12}\text{H}_{13}\text{O}_3\text{S}$ $[\text{M} + \text{H}]^+$ 237.0585, found 237.0584.

Ethyl 5-(4-methoxyphenyl)-2-methylthiophene-3-carboxylate (7d): This compound was synthesized using Method E. Yellow oil (66% yield, eluent = hexane/EtOAc (95:5)); **¹H NMR** (400 MHz, CDCl₃): δ 7.01 (d, *J* = 0.6 Hz, 1H), 4.28 (q, *J* = 7.1 Hz, 2H), 2.65 (s, 3H), 2.02–1.86 (m, 1H), 1.35 (t, *J* = 7.1 Hz, 3H), 0.96–0.91 (m, 2H), 0.70–0.66 (m, 2H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.7, 146.3, 143.4, 127.7, 124.2, 60.1, 15.4, 14.4, 10.6, 9.2; **HRMS** (ESI) Calcd for C₁₁H₁₅O₂S [M + H]⁺ 211.0793, found 211.0796.

Ethyl 2,5-diphenylthiophene-3-carboxylate (7e): This compound was synthesized using Method E. Yellow solid (62% yield, eluent = hexane/EtOAc (95:5)), Mp = 44–46 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.74 (s, 1H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.58–7.55 (m, 2H), 7.45–7.41 (m, 5H), 7.35 (t, *J* = 7.4 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.23 (t, *J* = 7.1 Hz, 3H); **¹³C NMR** (100 MHz, CDCl₃): δ 163.3, 149.7, 142.5, 133.4, 133.5, 129.8, 129.0, 128.6, 128.0, 127.9, 125.7, 125.4, 60.6, 14.0; **HRMS** (ESI) Calcd for C₁₉H₁₇O₂S [M + H]⁺ 309.0949, found 309.0954.

Methyl 2-(4-methoxyphenyl)-5-phenylthiophene-3-carboxylate (7f): This compound was synthesized using Method E. White solid (62% yield, eluent = hexane/EtOAc (95:5)), Mp = 143–145 °C; **¹H NMR** (400 MHz, CDCl₃): δ 7.69 (s, 1H), 7.64–7.52 (m, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.94 (d, *J* = 8.7 Hz,

2H), 3.84 (s, 3H), 3.76 (s, 3H); **^{13}C NMR** (100 MHz, CDCl_3): δ 163.8, 160.1, 150.4, 141.9, 133.5, 131.1, 129.0, 128.0, 127.8, 125.7, 125.50, 125.45, 113.5, 55.3, 51.6; **HRMS** (ESI) Calcd for $\text{C}_{19}\text{H}_{17}\text{O}_3\text{S}$ $[\text{M} + \text{H}]^+$ 325.0898, found 325.0893.

3.5 References

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Chapter 4. Synthesis of Highly Substituted Pyridines via Copper-Catalyzed Condensation of Oximes and α,β -Unsaturated Imines

4.1 Introduction

Pyridine cores are widely found in many natural products and synthetic pharmaceuticals. They also play pivotal roles in coordination chemistry and material science (Figure 4.1).¹ Consequently, the development of efficient and regioselective methods for the synthesis of pyridines has been among significant tasks in heterocyclic chemistry. To date, many classical, transition metal-catalyzed, and metal-free methods have been developed to access differently functionalized pyridines.^{2,3} Despite these advances, the development of new regioselective methods for the synthesis of highly functionalized pyridines, are still in demand, as many of the substitutions patterns desired still cannot be accessed easily from readily available starting materials.

Figure 4.1. Pyridine motifs in functional molecules

In this context, oxime derivatives, which can be readily prepared from commercially available starting materials, have emerged as extremely versatile intermediates for transition metal-catalyzed synthesis of pyridines,^{4,5} as well as other nitrogen-containing heterocycles due to the ability to undergo reductive N–O bond cleavage^{6,7} or serve as a directing group for C–H activation.^{8,9} In particular, α,β -unsaturated oxime derivatives have been utilized as C3N1 units for the synthesis of pyridines (Scheme 4.1). In 2008, Liebeskind *et al.* reported a copper-catalyzed coupling of alkenylboronic acid and α,β -unsaturated ketoxime to afford highly substituted pyridines as described also in Chapter 1 (Scheme 1.4a).^{4a} Several groups have developed pyridine-forming reactions based on the coupling of α,β -unsaturated oximes with alkynes or alkenes. For example, Cheng *et al.* reported a rhodium-catalyzed coupling of α,β -unsaturated ketoximes and alkynes via chelation-assisted C–H activation, which affords multisubstituted pyridines.^{4b} The reaction is considered to generate an azatriene intermediate, which subsequently undergoes electrocyclization and elimination of water to afford the pyridine product. In 2013, Rovis *et al.* reported a rhodium-catalyzed coupling of α,β -unsaturated *O*-pivaloyl oximes and activated alkenes to afford pyridines.^{4f} The reaction is proposed to proceed via C–H activation of the oxime, alkene insertion, and simultaneous C–N bond formation/ N–O bond cleavage.

Scheme 4.1. Synthesis of pyridines via α,β -unsaturated ketoximes

O-acetyl oximes bearing α -protons have also been widely used as C2N1 units for pyridine synthesis (Scheme 4.2). Guan *et al.* developed a series of pyridine-forming reactions via the coupling of *O*-acetyl oximes and aldehydes, DMF or dimethylaniline catalyzed by copper, ruthenium, or iron, respectively.^{5a-c} Despite the simplicity, pyridines accessible by these reactions are largely limited to disubstituted or symmetrical derivatives. In 2013, our group developed a copper-catalyzed [3+3]-type pyridine synthesis starting from *O*-acetyl oximes and enals.^{5d} In 2015, Jiang *et al.* reported a three-component coupling of oximes, aldehydes and active methylene compounds such as β -ketoesters to afford highly substituted pyridines.^{5e} While these reactions proved to be attractive methods for the synthesis of highly substituted pyridines, they do not allow the use of unactivated enones, which limits the substitution patterns of the accessible pyridines. Under our previously developed conditions,^{5d} the reaction of preformed iminium salts derived from enones and *O*-acetyl oximes failed to give the desired pyridine, which illustrates the difficulty with the expansion of the substrate scope.

Scheme 4.2. Synthesis of pyridines via *O*-acetyl oximes derivativesa) Pyridine synthesis via *O*-acetyl oximes b) Reaction of *O*-acetyl oximes with iminium salts

To remove the above-mentioned limitations, we explored enone equivalents that can participate in copper-catalyzed condensation with *O*-acetyl oximes to afford pyridine derivatives. This effort led us to develop a copper-catalyzed pyridine synthesis starting from *O*-acetyl oxime and α,β -unsaturated *N*-tosyl ketimines (Scheme 4.3). The method features simple and mild reaction conditions and a broad substrate scope, and allows for the regioselective formation of highly substituted pyridines with substitution patterns not readily accessible by conventional condensation methods.

Scheme 4.3. Copper-catalyzed condensation of *O*-acetyl oximes and α,β -unsaturated ketimines

4.2 Results and Discussion

We commenced the study of the reaction between *O*-acetyl oxime **1a** derived from propiophenone and α,β -unsaturated *N*-tosyl ketimine **2a** derived from chalcone as summarized in Table 4.1. The condensation of these starting materials proceeded smoothly in the presence of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (5 mol%) and NaHSO_3 (1 equiv) in DMSO at 60 °C to afford the desired pyridine **3aa** in a quantitative yield. In order to demonstrate the practicality of the reaction, the model reaction was performed on a gram scale (5 mmol), which afforded the product **3aa** in 95% yield. The use of other copper salts such as copper(I) chloride, copper(I) bromide, and copper(I) iodide afforded **3aa** in slightly lower yields (entries 2-4). The use of NaHSO_3 as the additive proved to be critical for the reaction, as its absence led to a significant drop in the yield (entry 5).^{5a,10} As the overall transformation is redox-neutral, we are not sure whether NaHSO_3 participates in any redox process, while we suspect that it might serve as a proton source for the reaction. When DMF was used instead of DMSO, the reaction afforded modest yield of the product (entry 6). The reaction also tolerated imine **2a'** bearing a *p*-methoxyphenyl group, which afforded the desired product **3aa** in a good yield under slightly modified conditions, by increasing the catalyst loading (10 mol%) and the reaction temperature to 90 °C (entries 7 and 8). Not surprisingly, when chalcone **2a''** was used instead of the imine **2a**, we could only observe a trace amount of **3aa**. A notable side product, 2,5-diphenyl-3,4-

dimethylpyrrole¹¹ resulting from the homocoupling of **1a**, was observed when oxime **1a** was added in excess (> 2 equiv).

Table 4.1. Screening of reaction conditions

Entry	X	Deviation from the standard conditions	Yield (%) ^b
1	NTs	None	99 (95) ^c
2	NTs	CuCl instead of $[\text{Cu}(\text{MeCN})_4][\text{PF}_6]$	84
3	NTs	CuBr instead of $[\text{Cu}(\text{MeCN})_4][\text{PF}_6]$	85
4	NTs	CuI instead of $[\text{Cu}(\text{MeCN})_4][\text{PF}_6]$	84
5	NTs	NaHSO_3 omitted	10
6	NTs	DMF instead of DMSO	68
7	NPMP	None	75
8	NPMP	10 mol% catalyst, $T = 90\text{ }^\circ\text{C}$	87
9	O	None	<5

^a PMP = *p*-methoxyphenyl

^b Determined by GC using tridecane as internal standard.

^c Isolated yield of 5 mmol scale

Having identified the optimum reaction conditions, we explored the substrate scope of the present reaction with respect to α,β -unsaturated ketimines (Scheme 4.4). α,β -Unsaturated ketimines **2b-2s** participated well in the reaction with *O*-acetyl oxime **1a** to afford polysubstituted pyridines **3ab-3as** in moderate to excellent yields. The reaction tolerated differently functionalized unsaturated imines bearing electron-donating and electron-withdrawing substituents such as methoxy, methylthio, chloro, bromo, cyano, nitro and trifluoromethyl groups to afford pyridines **3ab-3al** in excellent yields. Heteroaryl-substituted imines bearing furan and thiophene moieties were also well tolerated to afford pyridines **3am-3ao** in good yields. The R¹ and R³ substituent of the

α,β -unsaturated ketimines could be modified to alkyl groups for the preparation of pyridines **3ap** and **3aq** in modest yields. Notably, pentasubstituted pyridines **3ar** and **3as** could be prepared in modest yields, by increasing the reaction temperature to 90 °C.

Scheme 4.4. Condensation of various α,β -unsaturated imines with **1a**^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 4.1. ^b *N*-PMP imine was employed, and the reaction conditions was performed under the conditions in Table 4.1, entry 8. ^c Reaction was performed at 90 °C

We then moved on to explore the reaction of various *O*-acetyl oximes **1b-1w** with unsaturated imine **2a** (Scheme 4.5). We found that the reaction of acetophenone-derived oxime **1b** and **2a** was relatively sluggish under the standard conditions, affording the desired pyridine **3ba** in only 76% yield. Upon further screening, we were able to obtain **3ba** in near quantitative yield by changing the number of equivalents of oxime **1b** (1.6 equiv) and increasing the reaction temperature (90 °C). Under the modified conditions, various *O*-acetyl oximes **1c-1k** derived from aryl methyl ketones bearing substituents such as methoxy, cyano, iodo, trifluoromethyl, and nitro groups participated in the reaction with **2a** to afford pyridines **3ca-3ka** in moderate to excellent yields. The reaction also tolerated oximes bearing heteroaryl substituents such as thiophene, furan and pyridine moieties to afford pyridines **3la-3na** in good yields. Aryl alkyl oximes **1o-1q** derived from tetralone, deoxybenzoin, and phenyl 3-butenyl ketone reacted smoothly under the original conditions to afford pyridines **3oa-3qa** in excellent yields. Interestingly, *O*-acetyl oxime **1r** derived from isobutyrophenone afforded a dihydropyridine derivative **3ra** in a modest yield. Besides aryl alkyl oximes, alkyl oximes **1s-1w** derived from acetone, pinacolone, ethyl pyruvate, and cycloalkanones were also well tolerated to afford pyridines **3sa-3wa** in modest to excellent yields. Bis-oxime **1x** derived from 1,3-diacetylbenzene gave a two-fold condensation product **3xa** albeit in a low yield.

Scheme 4.5. Condensation of various *O*-acetyl oximes with **2a**^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 4.1. ^b Reaction was performed using 1.6 equiv of oxime at 90 °C. ^c Oxime derived from isobutyrophenone was used. ^d Oxime derived from 1,3-diacetylbenzene and 2 equiv of **2a** were used at 90 °C

To further clarify the scope of the present condensation reaction, we examined a series of *O*-acetyl oximes bearing two distinct enolizable α -positions, which could potentially produce two isomers of pyridines (Scheme 4.6). Notably, in all the reactions

we could only observe one regioisomer of the desired product. The reaction of *O*-acetyl oxime **1y** derived from 2-hexanone with imine **2a** afforded the pyridine product **3ya** as a single isomer as a result of C–C bond formation at secondary carbon of the butyl group. The formation of the other possible isomer was not detectable by gas chromatographic analysis. Likewise, *O*-acetyl oximes **1z** and **1aa** derived from phenylacetone and methoxyacetone, respectively, also underwent regioselective C–C bond formation at the secondary carbon to afford the corresponding pyridine **3za** and **3aaa**. *O*-acetyl oxime **1ab** derived from cyclopropyl methyl ketone afforded pyridine **3aba** via regioselective C–C bond formation at the methyl group. *O*-acetyl oxime **1ac** derived from cyclohexyl ethyl ketone underwent regioselective C–C bond formation at the ethyl group to give pyridine **3aca**. The regioselectivities in these reactions may be associated with the thermodynamic stability as well as reactivity of a copper enamide species (*vide infra*).

Scheme 4.6. Regioselective formation of pyridine derivatives from oximes bearing two distinct α -positions^a

^a The reaction was performed on a 0.2 mmol scale according to standard conditions described in Table 4.1 with 1.6 equiv of oxime

In order to gain mechanistic insights into the present reaction, we performed some competition and control experiments as shown in Scheme 4.7. First, a mixture of *O*-acetyl oximes **1a** and **1b** derived from propiophenone and acetophenone, respectively, was subjected to the standard reaction conditions with **2a**, which resulted in preferential reaction of the former oxime to afford **3aa** as the major product. This observation is consistent with the milder reaction conditions required for **1a** as compare to **1b**, as well as the regioselectivity observed in Scheme 4.6. Next, a competition experiment was conducted using *N*-Ts imine and *N*-PMP imine derived from electronically similar chalcone derivatives. Interestingly, the competition resulted in the formation of pyridines derived from both the imines in similar yields. Lastly, the condensation reaction of **1a** and **2a** was largely suppressed by the addition of TEMPO, while 1,1-diphenylethylene did not interfere with the reaction.

Scheme 4.7. Competition and control experimentsa) Competition between different *O*-acetyl oximes b) Competition between different *N*-substituted imines

c) Control experiments

In reference to the previous studies on copper catalysis of oximes⁹ and our observations, we propose the following reaction pathways in Scheme 4.8. Firstly, sequential single electron reduction of oxime **1a** with two equivalents of copper(I) would generate an iminyl radical species **A** and subsequently an iminyl copper(II) species **B**, which can undergo tautomerization to a copper(II) enamide species **C**.¹² Next, conjugate addition of **C** to the α,β -unsaturated ketimine **2** with the assistance of copper(II) would take place to afford an intermediate **D**, which would undergo intramolecular cyclization and liberation of *p*-toluenesulfonamide to afford a dihydropyridine intermediate **F** (*cf.* product **3ra** in Scheme 4.5). The intermediate **F** would be oxidized by copper(II) to furnish the pyridine product with regeneration of the copper(I) catalyst. Besides this ionic pathway for C-C bond formation, we may not exclude an alternative pathway involving

an α -imino radical species **C'** formed via a homolytic N–Cu cleavage of **C**. Addition of the radical **C'** to **2** would generate an intermediate **D'**, and subsequent single electron reduction and protonation would lead to the common intermediate **E**. It should be noted that the radical species **C'** was proposed as the intermediate for the copper-catalyzed homocoupling reaction of propiophenone-derived *O*-acetyl oxime to furnish 2,5-diphenyl-3,4-dimethylpyrrole,¹¹ which was also observed in the present reaction using an excess amount of the oxime.

Scheme 4.8. Proposed reaction pathways

4.3 Conclusion

In summary, we have developed a copper-catalyzed condensation reaction of *O*-acetyl oximes and α,β -unsaturated imines for the regioselective synthesis of highly substituted pyridines. The reaction features a simple catalytic system and readily available starting materials. The scope of the reaction covers a broad range of imines and *O*-acetyl oximes derived from aryl alkyl-, dialkyl-, acyclic and cyclic ketones allowing regioselective access to multisubstituted pyridines. As such, we have been able to remove the previous limitation of the pyridine synthesis based on copper catalysis of oximes (*vide supra*). It should be emphasized that the thus-synthesized pyridines are not readily accessible by conventional condensation methods such as the Kröhnke synthesis and its variants.

4.4 Experimental

Materials and Methods

General. All reactions dealing with air- and moisture-sensitive compounds were carried out in oven dried reaction vessels under a nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Bruker 300, 400, 500 MHz NMR spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0.00 ppm) and CHCl_3 (77.26 ppm), respectively. Chemical shifts are reported in ppm and the multiplicities are reflected by s (singlet), d (doublet), q (quartet), and m (multiplet). Coupling constants are represented by J in hertz (Hz). Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 μm film thickness). High-resolution mass spectra (HRMS) were obtained with a Q-ToF Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected.

Materials. Unless otherwise noted, materials were purchased from Aldrich, Alfa Aesar, and other commercial suppliers and were used as received.

Preparation of Starting Materials

Synthesis of Imines

All imines were synthesized by condensation of the *p*-toluenesulfonamide and corresponding chalcones according to the literature procedure,¹³ and purified by flash column chromatography. Below is the summarized characterization data for newly synthesized imine. ^1H and ^{13}C NMR spectral data for the rest of the imines showed good agreement with literature data.¹⁴

4-Methyl-N-((E)-3-(4-(methylthio)phenyl)-1-phenylallylidene)benzenesulfonamide

(2c): Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 158–160 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.13–7.85 (m, 3H), 7.61 (s, 2H), 7.57–7.41 (m, 5H), 7.30 (d, J = 8.0 Hz, 2H), 7.24 (t, J = 7.5 Hz, 2H), 7.02 (d, J = 16.0 Hz, 1H), 2.50 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 177.5, 148.6, 143.5, 143.4, 138.8, 131.0, 129.4, 129.1, 128.4, 127.2, 125.9, 21.6, 15.0 ; **HRMS** (ESI) Calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M} + \text{H}]^+$ 408.1092, found 408.1092.

N-((E)-3-(4-Cyanophenyl)-1-phenylallylidene)-4-methylbenzenesulfonamide (2f):

White solid (eluent = hexane/EtOAc (80:20)); Mp = 189–191 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.12 (s, 1H), 7.92 (d, J = 6.9 Hz, 2H), 7.71–7.67 (m, 6H), 7.57 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.02 (d, J = 16.2 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.3, 144.8, 143.8, 138.8, 138.3, 132.7, 129.6, 128.8, 128.6, 127.3, 118.3, 113.9, 21.6; **HRMS** (ESI) Calcd for $\text{C}_{23}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ $[\text{M} + \text{H}]^+$ 387.1167, found 387.1169.

4-Methyl-*N*-((*E*)-1-phenyl-3-(3-

(trifluoromethyl)phenyl)allylidene)benzenesulfonamide (2h): White solid (eluent = hexane/EtOAc (90:10)); Mp = 109–111 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.17–8.00 (m, 1H), 7.92 (d, *J* = 7.1 Hz, 2H), 7.80 (s, 1H), 7.74–7.63 (m, 4H), 7.56 (q, *J* = 7.0 Hz, 2H), 7.45 (t, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 16.1 Hz, 1H), 2.42 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.9, 146.1, 143.7, 138.5, 135.4, 132.2, 131.8, 131.4, 131.0, 130.1, 129.6, 129.5, 128.5, 127.3, 125.6, 125.1, 122.4, 21.6; HRMS (ESI) Calcd for C₂₃H₁₉F₃NO₂S [M + H]⁺ 430.1089, found 430.1087.

4-Methyl-*N*-((*E*)-3-(naphthalen-1-yl)-1-phenylallylidene)benzenesulfonamide (2i):

Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 146–148 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (s, 1H), 8.03–7.80 (m, 7H), 7.76 (d, *J* = 5.5 Hz, 2H), 7.62–7.44 (m, 6H), 7.30 (d, *J* = 8.1 Hz, 2H), 2.40 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 177.6, 145.4, 143.5, 138.8, 133.7, 131.9, 131.5, 131.4, 130.3, 129.5, 129.0, 128.5, 127.3, 127.2, 126.3, 126.2, 125.8, 122.9, 21.6; HRMS (ESI) Calcd for C₂₆H₂₂NO₂S [M + H]⁺ 412.1371, found 412.1371.

***N*-((*E*)-1-(4-Bromophenyl)-3-(4-(tert-butyl)phenyl)allylidene)-4-**

methylbenzenesulfonamide (2k): Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 54–56 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (s, 1H), 7.90 (d, *J* = 7.5 Hz, 2H), 7.58–

7.39 (m, 8H), 7.29 (t, $J = 7.2$ Hz, 2H), 7.11–6.92 (m, 1H), 2.40 (s, 3H), 1.32 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.6, 155.3, 149.1, 143.6, 138.7, 131.70, 131.67, 131.3, 129.5, 128.9, 128.8, 127.6, 127.2, 126.1, 125.2, 35.1, 31.1, 21.6; HRMS (ESI) Calcd for $\text{C}_{26}\text{H}_{27}\text{BrNO}_2\text{S}$ $[\text{M} + \text{H}]^+$ 496.0946, found 496.0948.

***N*-((*E*)-1-(4-Methoxyphenyl)-3-(*o*-tolyl)allylidene)-4-methylbenzenesulfonamide (2l):**

Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 93–95 °C; ^1H NMR (400 MHz, CDCl_3) δ 7.97 (d, $J = 7.9$ Hz, 2H), 7.88 (d, $J = 14.7$ Hz, 1H), 7.78 (t, $J = 8.2$ Hz, 3H), 7.43–7.27 (m, 5H), 7.23 (d, $J = 6.8$ Hz, 1H), 6.97 (d, $J = 8.5$ Hz, 2H), 3.89 (s, 3H), 2.45 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 176.9, 163.4, 145.0, 143.3, 139.1, 137.8, 133.8, 132.6, 130.8, 130.5, 129.7, 129.4, 127.14, 127.08, 126.7, 113.8, 55.6, 21.6, 19.8; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{24}\text{NO}_3\text{S}$ $[\text{M} + \text{H}]^+$ 406.1477, found 406.1477.

(*Z*)-4-Methoxy-*N*-((*E*)-3-(5-methylfuran-2-yl)-1-phenylallylidene)aniline (2m):

Yellow solid ($E/Z = 75:25$; eluent = hexane/EtOAc (90:10)); Mp = 71–73 °C; ^1H NMR (400 MHz, CDCl_3 *E* isomer) δ 7.73–7.66 (m, 2H), 7.51–7.45 (m, 2H), 7.31 (dd, $J = 9.2$, 6.9 Hz, 1H), 7.19–7.11 (m, 1H), 7.02–6.94 (m, 3H), 6.72–6.56 (m, 2H), 6.32 (d, $J = 3.2$ Hz, 1H), 6.04 (d, $J = 3.2$ Hz, 1H), 3.87 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.2, 156.4, 154.8, 150.4, 144.4, 139.8, 129.5, 129.3, 129.0, 128.7, 128.5,

128.3, 128.2, 123.0, 122.4, 118.1, 114.5, 114.1, 113.6, 108.7, 55.5, 13.9; **HRMS** (ESI)

Calcd for $C_{21}H_{20}NO_2$ $[M + H]^+$ 318.1494, found 318.1499.

4-Methyl-N-((E)-1-(5-methylfuran-2-yl)-3-phenylallylidene)benzenesulfonamide

(2n): Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 157–159 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.79–7.75 (m, 1H), 7.61 (dd, J = 6.4, 2.7 Hz, 2H), 7.45–7.40 (m, 4H), 7.31 (t, J = 7.3 Hz, 3H), 6.27 (d, J = 3.4 Hz, 1H), 2.46 (s, 3H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.1, 149.3, 144.2, 143.1, 139.2, 135.0, 130.6, 129.4, 129.0, 128.4, 127.2, 124.7, 121.8, 110.3, 21.6, 14.4; **HRMS** (ESI) Calcd for $C_{21}H_{20}NO_3S$ $[M + H]^+$ 366.1164, found 366.1160.

4-Methyl-N-((E)-3-phenyl-1-(thiophen-2-yl)allylidene)benzenesulfonamide (2o):

Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 145–147 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 7.97–7.91 (m, 3H), 7.71–7.68 (m, 2H), 7.63 (dd, J = 6.4, 2.8 Hz, 2H), 7.49–7.44 (m, 3H), 7.37–7.28 (m, 3H), 7.20–7.15 (m, 1H), 2.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 169.7, 145.6, 143.4, 142.3, 138.7, 135.2, 134.7, 134.6, 130.8, 129.4, 129.1, 128.5, 128.3, 127.2, 122.2, 21.6; **HRMS** (ESI) Calcd for $C_{20}H_{18}NO_2S_2$ $[M + H]^+$ 368.0779, found 368.0783.

***N*-((*E*)-3-Cyclohexyl-1-phenylallylidene)-4-methylbenzenesulfonamide (2q):** Yellow solid (eluent = hexane/EtOAc (90:10)); Mp = 120–122 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.93 (d, J = 7.2 Hz, 2H), 7.68–7.49 (m, 3H), 7.49–7.25 (m, 5H), 6.35 (dd, J = 15.8, 7.0 Hz, 1H), 2.43 (s, 3H), 2.33 (d, J = 5.8 Hz, 1H), 1.92–1.67 (m, 5H), 1.42–1.13 (m, 5H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 178.3, 159.5, 143.3, 138.9, 131.9, 131.4, 130.2, 129.4, 128.4, 128.2, 127.9, 127.2, 41.9, 31.7, 25.9, 25.6, 21.6; **HRMS** (ESI) Calcd for $\text{C}_{22}\text{H}_{26}\text{NO}_2\text{S}$ $[\text{M} + \text{H}]^+$ 368.1684, found 368.1684.

4-Methyl-*N*-((*E*)-2-methyl-1,3-diphenylallylidene)benzenesulfonamide (2r): White solid (eluent = hexane/EtOAc (90:10)); Mp = 94–96 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.84–7.82 (m, 2H), 7.59–7.21 (m, 12H), 6.86 (s, 1H), 2.46 (s, 3H), 2.23 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 143.2, 138.9, 135.8, 135.4, 129.7, 129.3, 128.4, 128.1, 127.3, 21.6; **HRMS** (ESI) Calcd for $\text{C}_{23}\text{H}_{22}\text{NO}_2\text{S}$ $[\text{M} + \text{H}]^+$ 376.1371, found 376.1379.

4-Methyl-*N*-((*E*)-1,2,3-triphenylallylidene)benzenesulfonamide (2s): White solid (eluent = hexane/EtOAc (90:10)); Mp = 136–138 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.29–6.89 (m, 20H), 2.44 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 139.0, 135.8, 130.1, 129.7, 129.3, 128.6, 128.3, 128.0, 127.2, 126.5, 21.6; **HRMS** (ESI) Calcd for $\text{C}_{28}\text{H}_{24}\text{NO}_2\text{S}$ $[\text{M} + \text{H}]^+$ 438.1528, found 438.1526.

Synthesis of *O*-acetyl Oxime

All *O*-acetyl oximes were synthesized according to literature procedure,¹⁵ and were purified by recrystallization with ethyl acetate/hexane or flash column chromatography. Below are summarized characterization data for newly synthesized diazocarbonyl compounds. ¹H and ¹³C NMR spectral data for the rest of the oxime compounds showed good agreement with literature data.¹⁶

1-(3-(1-(Acetoxyimino)ethyl)phenyl)ethanone *O*-acetyl oxime (1x): White solid (eluent = hexane/EtOAc (95:5)); Mp = 99-101 °C; ¹H NMR (500 MHz, CDCl₃) δ 8.07 (t, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 7.8, 1.8 Hz, 2H), 7.49 (d, *J* = 7.8 Hz, 1H), 2.43 (s, 6H), 2.29 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 168.7, 162.1, 135.5, 129.1, 128.9, 125.7, 19.8, 14.6; **HRMS** (ESI) Calcd for C₁₄H₁₇N₂O₄ [*M* + *H*]⁺ 277.1188, found 277.1190.

Hexan-2-one *O*-acetyl oxime (1y): Colourless oil (eluent = hexane/EtOAc (95:5)); ¹H NMR (400 MHz, CDCl₃) δ 2.36–2.28 (m, 2H), 2.15 (s, 3H), 1.96 (s, 3H), 1.53 (dt, *J* = 21.2, 7.4 Hz, 2H), 1.35 (dq, *J* = 14.5, 7.3 Hz, 2H), 0.91 (t, *J* = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 168.8, 166.6, 35.4, 28.4, 22.3, 19.7, 15.2, 13.7; **HRMS** (ESI) Calcd for C₈H₁₆NO₂ [*M* + *H*]⁺ 158.1181, found 158.1182.

1-Phenylpropan-2-one *O*-acetyl oxime (1z): Colourless oil (*E/Z* = 83:17; eluent = hexane/EtOAc (95:5)); ¹H NMR (400 MHz, CDCl₃, *E* isomer) δ 7.41–7.08 (m, 5H), 3.66

(s, 2H), 2.20 (s, 3H), 1.90 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.7, 165.2, 135.5, 129.1, 128.8, 127.2, 41.9, 19.7, 15.1; **HRMS** (ESI) Calcd for $\text{C}_{11}\text{H}_{14}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 192.1025, found 192.1025.

1-Methoxypropan-2-one O-acetyl oxime (1aa): Colourless oil (E/Z = 85:15; eluent = hexane/EtOAc (95:5)); ^1H NMR (300 MHz, CDCl_3 , E isomer) δ 4.05 (s, 2H), 3.31 (s, 3H), 2.15 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 168.5, 163.4, 72.8, 58.3, 19.5, 13.0; **HRMS** (ESI) Calcd for $\text{C}_6\text{H}_{12}\text{NO}_3$ $[\text{M} + \text{H}]^+$ 146.0817, found 146.0816.

1-Cyclohexylpropan-1-one O-acetyl oxime (1ac): Colourless oil (E/Z = 79:21; eluent = hexane/EtOAc (95:5)); ^1H NMR (500 MHz, CDCl_3 , E isomer) δ 2.40–2.28 (m, 3H), 2.14 (s, 3H), 1.78 (d, J = 10.5 Hz, 4H), 1.68 (d, J = 10.3 Hz, 1H), 1.42–1.06 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.7, 169.1, 43.9, 29.9, 25.94, 25.87, 25.8, 21.3, 19.8, 11.0; **HRMS** (ESI) Calcd for $\text{C}_{11}\text{H}_{20}\text{NO}_2$ $[\text{M} + \text{H}]^+$ 198.1494, found 198.1496.

Copper-Catalyzed Condensation of Oximes and α,β -Unsaturated Imines

General Procedure A: A 10 mL Schlenk tube equipped with a stirrer bar was charged with imine (0.20 mmol), oxime (0.24 mmol), $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (3.7 mg, 0.01 mmol, 5 mol%) and NaHSO_3 (0.20 mmol) followed by the addition of DMSO (1.0 mL). The resulting mixture was stirred at 60 °C for 12 h. Upon cooling to room temperature, the reaction mixture was diluted by ethyl acetate (3 mL) and concentrated under reduced

pressure. The residue was then purified by flash chromatography on silica gel to afford the pyridine product.

General Procedure B: A 10 mL Schlenk tube equipped with a stirrer bar was charged with imine (0.20 mmol), oxime (0.32 mmol), $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ (3.7 mg, 0.01 mmol, 5 mol%) and NaHSO_3 (0.20 mmol) followed by the addition of DMSO (1.0 mL). The resulting mixture was stirred at 90 °C for 12 h. Upon cooling to room temperature, the reaction mixture was diluted by ethyl acetate (3 mL) and concentrated under reduced pressure. The residue was then purified by flash chromatography on silica gel to afford the pyridine product.

3-Methyl-2,4,6-triphenylpyridine (3aa): The reaction was performed on a 5 mmol scale in a 100 mL Schlenk tube, following the same reaction stoichiometry and conditions as that of the general procedure A. Yellow solid (95% yield, eluent = hexane/EtOAc (98:2)); $\text{Mp} = 141\text{--}143\text{ }^\circ\text{C}$; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.17–8.11 (m, 2H), 7.77–7.72 (m, 2H), 7.68 (s, 1H), 7.57–7.42 (m, 11H), 2.32 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.5, 154.1, 151.7, 141.4, 140.7, 139.4, 129.5, 128.8, 128.7, 128.5, 128.1, 127.9, 126.99, 126.95, 120.0, 18.0; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{20}\text{N}$ $[\text{M} + \text{H}]^+$ 322.1596, found 322.1597.

4-(4-Methoxyphenyl)-3-methyl-2,6-diphenylpyridine (3ab): Following Procedure A, Yellow solid (95% yield, eluent = hexane/EtOAc (98:2)); Mp = 138–140 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.15–8.02 (m, 2H), 7.73–7.69 (m, 2H), 7.64 (s, 1H), 7.54–7.38 (m, 8H), 7.06 (d, *J* = 8.7 Hz, 2H), 3.92 (s, 3H), 2.31 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.5, 159.4, 154.1, 151.3, 141.6, 139.5, 132.6, 130.1, 129.5, 128.6, 128.1, 127.9, 127.1, 126.9, 120.1, 113.9, 55.4, 18.1; **HRMS** (ESI) Calcd for C₂₅H₂₂NO [M + H]⁺ 352.1701, found 352.1699.

3-Methyl-4-(4-(methylthio)phenyl)-2,6-diphenylpyridine (3ac): Following Procedure A, Yellow solid (91% yield, eluent = hexane/EtOAc (98:2)); Mp = 128–130 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.18–8.11 (m, 2H), 7.74–7.69 (m, 2H), 7.64 (s, 1H), 7.57–7.42 (m, 6H), 7.41 (s, 4H), 2.59 (s, 3H), 2.31 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.6, 154.2, 151.0, 141.5, 139.4, 138.7, 136.9, 129.5, 129.3, 128.70, 128.67, 128.1, 127.9, 127.0, 126.9, 126.3, 119.9, 18.1, 15.7; **HRMS** (ESI) Calcd for C₂₅H₂₂NS [M + H]⁺ 368.1473, found 368.1472.

4-(4-Chlorophenyl)-3-methyl-2,6-diphenylpyridine (3ad): Following Procedure A, Yellow solid (98% yield, eluent = hexane/EtOAc (98:2)); Mp = 128–130 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.15–8.02 (m, 2H), 7.73–7.68 (m, 2H), 7.62 (s, 1H), 7.58–7.44 (m, 10H), 2.29 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.6, 152.8, 151.8, 141.3, 140.2, 137.8, 134.7, 129.4, 128.80, 128.77, 128.5, 128.18, 128.15, 128.0, 127.4, 119.7, 18.0; **HRMS** (ESI) Calcd for C₂₄H₁₉ClN [M + H]⁺ 356.1206, found 356.1207.

4-(4-Bromophenyl)-3-methyl-2,6-diphenylpyridine (3ae): Following Procedure A, White solid (99% yield, eluent = hexane/EtOAc (98:2)); Mp = 123–125 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.15–8.08 (m, 2H), 7.73–7.65 (m, 4H), 7.62 (s, 1H), 7.57–7.41 (m, 6H), 7.37–7.33 (m, 2H), 2.29 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.7, 154.2, 150.4, 141.3, 139.1, 131.7, 130.5, 129.5, 128.8, 128.7, 128.2, 128.0, 127.9, 126.8, 122.3, 119.7, 18.0; **HRMS** (ESI) Calcd for C₂₄H₁₉BrN [M + H]⁺ 400.0701, found 400.0703.

4-(3-Methyl-2,6-diphenylpyridin-4-yl)benzonitrile (3af): Following Procedure A, Brown solid (86% yield, eluent = hexane/EtOAc (90:10)); Mp = 174–176 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.08–8.02 (m, 2H), 7.83–7.71 (m, 2H), 7.66–7.62 (m, 2H), 7.57–

7.33 (m, 9H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.9, 154.4, 149.7, 145.0, 141.0, 138.9, 132.4, 129.7, 129.4, 129.0, 128.7, 128.20, 128.16, 126.9, 126.4, 119.3, 118.6, 112.0, 17.9; **HRMS** (ESI) Calcd for $\text{C}_{25}\text{H}_{19}\text{N}_2$ $[\text{M} + \text{H}]^+$ 347.1548, found 347.1547.

3-Methyl-4-(4-nitrophenyl)-2,6-diphenylpyridine (3ag): Following Procedure A, Brown solid (77% yield, eluent = hexane/EtOAc (90:10)); Mp = 167–169 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.50–8.28 (m, 2H), 8.23–7.89 (m, 2H), 7.72–7.67 (m, 2H), 7.67–7.59 (m, 3H), 7.57–7.42 (m, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.9, 154.4, 149.4, 147.6, 146.9, 140.9, 138.8, 129.9, 129.5, 129.4, 129.0, 128.8, 128.2, 126.9, 126.4, 123.8, 119.2, 17.9; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{19}\text{N}_2\text{O}_2$ $[\text{M} + \text{H}]^+$ 367.1447, found 367.1447.

3-Methyl-2,6-diphenyl-4-(3-(trifluoromethyl)phenyl)pyridine (3ah): Following Procedure A, Brown solid (99% yield, eluent = hexane/EtOAc (98:2)); Mp = 134–136 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.18–7.97 (m, 2H), 7.78–7.65 (m, 6H), 7.64 (s, 1H), 7.57–7.41 (m, 6H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 159.8, 154.4, 150.1, 141.2,

141.1, 139.1, 132.2, 131.1 (q, $J_{C-F} = 32.4$ Hz) 129.4, 129.1, 128.9, 128.7, 128.2, 128.1, 126.9, 126.8, 125.6 (q, $J_{C-F} = 3.8$ Hz), 124.8 (q, $J_{C-F} = 3.8$ Hz), 124.0 (q, $J_{C-F} = 272.4$ Hz) 119.7, 17.9; **HRMS** (ESI) Calcd for $C_{25}H_{19}F_3N$ $[M + H]^+$ 390.1470, found 390.1468.

3-Methyl-4-(naphthalen-1-yl)-2,6-diphenylpyridine (3ai): Following Procedure A, Brown solid (97% yield, eluent = hexane/EtOAc (98:2)); Mp = 127–129 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.15–8.07 (m, 2H), 7.92 (dd, $J = 8.2, 4.2$ Hz, 2H), 7.75–7.69 (m, 2H), 7.66 (s, 1H), 7.60–7.34 (m, 11H), 2.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.2, 154.0, 150.4, 141.4, 139.3, 138.1, 133.6, 131.2, 129.6, 128.79, 128.76, 128.7, 128.5, 128.4, 128.1, 128.0, 127.0, 126.7, 126.3, 126.2, 125.7, 125.5, 120.7, 17.5; **HRMS** (ESI) Calcd for $C_{28}H_{22}N$ $[M + H]^+$ 372.1752, found 372.1754.

6-(4-Chlorophenyl)-3-methyl-2,4-diphenylpyridine (3aj): Following Procedure A, Brown solid (98% yield, eluent = hexane/EtOAc (98:2)); Mp = 117–119 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.19–8.05 (m, 2H), 7.73–7.69 (m, 2H), 7.61 (s, 1H), 7.57–7.36 (m, 10H), 2.28 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.7, 154.2, 150.4, 141.3, 139.2, 138.7, 134.1, 130.2, 129.5, 128.80, 128.76, 128.7, 128.1, 128.0, 126.9, 126.8, 119.8, 18.0; **HRMS** (ESI) Calcd for $C_{24}H_{19}ClN$ $[M + H]^+$ 356.1206, found 356.1208.

6-(4-Bromophenyl)-4-(4-(tert-butyl)phenyl)-3-methyl-2-phenylpyridine (3ak):

Following Procedure A, Brown solid (92% yield, eluent = hexane/EtOAc (98:2)); Mp = 158–160 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.04–7.99 (m, 2H), 7.73–7.69 (m, 2H), 7.65–7.51 (m, 7H), 7.50–7.44 (m, 1H), 7.44–7.39 (m, 2H), 2.33 (s, 3H), 1.45 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 159.6, 152.8, 151.8, 151.1, 141.4, 138.3, 137.1, 131.8, 129.5, 128.6, 128.5, 128.1, 128.0, 127.6, 125.4, 123.0, 119.9, 34.7, 31.4, 18.1; **HRMS** (ESI) Calcd for $\text{C}_{28}\text{H}_{27}\text{BrN}$ $[\text{M} + \text{H}]^+$ 456.1327, found 456.1329.

6-(4-Methoxyphenyl)-3-methyl-2-phenyl-4-(o-tolyl)pyridine (3al): Following

Procedure A, Brown solid (98% yield, eluent = hexane/EtOAc (98:2)); Mp = 154–156 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.09–7.97 (m, 2H), 7.70–7.62 (m, 2H), 7.52–7.36 (m, 4H), 7.36–7.23 (m, 3H), 7.19 (t, J = 10.1 Hz, 1H), 7.00–6.91 (m, 2H), 3.82 (s, 3H), 2.16 (s, 3H), 2.05 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.3, 159.0, 153.6, 151.5, 141.5, 140.1, 135.2, 132.0, 130.2, 129.5, 128.6, 128.2, 128.1, 128.0, 127.9, 126.8, 126.0, 119.0,

114.0, 55.4, 19.9, 17.1; **HRMS** (ESI) Calcd for $C_{26}H_{24}NO$ $[M + H]^+$ 366.1858, found 366.1866.

3-Methyl-4-(5-methylfuran-2-yl)-2,6-diphenylpyridine (3am): Following Procedure B, Brown solid (80% yield, eluent = hexane/EtOAc (98:2)); Mp = 98–100 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.19–8.12 (m, 2H), 8.09 (s, 1H), 7.70–7.65 (m, 2H), 7.56–7.39 (m, 6H), 6.76 (d, J = 3.3 Hz, 1H), 6.25 – 6.18 (m, 1H), 2.51 (s, 3H), 2.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 160.1, 154.2, 153.3, 149.9, 141.6, 139.6, 139.1, 129.6, 128.6, 128.1, 127.8, 127.0, 124.5, 115.7, 113.5, 108.3, 18.8, 13.8; **HRMS** (ESI) Calcd for $C_{23}H_{20}NO$ $[M + H]^+$ 326.1545, found 326.1544.

3-Methyl-6-(5-methylfuran-2-yl)-2,4-diphenylpyridine (3an): Following Procedure A, Yellow solid (89% yield, eluent = hexane/EtOAc (98:2)); Mp = 141–143 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.9 Hz, 2H), 7.51 (s, 1H), 7.49–7.36 (m, 8H), 6.96 (d, J = 2.9 Hz, 1H), 6.15–6.01 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 159.4, 153.1, 152.3, 151.4, 146.7, 141.3, 140.3, 129.5, 128.8, 128.4, 128.1, 127.9, 127.8, 126.2, 117.7, 109.5, 108.2, 18.1, 13.9; **HRMS** (ESI) Calcd for $C_{23}H_{20}NO$ $[M + H]^+$ 326.1545, found 326.1544.

3-Methyl-2,4-diphenyl-6-(thiophen-2-yl)pyridine (3ao): Following Procedure A, Yellow solid (69% yield, eluent = hexane/EtOAc (98:2)); Mp = 149–151 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.67–7.62 (m, 2H), 7.58 (dd, *J* = 3.6, 1.0 Hz, 1H), 7.50–7.37 (m, 9H), 7.32 (dd, *J* = 5.0, 1.0 Hz, 1H), 7.07 (dd, *J* = 5.0, 3.7 Hz, 1H), 2.21 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.2, 151.7, 149.5, 145.1, 141.0, 140.1, 129.6, 128.8, 128.5, 128.1, 128.0, 127.9, 127.1, 126.9, 124.3, 118.4, 18.1; **HRMS** (ESI) Calcd for C₂₂H₁₈NS [M + H]⁺ 328.1160, found 328.1159.

3,6-Dimethyl-2,4-diphenylpyridine (3ap): Following Procedure A, Yellow oil (63% yield, eluent = hexane/EtOAc (98:2)); **¹H NMR** (400 MHz, CDCl₃) δ 7.62–7.52 (m, 2H), 7.52–7.36 (m, 8H), 7.06 (s, 1H), 2.63 (s, 3H), 2.17 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.2, 154.9, 151.1, 141.4, 140.2, 129.1, 128.7, 128.4, 128.2, 127.74, 127.71, 125.2, 122.9, 24.1, 17.6; **HRMS** (ESI) Calcd for C₁₉H₁₈N [M + H]⁺ 260.1439, found 260.1440.

4-Cyclohexyl-3-methyl-2,6-diphenylpyridine (3aq): Following Procedure A, White solid (55% yield, eluent = hexane/EtOAc (98:2)); Mp = 125–127 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.19–7.98 (m, 2H), 7.67–7.54 (m, 3H), 7.54–7.37 (m, 6H), 2.93–2.83 (m, 1H), 2.35 (s, 3H), 2.00–1.90 (m, 4H), 1.87 (d, *J* = 12.3 Hz, 1H), 1.73–1.29 (m, 5H); **¹³C NMR** (100 MHz, CDCl₃) δ 159.1, 156.0, 154.4, 142.0, 140.1, 129.5, 128.6, 128.4, 128.0, 127.6, 127.0, 126.8, 116.3, 40.4, 33.2, 27.0, 26.2, 15.6; **HRMS** (ESI) Calcd for C₂₄H₂₆N [M + H]⁺ 328.2065, found 328.2066.

3,5-Dimethyl-2,4,6-triphenylpyridine (3ar): Following Procedure B, White solid (52% yield, eluent = hexane/EtOAc (98:2)); Mp = 128–130 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.64–7.59 (m, 4H), 7.56–7.49 (m, 2H), 7.49–7.43 (m, 5H), 7.43–7.36 (m, 2H), 7.31–7.23 (m, 2H), 2.06 (s, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 156.2, 151.8, 141.4, 139.8, 129.4, 128.9, 128.2, 128.1, 127.6, 127.43, 127.38, 18.2; **HRMS** (ESI) Calcd for C₂₅H₂₂N [M + H]⁺ 336.1752, found 336.1758.

3-Methyl-2,4,5,6-tetraphenylpyridine (3as): Following Procedure B, White solid (44% yield, eluent = hexane/EtOAc (98:2)); Mp = 178–180 °C; **¹H NMR** (400 MHz, CDCl₃) δ 7.74 (d, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.37 (dd, *J* = 6.3, 2.8 Hz, 2H), 7.29–7.16 (m, 6H), 7.07 (d, *J* = 7.0 Hz, 2H), 7.05–7.00 (m, 3H), 6.91 (dd, *J* = 6.1, 2.8 Hz, 2H), 2.17 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.9, 154.7, 151.2, 141.3, 140.9, 139.0, 138.5, 133.7, 131.2, 130.1, 129.5, 129.4, 128.1, 127.9, 127.7,

127.5, 127.3, 127.1, 126.8, 126.2, 18.7; **HRMS** (ESI) Calcd for $C_{30}H_{24}N$ $[M + H]^+$ 398.1909, found 398.1910.

2,4,6-Triphenylpyridine (3ba): Following Procedure B, Yellow solid (98% yield, eluent = hexane/EtOAc (98:2)); Mp = 138–140 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.33–8.25 (m, 4H), 7.95 (s, 2H), 7.83–7.79 (m, 2H), 7.62–7.47 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.6, 150.2, 139.7, 139.1, 129.2, 129.1, 129.0, 128.8, 127.24, 127.19, 117.2; **HRMS** (ESI) Calcd for $C_{23}H_{18}N$ $[M + H]^+$ 308.1439, found 308.1433.

2,4-Diphenyl-6-(p-tolyl)pyridine (3ca): Following Procedure B, Yellow solid (94% yield, eluent = hexane/EtOAc (98:2)); Mp = 117–119 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.28–8.23 (m, 2H), 8.18–8.14 (m, 2H), 7.91 (s, 2H), 7.81–7.77 (m, 2H), 7.60–7.47 (m, 6H), 7.37 (d, J = 7.9 Hz, 2H), 2.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.5, 157.4, 150.1, 139.7, 139.2, 139.1, 136.8, 129.5, 129.1, 129.0, 128.9, 128.7, 127.22, 127.16, 127.0, 116.9, 116.8, 21.4; **HRMS** (ESI) Calcd for $C_{24}H_{20}N$ $[M + H]^+$ 322.1596, found 322.1593.

2-(4-Methoxyphenyl)-4,6-diphenylpyridine (3da): Following Procedure B, Yellow solid (92% yield, eluent = hexane/EtOAc (98:2)); Mp = 87–89 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.17 (dd, J = 12.0, 8.2 Hz, 4H), 7.80 (dd, J = 4.2, 1.3 Hz, 2H), 7.73–7.69 (m, 2H), 7.53–7.39 (m, 6H), 7.01 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.6, 157.4, 157.2, 150.1, 139.8, 139.3, 132.3, 129.1, 129.01, 128.95, 128.7, 128.5, 127.22, 127.17, 116.5, 116.4, 114.1, 55.4; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{20}\text{NO}$ [$\text{M} + \text{H}$] $^+$ 338.1545, found 338.1545.

4-(4,6-Diphenylpyridin-2-yl)benzonitrile (3ea): Following Procedure B, Brown solid (83% yield, eluent = hexane/EtOAc (98:2)); Mp = 154–156 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.30–8.26 (m, 2H), 8.19–8.12 (m, 2H), 7.92 (d, J = 1.4 Hz, 1H), 7.86 (d, J = 1.4 Hz, 1H), 7.77–7.67 (m, 4H), 7.56–7.42 (m, 6H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 157.9, 155.2, 150.7, 143.7, 139.1, 138.5, 132.5, 129.4, 129.34, 129.27, 128.9, 127.6, 127.2, 127.1, 119.0, 118.2, 117.5, 112.5; **HRMS** (ESI) Calcd for $\text{C}_{24}\text{H}_{17}\text{N}_2$ [$\text{M} + \text{H}$] $^+$ 333.1392, found 333.1389.

2-(4-Bromophenyl)-4,6-diphenylpyridine (3fa): Following Procedure B, White solid (95% yield, eluent = hexane/EtOAc (98:2)); Mp = 151–153 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.16 (d, *J* = 7.8 Hz, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 7.85 (s, 1H), 7.79 (s, 1H), 7.69 (d, *J* = 7.6 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.54–7.40 (m, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.6, 156.3, 150.4, 139.4, 138.9, 138.5, 131.9, 129.22, 129.18, 129.1, 128.8, 128.7, 127.21, 127.15, 123.5, 117.4, 116.8; **HRMS** (ESI) Calcd for C₂₃H₁₇BrN [M + H]⁺ 386.0544, found 386.0544.

2-(4-Iodophenyl)-4,6-diphenylpyridine (3ga): Following Procedure B, White solid (96% yield, eluent = hexane/EtOAc (98:2)); Mp = 165–167 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.20–8.09 (m, 2H), 7.94–7.88 (m, 2H), 7.86 (d, *J* = 1.4 Hz, 1H), 7.83–7.78 (m, 3H), 7.73–7.66 (m, 2H), 7.55–7.39 (m, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.6, 156.4, 150.4, 139.4, 139.1, 138.9, 137.9, 129.22, 129.19, 129.1, 128.9, 128.8, 127.22, 127.16, 117.5, 116.8, 95.5; **HRMS** (ESI) Calcd for C₂₃H₁₇IN [M + H]⁺ 434.0406, found 434.0404.

2,4-Diphenyl-6-(4-(trifluoromethyl)phenyl)pyridine (3ha): Following Procedure B, White solid (93% yield, eluent = hexane/EtOAc (98:2)); Mp = 135–137 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.35 (d, *J* = 8.1 Hz, 2H), 8.28–8.22 (m, 2H), 7.98 (d, *J* = 1.4 Hz, 1H), 7.94 (d, *J* = 1.4 Hz, 1H), 7.83–7.76 (m, 4H), 7.65–7.46 (m, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.8, 156.0, 150.5, 142.9, 139.3, 138.7, 130.9 (q, *J*_{C-F} = 32.4 Hz), 129.3, 129.2, 128.8, 127.4, 127.20, 127.15, 125.7 (q, *J*_{C-F} = 3.7 Hz), 121.6 (q, *J*_{C-F} = 272.3 Hz), 117.9, 117.4; **HRMS** (ESI) Calcd for C₂₄H₁₇F₃N [M + H]⁺ 376.1313, found 376.1312.

2-(3-Nitrophenyl)-4,6-diphenylpyridine (3ia): Following Procedure B, Yellow solid (54% yield, eluent = hexane/EtOAc (98:2)); Mp = 140–142 °C; **¹H NMR** (400 MHz, CDCl₃) δ 9.02 (t, *J* = 1.9 Hz, 1H), 8.57 (ddd, *J* = 7.8, 1.6, 1.1 Hz, 1H), 8.28 (ddd, *J* = 8.2, 2.3, 1.0 Hz, 1H), 8.23–8.17 (m, 2H), 7.96 (d, *J* = 1.3 Hz, 1H), 7.93 (d, *J* = 1.3 Hz, 1H), 7.80–7.71 (m, 2H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.60–7.41 (m, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ 158.0, 154.8, 150.8, 148.8, 141.3, 139.0, 138.5, 133.0, 129.7, 129.4, 129.34, 129.26, 128.9, 127.2, 127.1, 123.7, 121.9, 118.2, 117.2; **HRMS** (ESI) Calcd for C₂₃H₁₇N₂O₂ [M + H]⁺ 358.1290, found 358.1295.

2,4-Diphenyl-6-(*o*-tolyl)pyridine (3ja): Following Procedure B, Yellow oil (92% yield, eluent = hexane/EtOAc (98:2)); **¹H NMR** (400 MHz, CDCl₃) δ 8.24–8.18 (m, 2H), 7.97 (d, *J* = 1.5 Hz, 1H), 7.82–7.77 (m, 2H), 7.66–7.45 (m, 8H), 7.43–7.34 (m, 3H), 2.61 (s, 3H); **¹³C NMR** (100 MHz, CDCl₃) δ 160.5, 157.3, 149.6, 140.7, 139.7, 138.9, 136.3, 131.0, 129.9, 129.2, 129.04, 129.02, 128.8, 128.4, 127.2, 126.0, 120.7, 116.6, 20.8; **HRMS** (ESI) Calcd for C₂₄H₂₀N [M + H]⁺ 322.1596, found 322.1595.

2-(Naphthalen-2-yl)-4,6-diphenylpyridine (3ka): Following Procedure B, White solid (98% yield, eluent = hexane/EtOAc (98:2)); Mp = 117–119 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.63 (s, 1H), 8.35 (d, *J* = 8.6 Hz, 1H), 8.22 (d, *J* = 8.1 Hz, 2H), 7.99–7.93 (m, 3H), 7.88–7.82 (m, 2H), 7.76–7.71 (m, 2H), 7.57–7.41 (m, 8H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.7, 157.4, 150.3, 139.7, 139.1, 137.0, 133.9, 133.6, 129.19, 129.16, 129.1, 128.84, 128.81, 128.4, 127.8, 127.3, 126.6, 126.5, 126.3, 125.0, 117.4, 117.3; **HRMS** (ESI) Calcd for C₂₇H₂₀N [M + H]⁺ 358.1596, found 358.1595.

2,4-Diphenyl-6-(thiophen-2-yl)pyridine (3la): Following Procedure B, Yellow solid (87% yield, eluent = hexane/EtOAc (98:2)); Mp = 112–114 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.26–8.22 (m, 2H), 8.13 (dd, *J* = 3.0, 1.2 Hz, 1H), 7.91–7.86 (m, 2H), 7.82–7.75 (m, 3H), 7.62–7.44 (m, 7H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.5, 153.7, 150.2, 142.6, 139.6, 139.0, 129.2, 129.1, 129.0, 128.7, 127.19, 127.15, 126.6, 126.2, 123.9, 116.90, 116.87; **HRMS** (ESI) Calcd for C₂₁H₁₆NS [M + H]⁺ 312.1003, found 314.1006.

2-(Furan-2-yl)-4,6-diphenylpyridine (3ma): Following Procedure B, Brown solid (84% yield, eluent = hexane/EtOAc (98:2)); Mp = 90–92 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.22–8.11 (m, 2H), 7.87 (d, *J* = 1.5 Hz, 1H), 7.80 (d, *J* = 1.5 Hz, 1H), 7.77–7.70 (m, 2H), 7.57–7.40 (m, 7H), 7.30–7.23 (m, 1H), 6.56 (dd, *J* = 3.4, 1.8 Hz, 1H); **¹³C NMR** (100 MHz, CDCl₃) δ 157.7, 154.2, 150.0, 149.8, 143.2, 139.4, 138.8, 129.11, 129.08, 128.7, 127.2, 116.9, 115.1, 112.1, 109.1; **HRMS** (ESI) Calcd for C₂₁H₁₆NO [M + H]⁺ 298.1232, found 298.1231.

4,6-Diphenyl-2,4'-bipyridine (3na): Following Procedure B, Yellow solid (89% yield, eluent = hexane/EtOAc (98:2)); Mp = 176–178 °C; **¹H NMR** (400 MHz, CDCl₃) δ 8.75 (d, *J* = 5.5 Hz, 2H), 8.17 (d, *J* = 7.7 Hz, 2H), 8.06 (d, *J* = 5.5 Hz, 2H), 7.94 (s, 1H), 7.90 (s, 1H), 7.71 (d, *J* = 7.4 Hz, 2H), 7.57–7.42 (m, 6H); **¹³C NMR** (100 MHz, CDCl₃) δ

158.0, 154.7, 150.6, 150.5, 146.6, 139.0, 138.5, 129.4, 129.32, 129.25, 128.8, 127.2, 127.1, 121.3, 118.7, 117.4; **HRMS** (ESI) Calcd for $C_{22}H_{17}N_2$ $[M + H]^+$ 309.1392, found 309.1392.

2,4-Diphenyl-5,6-dihydrobenzo[h]quinoline (30a): Following Procedure A, Brown solid (99% yield, eluent = hexane/EtOAc (98:2)); Mp = 126–128 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.58 (dd, J = 7.7, 1.1 Hz, 1H), 8.17 (dd, J = 5.2, 3.3 Hz, 2H), 7.58 (s, 1H), 7.52–7.37 (m, 9H), 7.31 (td, J = 7.4, 1.4 Hz, 1H), 7.24–7.15 (m, 1H), 2.97–2.89 (m, 2H), 2.83 (dd, J = 8.5, 5.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 154.5, 152.6, 149.3, 139.6, 139.4, 138.2, 135.3, 129.1, 128.9, 128.8, 128.7, 128.5, 128.1, 128.0, 127.5, 127.1, 126.9, 125.8, 120.0, 28.2, 25.3; **HRMS** (ESI) Calcd for $C_{25}H_{20}N$ $[M + H]^+$ 334.1596, found 334.1595.

2,3,4,6-Tetraphenylpyridine (3pa): Following Procedure A, Yellow solid (93% yield, eluent = hexane/EtOAc (98:2)); Mp = 180–182 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.25–8.19 (m, 2H), 7.83 (s, 1H), 7.56–7.49 (m, 2H), 7.49–7.41 (m, 3H), 7.31–7.20 (m, 6H), 7.20–7.15 (m, 2H), 7.15–7.08 (m, 3H), 7.01–6.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 158.0, 155.6, 150.7, 141.0, 139.9, 139.1, 137.9, 132.9, 131.5, 130.2, 129.4, 129.0, 128.7, 128.0, 127.7, 127.5, 127.39, 127.36, 127.1, 126.6, 120.4; **HRMS** (ESI) Calcd for $C_{29}H_{22}N$ $[M + H]^+$ 384.1752, found 384.1752.

3-Allyl-2,4,6-triphenylpyridine (3qa): Following Procedure A, White solid (99% yield, eluent = hexane/EtOAc (98:2)); Mp = 127–129 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.14 (d, J = 7.5 Hz, 2H), 7.77–7.58 (m, 3H), 7.57–7.40 (m, 11H), 5.69 (dq, J = 10.4, 5.5 Hz, 1H), 4.94 (d, J = 10.2 Hz, 1H), 4.64 (d, J = 17.2 Hz, 1H), 3.47 (d, J = 5.3 Hz, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 160.1, 154.4, 152.1, 141.5, 140.1, 139.2, 136.8, 129.2, 128.8, 128.72, 128.67, 128.3, 128.0, 127.9, 127.0, 120.7, 116.1, 33.5; **HRMS** (ESI) Calcd for $\text{C}_{26}\text{H}_{22}\text{N}$ $[\text{M} + \text{H}]^+$ 348.1752, found 348.1750.

3,3-Dimethyl-2,4,6-triphenyl-3,4-dihydropyridine (3ra): Following Procedure A, Orange oil (40% yield, eluent = hexane/EtOAc (98:2)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 7.99–7.83 (m, 2H), 7.51–7.45 (m, 2H), 7.44–7.37 (m, 5H), 7.37–7.25 (m, 6H), 6.22 (d, J = 5.6 Hz, 1H), 3.40 (d, J = 5.6 Hz, 1H), 1.46 (s, 3H), 0.99 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 175.5, 143.1, 140.5, 139.3, 138.2, 129.3, 128.4, 128.3, 127.84, 127.79, 127.7, 127.6, 127.2, 125.6, 114.2, 51.7, 38.2, 26.8, 23.0; **HRMS** (ESI) Calcd for $\text{C}_{25}\text{H}_{24}\text{N}$ $[\text{M} + \text{H}]^+$ 338.1909, found 338.1906.

2-Methyl-4,6-diphenylpyridine (3sa): Following Procedure B, Yellow oil (51% yield, eluent = hexane/EtOAc (98:2)); $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.09–8.05 (m, 2H), 7.76 (d, $J = 0.9$ Hz, 1H), 7.74–7.69 (m, 2H), 7.58–7.43 (m, 6H), 7.36 (d, $J = 1.2$ Hz, 1H), 2.73 (s, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 158.9, 157.7, 149.5, 139.9, 138.9, 129.1, 128.9, 128.8, 128.7, 127.2, 127.1, 119.8, 116.2, 24.9; **HRMS** (ESI) Calcd for $\text{C}_{18}\text{H}_{16}\text{N}$ $[\text{M} + \text{H}]^+$ 246.1283, found 246.1286.

2-(Tert-butyl)-4,6-diphenylpyridine (3ta): Following Procedure B, Yellow solid (71% yield, eluent = hexane/EtOAc (98:2)); Mp = 87–89 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.24–8.10 (m, 2H), 7.79 (d, $J = 1.4$ Hz, 1H), 7.76–7.67 (m, 2H), 7.59–7.42 (m, 7H), 1.52 (s, 9H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 169.6, 156.1, 149.5, 140.0, 139.7, 129.0, 128.7, 128.64, 128.61, 127.2, 127.0, 115.8, 115.5, 37.9, 30.3; **HRMS** (ESI) Calcd for $\text{C}_{21}\text{H}_{22}\text{N}$ $[\text{M} + \text{H}]^+$ 288.1752, found 288.1752.

Ethyl 4,6-diphenylpicolinate (3ua): Following Procedure B, Yellow solid (58% yield, eluent = hexane/EtOAc (98:2)); Mp = 79–81 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.31 (d, $J = 1.6$ Hz, 1H), 8.18–8.13 (m, 2H), 8.12 (d, $J = 1.6$ Hz, 1H), 7.79–7.74 (m, 2H), 7.60–7.45 (m, 6H), 4.55 (q, $J = 7.1$ Hz, 2H), 1.52 (t, $J = 7.1$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 165.6, 158.4, 150.4, 149.0, 138.7, 137.8, 129.5, 129.3, 128.8, 127.4, 127.2, 121.54,

121.47, 61.9, 14.4; **HRMS** (ESI) Calcd for $C_{20}H_{18}NO_2$ $[M + H]^+$ 304.1338, found 304.1336.

2,4-Diphenyl-5,6,7,8-tetrahydroquinoline (3va): Following Procedure A, White solid (95% yield, eluent = hexane/EtOAc (98:2)); Mp = 102–104 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.01 (d, J = 7.5 Hz, 2H), 7.53–7.36 (m, 9H), 3.13 (t, J = 6.6 Hz, 2H), 2.69 (t, J = 6.3 Hz, 2H), 2.04–1.92 (m, 2H), 1.84–1.76 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 157.7, 154.3, 150.3, 139.81, 139.78, 128.7, 128.6, 128.5, 128.4, 127.8, 126.9, 119.1, 33.4, 27.3, 23.2, 23.1; **HRMS** (ESI) Calcd for $C_{21}H_{20}N$ $[M + H]^+$ 286.1596, found 286.1596.

2,4-Diphenyl-5,6,7,8,9,10-hexahydrocycloocta[b]pyridine (3wa): Following Procedure A, Brown solid (92% yield, eluent = hexane/EtOAc (98:2)); Mp = 136–138 °C; **1H NMR** (400 MHz, $CDCl_3$) δ 8.09–7.92 (m, 2H), 7.46–7.28 (m, 9H), 3.20–3.01 (m, 2H), 2.79–2.70 (m, 2H), 1.96–1.82 (m, 2H), 1.54–1.42 (m, 4H), 1.42–1.34 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 161.9, 154.0, 150.3, 140.7, 139.8, 131.8, 128.64, 128.57, 128.4, 128.2, 127.5, 126.9, 119.7, 35.7, 31.4, 31.0, 27.1, 26.6, 25.9; **HRMS** (ESI) Calcd for $C_{23}H_{24}N$ $[M + H]^+$ 314.1909, found 314.1909.

1,3-Bis(4,6-diphenylpyridin-2-yl)benzene (3xa): Following Procedure B with 1:2 ratio of oxime to imine, White solid (21% yield, eluent = hexane/EtOAc (98:2)); Mp = 219–221 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 9.06 (s, 1H), 8.37–8.26 (m, 6H), 8.05 (d, J = 1.1 Hz, 2H), 7.97 (d, J = 1.1 Hz, 2H), 7.88–7.80 (m, 4H), 7.71 (t, J = 7.7 Hz, 1H), 7.63–7.47 (m, 12H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 157.52, 157.48, 150.3, 140.1, 139.6, 139.1, 129.2, 129.1, 129.0, 128.8, 127.9, 127.3, 127.2, 126.0, 117.4, 117.3; **HRMS** (ESI) Calcd for $\text{C}_{40}\text{H}_{29}\text{N}_2$ $[\text{M} + \text{H}]^+$ 537.2331, found 537.2332.

2-Methyl-4,6-diphenyl-3-propylpyridine (3ya): Following Procedure A with 1.6 equiv. of oxime, Yellow solid (53% yield, eluent = hexane/EtOAc (98:2)); Mp = 87–89 °C; $^1\text{H NMR}$ (400 MHz, CDCl_3) δ 8.03–7.95 (m, 2H), 7.48–7.28 (m, 9H), 2.70 (s, 3H), 2.62–2.49 (m, 2H), 1.54–1.39 (m, 2H), 0.82 (t, J = 7.3 Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) δ 157.3, 153.6, 150.6, 140.6, 139.6, 132.2, 128.63, 128.55, 128.4, 128.2, 127.6, 126.8, 119.6, 31.3, 23.3, 23.0, 14.4; **HRMS** (ESI) Calcd for $\text{C}_{21}\text{H}_{22}\text{N}$ $[\text{M} + \text{H}]^+$ 288.1752, found 288.1757.

2-Methyl-3,4,6-triphenylpyridine (3za): Following Procedure A with 1.6 equiv. of oxime, White solid (86% yield, eluent = hexane/EtOAc (98:2)); Mp = 97–99 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.14 (d, J = 7.2 Hz, 2H), 7.69 (s, 1H), 7.54 (t, J = 7.4 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.35–7.23 (m, 6H), 7.21–7.14 (m, 4H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 157.0, 155.6, 149.6, 139.8, 139.5, 138.5, 133.8, 130.4, 129.3, 128.84, 128.78, 128.1, 127.9, 127.3, 127.1, 127.0, 119.3, 24.4; HRMS (ESI) Calcd for $\text{C}_{24}\text{H}_{20}\text{N}$ $[\text{M} + \text{H}]^+$ 322.1596, found 322.1595.

3-Methoxy-2-methyl-4,6-diphenylpyridine (3aaa): Following Procedure A with 1.6 equiv. of oxime, White solid (44% yield, eluent = hexane/EtOAc (98:2)); Mp = 76–78 °C; ^1H NMR (400 MHz, CDCl_3) δ 8.00–7.93 (m, 2H), 7.69–7.62 (m, 2H), 7.53 (s, 1H), 7.49–7.35 (m, 6H), 3.44 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 153.2, 152.4, 151.0, 141.9, 139.4, 136.6, 128.73, 128.68, 128.6, 128.40, 128.37, 126.8, 120.2, 60.2, 19.8; HRMS (ESI) Calcd for $\text{C}_{19}\text{H}_{18}\text{NO}$ $[\text{M} + \text{H}]^+$ 276.1388, found 276.1393.

2-Cyclopropyl-4,6-diphenylpyridine (3aba): Following Procedure B, Colourless oil (80% yield, eluent = hexane/EtOAc (98:2)); ^1H NMR (400 MHz, CDCl_3) δ 8.21–7.99 (m, 2H), 7.78–7.64 (m, 3H), 7.64–7.40 (m, 6H), 7.33 (d, J = 1.5 Hz, 1H), 1.96–1.77 (m, 1H), 1.40–1.19 (m, 2H), 1.18–0.97 (m, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.0, 157.0,

149.1, 139.8, 139.2, 129.0, 128.79, 128.75, 128.6, 127.2, 127.0, 118.0, 115.5, 17.5, 9.9;

HRMS (ESI) Calcd for $C_{20}H_{18}N$ $[M + H]^+$ 272.1439, found 272.1443.

2-Cyclohexyl-3-methyl-4,6-diphenylpyridine (3aca): Following Procedure A with 1.6 equiv. of oxime, Yellow oil (86% yield, eluent = hexane/EtOAc (98:2)); **1H NMR** (400 MHz, $CDCl_3$) δ 8.14–8.05 (m, 2H), 7.48–7.30 (m, 9H), 3.04–2.94 (m, 1H), 2.23 (s, 3H), 1.98–1.85 (m, 6H), 1.85–1.71 (m, 1H), 1.55–1.35 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 164.4, 153.0, 150.5, 140.9, 139.9, 128.9, 128.6, 128.4, 128.3, 127.6, 126.7, 125.9, 118.4, 42.7, 32.1, 27.0, 26.3, 15.2; **HRMS** (ESI) Calcd for $C_{24}H_{26}N$ $[M + H]^+$ 328.2065, found 328.2065.

4.5 References

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List of Publications

1. Pd(II)/Bu₄NBr/DMSO Catalytic System for Practical Synthesis of Indoles and Pyrroles from Imines through Aerobic Dehydrogenative Cyclization. Tan, W. W.; Hou, X.; Yoshikai, N. *Synthesis* **2014**, 46, 2727-2730.
2. Copper-Catalyzed Condensation of Imines and α -Diazo- β -dicarbonyl Compounds: Modular and Regiocontrolled Synthesis of Multisubstituted Pyrroles. Tan, W. W.; Yoshikai, N. *Chem. Sci.* **2015**, 6, 6448-6455.
3. Copper-Catalyzed Coupling of 2-Siloxy-1-alkenes and Diazocarbonyl Compounds: Approach to Multisubstituted Furans, Pyrroles and Thiophenes. Tan, W. W.; Yoshikai, N. *J. Org. Chem.* **2016**, 81, 5566-5573.