STUDIES ON TRANSITION METAL–MEDIATED FUNCTIONALIZATION OF ALKYNES FOR SYNTHESIS OF AZAHETEROCYCLES

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With deepest gratitude,

Pei Chui
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>Δ</td>
<td>heating</td>
</tr>
<tr>
<td>ºC</td>
<td>degree centigrade</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>APC</td>
<td>allylpalladium(II) chloride dimer</td>
</tr>
<tr>
<td>atm</td>
<td>standard atmosphere</td>
</tr>
<tr>
<td>brs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxycarbonyl</td>
</tr>
<tr>
<td>Bu</td>
<td>butyl</td>
</tr>
<tr>
<td>Calcd</td>
<td>calculated</td>
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<tr>
<td>CAS</td>
<td>camphorsulfonic acid</td>
</tr>
<tr>
<td>CDCl₃</td>
<td>deuterated chloroform</td>
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<tr>
<td>Cp*</td>
<td>1,2,3,4,5-pentamethylcyclopentadiene</td>
</tr>
<tr>
<td>cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
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<tr>
<td>d</td>
<td>doublet</td>
</tr>
<tr>
<td>D</td>
<td>deuterium</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<td>--------------</td>
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<tr>
<td>DBPO</td>
<td>dibenzoylperoxide</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicycloundec-7-ene</td>
</tr>
<tr>
<td>DCC</td>
<td>N,N'-dicyclohexylcarbodiimide</td>
</tr>
<tr>
<td>dd</td>
<td>doublets of doublet</td>
</tr>
<tr>
<td>ddd</td>
<td>doublets of doublets of doublet</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyanobenzoquinone</td>
</tr>
<tr>
<td>DMA</td>
<td>N,N-dimethylacetamide</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(N,N-dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMI</td>
<td>1,3-dimethyl-2-imidazolindinone</td>
</tr>
<tr>
<td>DMSO</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dppm</td>
<td>1,1-bis(diphenylphosphino)methane</td>
</tr>
<tr>
<td>dppe</td>
<td>1,1-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppf</td>
<td>1,1-bis(diphenylphosphino)ferrocene</td>
</tr>
<tr>
<td>dt</td>
<td>doublets of triplet</td>
</tr>
<tr>
<td>DTBMP</td>
<td>2,6-di-tert-butyl-4-methylpyridine</td>
</tr>
<tr>
<td>equiv</td>
<td>equivalent</td>
</tr>
<tr>
<td>ESI</td>
<td>electronspray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>Et3N</td>
<td>triethylamine</td>
</tr>
<tr>
<td>EtOH</td>
<td>ethanol</td>
</tr>
<tr>
<td>FT-IR</td>
<td>Fourier transform infrared spectroscopy</td>
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</table>
g  gram

h  hour

HRMS  high resolution mass spectroscopy

Hz  Hertz

$\textit{hv}$  photoirradiation

$i$-$\text{Pr}$  isopropyl

IR  infrared

$J$  coupling constants

kcal  kilocalorie

kg  kilogram

$M$  concentration (mol/dm$^3$)

$M^+$  parent ion peak (mass spectrum)

m  multiplet

Me  methyl

MeOH  methanol

mg  milligrams

MHz  megahertz

min  minutes

mL  milliliters

mmol  millimoles

mol  moles

MS 4 Å  molecular sieves 4 angstroms
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>NCS</td>
<td>N-chlorosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear overhauser enhancement spectroscopy</td>
</tr>
<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>Pd(TFA)</td>
<td>palladium(II) trifluoroacetate</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Piv</td>
<td>pivalyl</td>
</tr>
<tr>
<td>PivOH</td>
<td>pivalic acid</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>qd</td>
<td>quartet of doublet</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
<tr>
<td>sat.</td>
<td>saturated</td>
</tr>
<tr>
<td>t</td>
<td>triplet</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyldimethylsilyl</td>
</tr>
<tr>
<td>t-Bu</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>t-AmOH</td>
<td>2-methyl-2-butanol</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TfOH</td>
<td>trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
</tbody>
</table>
TLC  thin layer chromatography
TMS  trimethylsilyl
Tol  tolyl
Ts   2-p-toluenesulfonyl
TsOH p-toluenesulfonic acid
tt   triplet of triplet
tq   triplet of quartet
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  5.2.1 Synthesis of 2-alkynyl benzaldehydes
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5.3 Conclusion
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Abstract

In this thesis, intensive research effort was focused on the investigation of new methods towards the synthesis of azaheterocycles. Two different approaches have been discovered and developed: (1) Rh(III)-catalyzed C–H bond functionalizations (Chapters 2–4); (2) Cu(I)-mediated intramolecular annulation (Chapter 5).

The first approach has been successfully applied for the synthesis of isoquinolines from aryl ketone O-acetyl oximes and internal alkynes by using [Cp*RhCl₂]₂ as the catalyst via ortho C–H bond activation followed by alkyne insertion and final C–N bond formation (Chapter 2). This approach has also been extended for the synthesis of pyridines from α,β-unsaturated oximes and internal alkynes via similar mechanism (Chapter 3). The advantage of the approach is that the N–O bonds of anti-isomers of oximes could work as internal oxidants to maintain Rh^{III}–Rh^{I} catalytic cycle in a redox-neutral process. However, the limitation is that only anti-isomers of oximes could be applied for such transformation because the nitrogen lone-pair of oximes and ortho C–H bond must be in syn-geometry to achieve C–H bond activation. A modified approach under the Cu^{I}–Rh^{III} relay catalytic system has been realized to solve the stereochemical requirement of oximes, such that both syn- and anti-isomers of oximes could be utilized for the synthesis of isoquinolines and other azaheterocycles (Chapter 4).

The second approach utilized intramolecular annulations of alkynes as the key step for the synthesis of 4-bromoisoquinolones where CuBr acts as a mediator, a bromide source as well as an oxidant (Chapter 5).
First Approach
Chapter 2:
\[
\begin{align*}
\text{2-1a} & \quad + \quad \text{2-2a} \\
\xrightarrow{[\text{CpRhCl_2}]_2 (2.5 \text{ mol } \%), \text{NaOAc (30 mol %)} \atop \text{MeOH, 60 °C, 6 h}} & \quad \rightarrow \quad \text{2-3aa} \\
\end{align*}
\]
82%

Chapter 3:
\[
\begin{align*}
\text{3-1a} & \quad + \quad \text{3-2a} \\
\xrightarrow{[\text{Cp*RhCl_2}]_2 (2.5 \text{ mol } \%), \text{CsOOPiv (30 mol %)} \atop \text{MeOH, 60 °C, 7 h}} & \quad \rightarrow \quad \text{3-3aa} \\
\end{align*}
\]
79%

Chapter 4:
\[
\begin{align*}
\text{4-1a} & \quad + \quad \text{4-2a} \\
\xrightarrow{[\text{Cp*RhCl_2}]_2 (2.5 \text{ mol } \%), \text{Cu(OAc)_2 (10 mol %)} \atop \text{DMF, 60 °C, 4 h}} & \quad \rightarrow \quad \text{4-3aa} \\
\end{align*}
\]
syn:anti = 1:1

Second approach
Chapter 5:
\[
\begin{align*}
\text{5-1a} & \quad + \quad \text{5-2a} \\
\xrightarrow{\text{CuBr•SMe_2 (2.2 equiv)} \atop \text{benzene–pyridine (5:1)} \atop \text{SiO_2, 80 °C, 4 h} \atop \text{under O_2 (1 atm)}} & \quad \rightarrow \quad \text{5-3aa} \\
\end{align*}
\]
80%

Scheme 1. Representative reaction schemes for two different approaches
Chapter 1  General Introduction

1.1  Overview of the importance of nitrogen-containing heterocycles

Nitrogen-containing heterocycles (azaheterocycles) are one of the important components in various natural products, biologically active pharmaceutical drugs as well as various types of functional materials. In fact, azaheterocycles are the essential building blocks in our bodies that sustain life. Deoxyribonucleic acid (DNA) which is the carrier of all the genetic information and consists of simple units called nucleotides; each nucleotide is composed of a 5-carbon sugar (known as 2-deoxyribose), a nucleobase and phosphate group(s). Nucleobases are constituted of two types of azaheterocycles, which are bicyclic purines (adenine (A) and guanine (G)) and monocyclic pyrimidines (cytosine (C) and thymine (T)).

![Nucleobases in DNA](image)

Figure 1-1. Nucleobases are important azaheterocycles in DNA

Among the 20 amino acids that make up the proteins in living organisms, two of them have azaheterocyclic side chains (tryptophan and histidine with indole and imidazole derivatives, respectively, as side chains) and one of them has a pyrrolidine ring as the core structure (proline). In the presence of enzyme L-histidine decarboxylase as the catalyst, decarboxylation of histidine proceeds to give the hormone histamine, which is
involved in local immune responses to foreign pathogens as well as acting as a neurotransmitter.¹

![Figure 1-2. Three amino acids bearing azaheterocycles and one hormone](image)

In addition to azaheterocycles involved in protein synthesis and gene expression, water-soluble vitamins are essential azaheterocycles in human metabolism. Vitamin B₃ (niacin or nicotinamide) incorporated with adenine dinucleotide phosphate (ADP) to give nicotinamide adenine dinucleotide phosphate (NADP⁺), which is a large complex co-enzyme for oxidation and reduction process in our body.² On the other hand, vitamin B₆ (pyridoxine) is transformed into pyridoxal phosphate (PLP) with N-protonated pyridine derivatives as the active form. PLP-containing enzymes have numerous functions such as transfer an amino group from α-amino acids to α-keto acid, convert α-amino acid to amine via decarboxylation and transform α-amino acid to carboxylic acid via deamination.³

![Figure 1-3. Nicotinamide and pyridoxine and their co-enzymes](image)

Besides azaheterocycle-containing DNAs and amino acids, there are many plant-produced alkaloids bearing molecular structure based on isoquinolines (azaheterocycles).
Among them, berberine, which is a quaternary isoquinoline salt from the protoberberine group, is used as traditional medicine and has shown some activities against fungal infection. Papaverine is also an alkaloid based on isoquinoline. It was first been discovered by Georg Merck in 1848 and known for treatment of heart attack, chest pain and blood clot.

![Berberine and papaverine](image)

Figure 1-4. Berberine and papaverine

The kibdelones A–C are aromatic polyketide natural products that feature the isoquinolone and tetrahydroxanthone ring systems. They display significant antibiotic activity as well as potent cytotoxicity toward a range of human cancer cell lines. Fredericamycin A is one of the active antitumor antibiotics, which can be isolated from bacteria, *Streptomyces griseus*. It possesses both quinone and isoquinolone moieties and acts as inhibitor in RNA expression and protein synthesis.

![Kibdelones C and fredericamycin A](image)

Figure 1-5. Kibdelones C and fredericamycin A

In addition to biologically active natural compounds, isoquinolone-derived structures can also be found in pharmaceutical drugs. For example, indenoisoquinoline
NSC314622 which was first synthesized in 1978, and its derivatives both possess significant anti-cancer activity. Cytotoxicity analysis revealed that the indenoisoquinoline NSC314622 is potential topoisomerase I poison and its DNA strand breaking-site is different from camptothecin (CPT).

![indenoisoquinoline NSC314622 and camptothecin](image)

**Figure 1-6. Potent drugs for anti-cancer activity**

The pharmaceutical drugs used in human medicine include a wide range of chemical structures, but majority of them consists of azaheterocycles as their core structures or side chains. Of the top 3 best-selling drugs (by total dollars) in 2012, all of them are azaheterocyclic derivatives. The first top-selling drug is Nexium (esomeprazole); it contains pyridine and benzo-imidazole moieties. The potent drug is used to treat symptoms of heart burn and other conditions involving excessive stomach acid.

The second top-selling drug is Abilify (aripiprazole), which belongs to a class of medications called atypical antipsychotics and primarily used to treat the symptoms of mental disorders such as schizophrenia, bipolar disorder, major depressive disorder, and irritability associated with autism.

The third top-selling drug is Crestor (rosuvastatin); it contains 2-aminopyrimidine as the core structure. The potent drug is belongs to a drug class of statins, used in combination with exercise and diet to treat high cholesterol and related conditions, and to prevent cardiovascular disease.
Due to the abundance of natural products and pharmaceutical drugs are based on azaheterocyclic structures, the development of versatile approaches to construct azaheterocycles remains a challenging field. Despite of various classical methods such as the Pomeranz-Fritsch\textsuperscript{20} and the Bischler-Napieralski\textsuperscript{21} isoquinoline synthesis, as well as the Guareschi-Thorpe\textsuperscript{22} and the Hantzsch\textsuperscript{23} pyridine synthesis, the creation of novel synthetic routes of azaheterocycles with high efficiency is still attractive. In fact, recent advances have focused on the construction of azaheterocycles involving C–H bond activation of arenes or alkenes with simple directing groups using transition metals as the catalysts. It is noteworthy that the intramolecular annulations of alkynes via alkyne activation represent another useful approach for azaheterocycle synthesis.

1.2 Transition metal-catalyzed synthesis of azaheterocycles via C–H bond activation

In recent years, considerable attention has been drawn to the direct formation of C–C and C–X (X = heteroatom) bonds from unactivated C–H bonds via C–H bond activation. The approach shows enormous potential for development of chemical processes such as natural product synthesis or large-scale cGMP (current good manufacturing practice) because it can shorten the synthetic routes significantly by providing novel disconnections without the need for pre-activation steps.\textsuperscript{24}
Despite many advantages, the significant challenge of the approach is the high bond dissociation energy of C–H bonds in alkanes and arenes (e.g. CH3–H, 105 kcal mol−1; Ar–H, 113 kcal mol−1) compared to that of C–X (X = halides) bonds in traditional metal catalysis (e.g. Ar–I, 67 kcal mol−1). Thus, C–H bond activation step normally requires harsh reaction conditions and suffers from low yields and poor regioselectivity. Fortunately, intensive efforts have been made to achieve selective C–H bond activation and to understand their possible mechanisms.

In 1993, the breakthrough in sp2 C–H bond activation was achieved by Murai and co-workers to solve the drawback of low efficiency and poor regioselectivity. The key to their success is the involvement of a chelation assistance approach for selective ortho C–H bond activation, in this case, a ketone moiety is used as the directing group for Ru(0) (Scheme 1-1). To our knowledge, this is the first example of efficient catalytic additions of aromatic sp2 C–H bonds to olefins via chelation assistance.

![Scheme 1-1. An example of Ru(0)-catalyzed cross-couplings of arylketones and alkenes via chelation assistance](image)

Furthermore, selective C–H bond activation has also been successfully applied for the synthesis of azaheterocycles by combining C–H bond activation and C–N bond formation with the aid of directing groups. One early report by Buchward and co-workers revealed that by using a N-acetylamide moiety as the directing group, such strategy can be applied for the synthesis of carbazoles from 2-phenylacetanilide derivatives via intramolecular Pd(II)-catalyzed C–H aminations (Scheme 1-2). However, high temperature and N-acetyl protecting group are required due to high activation energy of the C–N bond reductive elimination step in the catalytic cycle.
To reduce the activation energy barrier of reductive elimination step, a strong oxidant is required to oxidize palladacycle(II) complexes to palladacycle(IV) complexes, which have lower activation barrier for C–N bond reductive elimination. Gaunt and co-workers revealed that by using Phl(OAc)₂ as the oxidant C–H aminations of N-benzyl 2-phenylaniline derivatives via Pd(II)/Pd(IV) catalysis can be achieved even at room temperature (Scheme 1-3).²⁸
In addition, by utilizing CuCl₂ as an oxidant, Yu and co-workers reported Pd(II)/Pd(IV)-catalyzed C–H aminations of N-methoxy-2-phenylacetamide derivatives for the synthesis of N-methoxy 2-indolinones (Scheme 1-4).²⁹ They proposed that the reaction may involve a chloronium ion which is generated from CuCl₂ to oxidize Pd(II) to Pd(IV) via the Shilov mechanism. Similarly, by using Ce(SO₄)₂ as a one-electron oxidant or F⁻ source as a two-electron oxidant, they applied Pd(II)/Pd(IV) catalysis for the synthesis of indolines from N-protected phenethylamine derivatives (Scheme 1-5).³⁰ In both cases, the presence of 1–6 equiv of DMF is crucial, possibly acts as a labile ligand.

![Proposed mechanism:](image)

Scheme 1-6. An example of Pd(0)-catalyzed aminations of O-acetyl oximes and its proposed catalytic cycle

In 2010, Hartwig and co-workers unveiled an alternative approach for an intramolecular C–H amination under a redox-neutral process (Scheme 1-6). The reaction involves the conversion of O-acetyl benzyloxime 1-1 to indole 1-2 using a catalytic amount of Pd(dba)₂ and a stoichiometric amount of Cs₂CO₃ (base) without external oxidant.³¹ The proposed catalytic cycle first involves oxidative addition of the N–O bond of 1-1 to Pd(0) to give intermediate A, then followed by tautomerization and C–H bond
activation to form palladacycle C. Final C–N bond reductive elimination provides indole 1-2 and regenerates Pd(0) for the next catalytic cycle.

Similar Pd(II)-catalyzed redox-neutral process could be applied for intermolecular couplings between O-acyl oximes and aryne precursors for the synthesis of phenanthridines as reported by Zhu and co-workers (Scheme 1-7). The reaction involves initial aminopalladation of O-acyl oxime 1-3 followed by sequential C–H bond activation, aryne (generated from 1-4) insertion, and final C–N bond reductive elimination to release phenanthridine 1-5. By replacing aryne precursor 1-4 with dimethyl acetylenedicarboxylate (1-6), isoquinoline 1-7 can be synthesized in a similar manner (Scheme 1-8).\(^{32}\) However, the reaction is only limited to highly electrophilic alkynes (such as dimethyl acetylenedicarboxylate) and failed to proceed with diphenylacetylene.

![Scheme 1-7. An example of Pd(II)-catalyzed annulations of O-acyloximes with aryne precursors](image)

The drawback of harsh reaction conditions in the palladium catalysis has drawn attention to discover other transition metals for C–H bond activation, for example Cp*Rh(III) complexes have emerged as leading candidates for this type of transformation. An early application of Cp*Rh(III) complex in aza heterocycle synthesis
was reported by Fagnou and Guimond. They presented oxidative cross-couplings/cyclizations of aryl aldimines and alkynes using [Cp*Rh(MeCN)₃][SbF₆]₂ as the catalyst (Scheme 1-9). As shown in the proposed catalytic cycle, the first step is commenced by C–H bond activation of imine 1-8 using Cp*Rh(III) complex to form intermediate A; insertion of 4-octyne into the C–Rh bond of A provides 7-membered rhodacycle B; C–N bond reductive elimination affords isoquinoline 1-9 and generates Cp*Rh(I), which is re-oxidized to Cp*Rh(III) by Cu(OAc)₂.

![Proposed mechanism]

During the past few years, extensive investigations showed that Cp*Rh(III) complexes especially [Cp*RhCl₂]₂, is one of the competent catalyst for chemical transformation involving sequential chelation-assisted C–H bond activation, alkyne insertion and C–N bond reductive elimination. Various azaheterocycles such as indoles, isoquinolines, isoquinolones, and pyrroles have been synthesized using [Cp*RhCl₂]₂ as a catalyst. The detail synthetic utilities of [Cp*RhCl₂]₂ will be discussed in Chapter 2.1.4.

Inspired by the successful application of [Cp*RhCl₂]₂ as the catalyst for the synthesis of diverse azaheterocycles, researchers started to investigate the possibility of
using ruthenium for C–H bond activation. As compared to Rh (Group 9), Ru (Group 8) is also a late transition metal in Period 5 of the periodic table, so they may share similar chemical reactivities. In fact, the oxidative annulations of benzamides and internal alkynes have been achieved using [RuCl₂(η-cymene)]₂ as the catalyst and Cu(OAc)₂ as the oxidant (Scheme 1-10).³⁴ Ru(II)-catalyzed processes generally required harsher conditions and resulted in slightly lower yields compared with their Cp*Rh(III) counterparts. However, in terms of cost, [RuCl₂(η-cymene)]₂ is economically more favorable than [Cp*RhCl₂]₂.

![Scheme 1-10. An example of Ru(II)-catalyzed oxidative annulations of benzamides and internal alkynes](image)

By changing benzamides to acrylamides, Ru(II)-catalyzed amide-directed alkene C–H bond activation also proceeds smoothly under the similar reaction conditions to give 2-pyridones in excellent yields (Scheme 1-11).³⁵

![Scheme 1-11. An example of Ru(II)-catalyzed oxidative annulations of acrylamides and internal alkynes](image)

In addition to the transition metals other than Pd, Rh and Ru, Ni is another choice for chemical transformations involving sequential C–H bond activation, alkyne insertion and C–N bond reductive elimination. Chatani and co-workers developed Ni(0)-catalyzed synthesis of isoquinolones via a chelation assistance ortho C–H bond activation (Scheme 1-12).³⁶ In contrast to the previous examples, the studies showed that only bidentate
directing groups with strong chelation properties worked well under the Ni(cod)$_2$–PPh$_3$ catalytic system. Among all the directing groups examined, 2-pyridinylmethylamine provided the best results. By utilizing similar bidentate system, Ni(II)-catalyzed direct alkylation of C–H bonds of benzamides and acrylamides with functionalized halides could be achieved. Later, numerous reports have appeared to support bidentate directing groups as the promising tools for chemical transformation that have not been achieved by monodentate directing groups.

![Scheme 1-12. An example of Ni(0)-catalyzed synthesis of isoquinolones via chelation-assisted ortho C–H activation](image)

### 1.3 Transition metal-catalyzed synthesis of azaheterocycles via an intramolecular annulation of alkynes

Intramolecular annulations of alkynes with nitrogen-containing nucleophiles represent a very convenient method for the preparation of azaheterocycles. In a typical annulation reaction involving nitrogen-containing nucleophile, transition metal with certain Lewis acidity is normally used as a catalyst for alkyne coordinate to facilitate the nucleophilic cyclization (Scheme 1-13). According to Baldwin's rules, there are two possible pathways for annulation of 4-ynylamines: (1) 5-exo-dig cyclization or (2) 6-endo-dig cyclization. Therefore, the control of the regioselectivity still remains a challenge.
In the effort to synthesize pyrroles, Gabriele and co-workers disclosed Cu(II)- and Pd(II)-catalyzed annulation of (Z)-(2-en-4-ynyl)amines via 5-exo-cyclization. In these studies, CuCl₂ appeared to be an excellent catalyst for the cyclization of (Z)-(2-en-4-ynyl)amine 1-10 with substituents at C-3 (Scheme 1-14), while the PdCl₂–KCl catalytic system turned out to be superior for the reaction of (Z)-(2-en-4-ynyl)amine 1-11 with hydrogen atom at C-3 (Scheme 1-15). The difference in the reactivity of Cu(II) and Pd(II) is due to the steric effect exerted by substituents at C-3 in the metal-alkyne coordination step. The steric effect is more obvious in Pd(II) catalysis because the larger ionic radius of Pd(II) with respect to Cu(II).

Hiroya and co-workers reported Cu(II)-catalyzed cyclizations of 2-ethynylanilines whereas Cu(OAc)₂ and Cu(OTf)₂ are the best catalyst for the synthesis of various N-sulfonylindoles and N-carboxyindoles respectively (Scheme 1-16). The method is quite general for the synthesis of various indole derivatives bearing electron-donating and
electron-withdrawing substituents on the aromatic ring. By using 1 equiv of Cu(OAc)$_2$ under similar reaction conditions, the indole moiety of hippadine, a natural alkaloid, was constructed in 80% yield (Scheme 1-17).

\[
\text{Cu(OAc)$_2$ (20 mol %), CICH$_2$CH$_2$Cl, reflux, 27 h } \quad 98\% \quad (R = \text{SO$_2$Me}) \\
\text{Cu(OTf)$_2$ (10 mol %), CICH$_2$CH$_2$Cl, reflux, 28 h } \quad 88\% \quad (R = \text{CO$_2$Et})
\]

\textbf{Scheme 1-16. Cu(II)-catalyzed cyclizations of 2-ethynylanilines to indoles}

Similarly, 6-membered azaheterocycles can be synthesized via Cu(I)-catalyzed intramolecular annulations of imines and alkynes. For example, Larock and co-workers revealed that cyclizations of 2-alkynyl benzaldimines proceeded smoothly into a variety of isoquinoline derivatives via 6-endo-cyclization in the presence of a catalytic amount of CuI. Various β- and γ-carbolines have been synthesized using similar reaction conditions (Scheme 1-18). More examples on the reactivity of 2-alkynyl benzaldimines will be explored in Chapter 5.1.4.
Besides Cu, other transition metals such as Au and Ag also exhibit high reactivity towards alkyne annulation. Toste and co-workers developed an Au(I)-catalyzed intramolecular acetylenic Schmidt reactions of homopropargyl azides for the synthesis of pyrroles (Scheme 1-19). Remarkably, the transformation required only very mild conditions with the extrusion of a molecular dinitrogen as the only side-product. In this case, Au(I) serves to activate alkyne for nucleophilic addition of an inner nitrogen atom of azide and also to donate electron density back into the ring-system to release a molecular dinitrogen.

By slight modification of the substrate, intramolecular hydroaminations of O-propargyl-N-Boc-hydroxylamines can also be achieved by employing Au(PPh3)OTf as a catalyst to construct 2,5-dihydroisoxazoles (Scheme 1-20 (a)). In addition, similar methodology has been successfully applied for the synthesis of communisin B as shown in Scheme 1-20 (b).
1.4 Perspective of thesis

Among numerous new synthetic transformations, the author has demonstrated that transition metal-catalyzed C–H functionalizations have emerged as one of the efficient synthetic approaches, since those methods can construct azaheterocycles directly from readily accessible starting materials under mild reaction conditions. Alternatively, transition metal-catalyzed intramolecular annulations of alkynes also serve a powerful route for the construction of azaheterocycles. However, there is still a huge room for the discovery and development of these two approaches for the synthesis of azaheterocycles.

Work documented in this thesis reported two different approaches for azaheterocycles synthesis (Scheme 1-21). The first approach is [Cp*RhCl2]2-catalyzed synthesis of azaheterocycles from oximes and internal alkynes via ortho C–H bond activation followed by alkyne insertion and final C–N bond formation. Isoquinoline and pyridine derivatives have been successfully synthesized from anti-isomers of oximes and alkynes by applying the above mentioned approach (Chapter 2 and Chapter 3, respectively). The advantage of the approach is that the N–O bonds of anti-isomers of
oximes could work as internal oxidants to maintain Rh$^{III}$–Rh$^{I}$ catalytic cycle in a redox-neutral process.

However, the limitation is that only anti-isomers of oximes could be applied for such transformation because the nitrogen lone-pair of oximes and ortho C–H bond must be in syn-geometry to achieve C–H bond activation. A modified approach under the Cu$^{I}$–Rh$^{III}$ relay catalytic system has been realized to solve the stereochemical requirement of oximes, such that both syn- and anti-isomers of oximes could be utilized for the synthesis of isoquinolines and other azaheterocycles (Chapter 4).$^{48}$

The second approach is utilizing intramolecular annulations of alkynes as the key step for the synthesis of 4-bromoisoquinolones where CuBr acts as a mediator, a bromide source as well as an oxidant (Chapter 5).$^{49}$

**First Approach**

\[
\text{syn-lanti-oximes} + [\text{Cp}^*\text{RhCl}_2]^2\text{carboxylate source} \rightarrow \text{isoquinolines/pyridines}
\]

**Second approach**

\[
\text{2-alkynylbenzaldehydes} + \text{CuBr-SMe}_2 (2.2 \text{ equiv}) \text{, benzene-pyridine (5:1)} \rightarrow \text{4-bromoisoquinolones}
\]

\[
\text{SiO}_2, 80 ^\circ\text{C} \text{, under O}_2 (1 \text{ atm})
\]

Scheme 1-21. Representative approaches for the synthesis of azaheterocycles
1.5 References


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19 Blankenship, K.; Erickson, C. A.; Stigler, K. A.; Posey, D. J.; McDougle, C. J. *Pediatric Health* 2010, 4, 375.


Chapter 2 Rhodium(III)-Catalyzed Synthesis of Isoquinolines from Aryl Ketone O-Acyl Oxime Derivatives and Internal Alkynes

2.1 Introduction

2.1.1 Overview

Isoquinoline (2-7) and quinoline (2-8) belong to a class of azaheterocycles known as benzopyridine where the structure consists of a benzene ring fused to a pyridine. Both of them are isolated from the same source (coal tar) in which isoquinoline was first isolated in 1885 by Hoogewerf and van Dorp.\(^1\)

![Figure 2-1. Benzopyridines: isoquinoline and quinoline](image)

Isoquinoline derivatives are present as the core structure in many alkaloids.\(^2\) Crispine B (2-9), an alkaloid which was isolated in 2002 from the extracts of Carduus crispus L, consists of pyrrolo[2,1-α]isoquinoline framework.\(^3\) It showed significant antitumor activity against human ovarian cancer cell and hepatoma cancer.\(^4\)

Ancistrobenomine A (2-10) is another alkaloid with biaryl and isoquinoline structures which can be found in the stem bark of Ancistrocladus benomensis (a tropical plant).\(^5\) It exhibits moderate antiplasmodial activities against the quinine-resistant strain of \(P. falciparum\) (malaria parasite). In addition, it also displays slight biological activity against African sleeping sickness, \(T. b. rhodesiense\).\(^6\)
2.1.2 Classical methods for the synthesis of isoquinolines

After discovering the importance of isoquinoline derivatives in biologically active natural products, numerous methodologies have been developed. As an early example, the Pomeranz-Fritsch synthesis\textsuperscript{7} is a two-step process which involves the initial condensation of benzaldehyde (2-11) with 2-aminoaldehyde acetal (2-12) to give aldimine 2-13, and followed by electrophilic cyclization under strong acid treatment to afford isoquinoline 2-7 (Scheme 2-1). For the synthesis of isoquinoline 2-16 with Cl-substituent, benzylamine 2-14 and glyoxal acetal 2-15 are used for the same transformation (Scheme 2-2).\textsuperscript{5}

![Figure 2.2. Alkaloids with isoquinoline derivatives as structural backbone](image)

**Figure 2.2. Alkaloids with isoquinoline derivatives as structural backbone**
However, decomposition of imines via hydrolysis during cyclization step is the major drawback of the Pomeranz-Fritsch synthesis and leads to low yields. In order to solve the limitation, imine 2-17 is first converted to amine 2-18 by NaBH₄ reduction or hydrogenation, and then protected with a tosyl group on the nitrogen atom. By treatment with acidic conditions, electrophilic cyclization and elimination of toluenesulfonic acid proceed to afford isoquinoline 2-19 in high yield (Scheme 2-3).⁹

![Scheme 2-3. An example of the modified Pomeranz-Fritsch synthesis](image)

The Bischler-Napieralski isoquinoline synthesis¹⁰ is another well-known classical method (Scheme 2-4). In a typical reaction, it involves the reaction between 2-phenylethanamine (2-20) and acetyl chloride to give acetamide 2-21 which is ready for electrophilic cyclization to give 3,4-dihydroisoquinoline 2-22 in the presence of phosphorus pentoxide (P₂O₅). By treatment with dehydrogenative conditions, 2-22 is converted to isoquinoline 2-23.

![Scheme 2-4. An example of the Bischler-Napieralski Isoquinoline synthesis](image)

The Pictet-Gams synthesis¹¹ is a modified version of the Bischler-Napieralski synthesis. A typical reaction involves the electrophilic cyclization of acetamide 2-24 bearing hydroxy group in the presence of P₂O₅ as a dehydrative agent (Scheme 2-5). The reaction provides a route for direct synthesis of isoquinoline 2-25 without the need for further oxidation.
The Pictet–Spengler synthesis involves the condensation between 2-phenylethylamine and formaldehyde to form imine which will then undergo a Mannich-type cyclization by treatment with acid to provide tetrahydroisoquinoline (Scheme 2-6). The electrophilic cyclization of imine normally required a strong donating substituent on the benzene ring for an efficient ring closure.

2.1.3 Recent advancements in the synthesis of isoquinolines

Over the past few decades, numerous novel and efficient synthetic routes have been developed for the synthesis of isoquinolines. Among them, transition metal-catalyzed transformations from rather simple starting materials are the-state-of-the-art in modern isoquinoline synthesis.

One of the recent examples is Pd(II)-catalyzed annulation reactions of internal alkynes with tert-butylimine of o-iodobenzaldehydes reported by Larock and co-workers (Scheme 2-7). As shown in the proposed catalytic cycle, the transformation involves initial oxidative addition of the C–I bond of o-iodobenzaldehyde to Pd(0) to produce aryl-Pd(II) intermediate A, then followed by alkyne insertion to generate vinyl-Pd(II)
intermediate B. Further intramolecular transformation of the intermediate B leads to 7-membered palladacyclic ammonium salt C. The subsequent C–N bond reductive elimination completes the catalytic cycle to provide isoquinoline 2-30 along with regeneration of Pd(0).

Proposed mechanism:

\[
\text{Ph} + \text{Ph} \xrightarrow{Pd(OAc)\, (5\, \text{mol\%})} \text{Pd}^{0}L_n \quad \text{PPh}_3 \, (10\, \text{mol\%}) \quad \text{Na}_2\text{CO}_3 \, (1\, \text{equiv}) \quad \text{DMF, 100 °C, 24 h} \quad 96\%
\]

Scheme 2-7. An example of Pd(II)-catalyzed annihilation reactions for the synthesis of isoquinolines and its proposed catalytic cycle

As reported by Cheng and co-workers, similar transformation can also be realized by using NiBr$_2$(dppe) as a catalyst (Scheme 2-8). Generally, high regioselectivity is observed for unsymmetrical alkynes leading to a major/sole product. Even alkyne bearing alkoxy group or terminal alkynes such as phenylacetylene and 1-hexyne are tolerated under the reaction conditions.

\[
\text{Ph} + \text{Ph} \xrightarrow{\text{NiBr}_2\text{(dppe)} \, (5\, \text{mol\%})} \text{Zn} \, (3\, \text{equiv}) \quad \text{CH}_3\text{CN, 80 °C} \quad 70\% \, (R^1 = \text{CH}_2\text{OH}, R^2 = \text{Ph}) \quad 94\% \, (R^1 = \text{H}, R^2 = \text{Ph}) \quad 76\% \, (R^1 = \text{H}, R^2 = \text{n-Bu})
\]

Scheme 2-8. Ni(II)-catalyzed annihilation reactions for the synthesis of isoquinolines
On the other hand, Cheng and co-workers also reported Rh(I)-catalyzed synthesis of isoquinolines from ketoximes and alkynes via ortho C–H bond activation (Scheme 2-9).\textsuperscript{15} The proposed mechanism involves ortho C–H oxidative addition to Rh(I) assisted by chelation of the nitrogen atom of ketoxime 2-31 to form 5-membered rhodacycle A, which is followed by alkyne insertion and reductive elimination to give ortho-alkenylation product 2-32. Subsequent thermal 6π-electrocyclization and dehydration affords isoquinoline 2-33.

\begin{center}
\textbf{Scheme 2-9. An example of Rh(I)-catalyzed synthesis of isoquinolines from ketoximes and alkynes}
\end{center}

Another interesting example reported by Liang and co-workers is Ag(I)-catalyzed synthesis of isoquinolines via cyclization of 2-alkynyl benzyl azides (Scheme 2-10).\textsuperscript{16} Ag(I) species is first coordinated to the alkynyl moiety of azide 2-34 to facilitate electrophilic cyclization of the internal nitrogen atom of azide onto alkyne via 6-endo-dig addition. The reaction is completed by denitrogenative aromatization to furnish isoquinoline 2-35 in good yield.

\begin{center}
\textbf{Scheme 2-10. An example of Ag(I)-catalyzed cyclizations of 2-alkynyl benzyl azides}
\end{center}
Recently, Wu and co-workers reported an unprecedented reaction between 2-alkynylbenzaldehyde 2-36 with isocyanooacetates 2-37 to give isoquinolines 2-38 using AgOTf as a catalyst and DBU as a base.\(^\text{17}\) They proposed the mechanism as follow: (1) isocyanooacetate 2-37 undergoes nucleophilic attack on the carbonyl group of 2-alkynylbenzaldehyde 2-36 in the presence of DBU to generate intermediate 2-39; (2) 2-39 is converted to oxazole 2-40, then followed by a rearrangement to form enamine 2-41;\(^\text{18}\) (3) 2-41 undergoes 6-exo-cyclization and decarbonylation to furnish isoquinoline 2-38 (Scheme 2-11).\(^\text{19}\)

![Proposed Mechanism](image)

Scheme 2-11. An example of unprecedented Ag(I)-catalyzed synthesis of isoquinolines and its proposed mechanism

2.1.4 Background of ortho C–H bond activation using [Cp*RhCl]_2 as a catalyst

Transition metal-catalyzed direct functionalization of sp\(^2\) C–H bonds has appeared to be an efficient method compared to the traditional functionalization of heteroarenes.\(^\text{20}\)
Many mechanisms for the C–H bond cleavage have been proposed and studied based on palladium cyclometallation.\textsuperscript{21} In one of the early detailed mechanistic studies on the ortho-palladation of N,N-dimethylbenzylamine (DMBA-H) using Pd(OAc)\textsubscript{2} reported by Ryabov and co-workers (the proposed mechanism is shown in Scheme 2-12), the kinetic studies indicated that cyclopalladation is an electrophilic process and the leaving proton is abstracted intramolecularly by the coordinated acetate.\textsuperscript{22} In a later mechanistic study by the same group, they stated "the transition state of the process involved concerted formation of the Pd–C bond and cleavage of the C–H bond with a nucleophilic assistance by the coordinated acetate."\textsuperscript{23}

\begin{center}
\begin{tikzpicture}
\t\node (A) at (0,0) [rectangle, draw, rounded corners] {\textbf{Scheme 2-12. Mechanism of cyclometallation of DMBA-H with Pd(OAc)\textsubscript{2}}};
\end{tikzpicture}
\end{center}

In general, these studies showed that Pd(OAc)\textsubscript{2} is the best source of Pd(II) because the coordinated acetate is believed to play multiple roles in C–H bond cleavage: (1) It facilitates the solvolysis of the reaction intermediates due to larger effective volume; (2) It enhances the electrophilicity of the Pd(II) center; (3) it acts as an intramolecular base for deprotonation.\textsuperscript{24} In fact, the addition of an acetate source can induce cyclometalation in several palladium catalytic systems.\textsuperscript{25}

\begin{center}
\begin{tikzpicture}
\t\node (A) at (0,0) [rectangle, draw, rounded corners] {\textbf{Scheme 2-13. Cyclometallation of [Cp*MCI\textsubscript{2}] and imine via ortho C–H activation}};
\end{tikzpicture}
\end{center}
In addition to acetate-promoted cyclopalladation, the cyclometallations of phenyl oxazolones can also be achieved using \([\text{Cp}^*\text{IrCl}_2]_2\) and NaOAc (the acetate source) via a similar mechanism. In that context, Davies and co-workers began to investigate the use of NaOAc to promote cyclometallations of nitrogen-containing ligands in the preparation of \([\text{Cp}^*\text{Rh(III)}]_2\) and \([\text{Cp}^*\text{Ir(III)}]_2\) complexes via C–H bond activation. Indeed, the reaction of \([\text{Cp}^*\text{RhCl}_2]_2\) or \([\text{Cp}^*\text{IrCl}_2]_2\) with imine in the presence of NaOAc leads to the formation of rhodacycle A and iridacycle B respectively via ortho C–H bond activation (Scheme 2-13). 

\[
\begin{align*}
\text{[Cp}^*\text{RhCl}_2]_2 & \xrightarrow{\Theta\text{OAc}} \text{A} \\
\text{B} & \xrightarrow{\Theta\text{OAc}} \text{C} \\
\text{D} & \xrightarrow{\Theta\text{Cl}} \text{Rh(III) cation intermediate D}
\end{align*}
\]

**Scheme 2-14. Proposed mechanism for ortho C–H activation of rhodacycle**

The reaction mechanism of the cyclometallation via C–H bond activation has been deeply investigated by Jones and co-workers (Scheme 2-14). On the basis of the kinetic studies, they proposed that compounds A–C are formed rapidly and always in equilibrium. Dissociation of the chloride ion or the acetate ion from B and C respectively generates Rh(III) cation D as the key intermediate. After the coordination of imine, C–H bond activation proceeds via an electrophilic substitution pathway with assistance of the coordinated acetate, where the acetate acts as the intramolecular base to abstract the leaving proton (Scheme 2-14). The proposed electrophilic C–H bond activation is supported by the fact that electron-donating groups on para-position of the phenyl ring favor the C–H bond activation while electron-withdrawing groups inhibit the C–H bond.
activation. These findings are in agreement with Ryabov's proposal on the mechanism of cyclometallation of DMBA-H with Pd(OAc)$_2$ as shown in Scheme 2-12.

Jones and co-workers also explored the reactivity of rhodacyclic complexes for the formation of isoquinoline salt C in 3 steps from [Cp*RhCl$_2$]$_2$ and imine 2-42 under very mild reaction conditions: (1) a stoichiometric amount of [Cp*RhCl$_2$]$_2$ undergoes facile ortho C–H bond cleavage of imine 2-42 to produce 5-membered rhodacycle A; (2) single alkyne insertion to afford 7-membered rhodacycle B; (3) Cu(II)-induced oxidative coupling of the C–N bond to liberate isoquinoline salt C (Scheme 2-15). The studies showed that ortho C–H bond activation, alkyne insertion, and subsequent C–N bond formation can be realized by utilizing [Cp*RhCl$_2$], NaOAc and a suitable nitrogen-containing directing group.

The unique reactivity of [Cp*RhCl$_2$]$_2$ in the process especially C–N bond formation step leads to the further development of [Cp*RhCl$_2$]$_2$-catalytic process for the synthesis of heterocycles involving C–N and C–O bond formation.

In one of the first few examples, Miura and Satoh revealed the direct oxidative couplings of benzoic acids and internal alkynes with [Cp*RhCl$_2$]$_2$ as the catalyst and Cu(OAc)$_2$ as the co-catalyst under an air atmosphere (Scheme 2-16). The reaction is initiated by the coordination of carboxyl oxygen of benzoic acid (2-43) to the Cp*Rh(III)
catalyst, and followed by ortho C–H bond activation to generate 5-membered rhodacycle A. The subsequent alkyne insertion and reductive elimination release isocoumarin 2-44. The resulting Cp*Rh(I) species is oxidized by Cu(II) to regenerate active Cp*Rh(III) species and Cu(I). In this case, molecular oxygen is used as the terminal oxidant to oxidized Cu(I) to Cu(II). In fact, the carboxyl moiety acts as the directing group and also involves in the C–O bond formation. Both electron-rich and electron-deficient benzoic acids are suitable substrates, and both aryl and alkyl alkynes are tolerated.

```
\[
\text{Ph} \quad \text{[Cp*RhCl]_2 (1 mol %)} \quad \text{Cu(OAc)_2-H_2O (5 mol %)} \\
\text{DMF, 120 °C, 2 h} \quad \text{under air} \\
\text{93%} \\
\text{Ph}
\]
```

**Proposed Mechanism:**

Under similar conditions, couplings of benzoic acids with acrylates takes place to provide 7-vinylphthalides via sequential divinylolation and cyclization (Scheme 2-17).
In 2008, Fagnou and co-workers reported the oxidative couplings of N-acetyl anilines and internal alkynes for the synthesis of highly functionalized indoles by using \([\text{Cp}^*\text{RhCl}_2]\_2\) as the catalyst (Condition A, Scheme 2-18).\(^{32}\) The reaction is more efficient by the addition of AgOTf, which sequesters Cl ligands on \([\text{Cp}^*\text{RhCl}_2]\_2\); inversely it is completely inhibited by the addition of LiCl. In this case, high temperatures and more than a stoichiometric amount of Cu(OAc)\_2 are required. To account for the drawback, a more general oxidative coupling has been developed by using \([\text{Cp}^*\text{Rh(MeCN)}\_2]\text{[SbF}_6\text{]}\_2\) under milder reaction conditions with molecular oxygen as the terminal oxidant (Condition B, Scheme 2-18).\(^{33}\)

\begin{align*}
\text{Condition A: } & [\text{Cp}^*\text{RhCl}_2]_2 (2.5 \text{ mol }\%), \text{AgSbF}_6 (10 \text{ mol }\%) \\
& \text{Cu(OAc)}_2 \cdot \text{H}_2 \text{O} \text{ (2.1 eq), 120 }^\circ \text{C.}} \\
\text{Condition B: } & [\text{Cp}^*\text{Rh(MeCN)}\_2]\text{[SbF}_6\text{]}\_2 \text{ (5 mol }\%)
\\
& \text{Cu(OAc)}_2 \cdot \text{H}_2 \text{O} \text{ (20 mol }\%), \text{60 }^\circ \text{C, O}_2 \text{ (1 atm).}}
\end{align*}

Scheme 2-18. An example of Rh(III)-catalyzed synthesis of indoles from anilines and alkynes

Recently, Huang and co-workers revealed a new synthetic approach towards unprotected indoles via triazene-directed C–H bond activation (Scheme 2-19).\(^{34}\) In a typical reaction involving triazene \(2-45\) and diphenylacetylene in the presence of \([\text{Cp}^*\text{RhCl}_2]\_2\) as the catalyst, similar ortho C–H bond activation and alkyne insertion proceed to form the corresponding 7-membered rhodacycle \(A\). The transformation from rhodacycle \(A\) to indole \(2-46\) may involves 2 possible pathways: (1) a 1,2-Rh(III) shift, reductive elimination and hydrolysis. However, it is not clear whether the diazonium intermediate undergoes hydrolysis prior to or after reductive elimination; (2) an N=N insertion to Rh–C bond followed by elimination of \(\text{Cp}^*\text{Rh(I)}\) and hydrolysis.
Pathway (1): 1,2-Rh(III) shift, reductive elimination and hydrolysis

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{OAc} & \quad \text{OAc} \\
\text{rhodacycle A} & \quad \text{rhodacycle A}
\end{align*}
\]

Pathway (2): N=N insertion, elimination of Rh(III) and hydrolysis

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{OAc} & \quad \text{OAc} \\
\text{rhodacycle A} & \quad \text{rhodacycle A}
\end{align*}
\]

Scheme 2-19. An example of Rh(III)-catalyzed synthesis of indoles from triazenes and alkynes and its possible mechanism

Besides that, oxidative coupling of benzophenone imine (2-47) and diphenylacetylene also proceeds via similar C–H and N–H bond activations to provide isoquinoline 2-48 using [Cp*RhCl₂]₂ as the catalyst. In the case of benzyldiene aniline (2-49), indenone imine 2-50 is indeed formed via a different pathway. A common intermediate, 7-membered rhodacycle A is proposed in both reaction pathways where C–N bond reductive elimination provides isoquinoline 2-48 or intramolecular imine insertion gives indenone imine 2-50 (Scheme 2-20).

In a spectacular application of this approach, Rovis reported [Cp*RhCl₂]₂-catalyzed oxidative cycloadditions of benzamides and alkynes via C–H and N–H bond activations where the amide moiety is used as a directing group (Scheme 2-21). A typical reaction proceeds through an initial N–H metalation of the amide, and followed by
ortho C–H bond activation, which is the turnover-limiting step. High regioselectivity is observed for unsymmetrical alkynes.

\[
\begin{align*}
R^1 &= \text{Ph, } R^2 = \text{H} \\
R^1 &= \text{H, } R^2 = \text{Ph}
\end{align*}
\]

Scheme 2-20. Rh(III)-catalyzed diverse synthesis of isoquinoline and indenone imine

More challenging allylic sp\(^3\) C–H bond activation can also be achieved. Glorious and co-workers developed a novel synthesis of pyrroles from enamines and alkynes under the [Cp*RhCl\(_2\)]\(_2\)-AgSbF\(_6\) catalytic system with Cu(OAc)\(_2\) as the oxidant (Scheme 2-22).\(^{37}\) However, the presence of an ester group at α-position of enamines is essential for selective allylic sp\(^3\) C–H bond activation.

In short, [Cp*RhCl\(_2\)]\(_2\) is a powerful and reactive catalyst for the synthesis of heterocycles via C–H bond activation. However, in order to achieve catalytic turnover,
such strategies normally require an external oxidant to encounter the change in oxidation state from Cp*Rh(III) to Cp*Rh(I) due to C–N or C–O bond reductive elimination.

\[
\begin{align*}
\text{R}_1^N \text{N}^\text{OR} + \text{Cp}^*\text{Rh}^\text{I} + \text{HX} & \rightarrow \text{R}_1^N \text{H} + \text{Cp}^*\text{Rh}^\text{III} \text{OR} \\
\end{align*}
\]

Scheme 2.23. Redox neutral process between N–O bond and Rh(I)

To address this drawback, a redox-neutral process employing a directing group with oxidizing properties surfaced as an attractive strategy for C–H bond activation and functionalization. One of the ways is to use a directing group bearing N–O bond where the N–O bond can be utilized as an internal oxidant to oxidize Cp*Rh(I) to Cp*Rh(III) species with the formation of N–H bond (Scheme 2.23).

\[
\text{Me} \quad -\equiv- \quad \text{Ph}
\]

Proposed Mechanism:

Scheme 2.24. An example of Rh(III)-catalyzed isoquinolone synthesis using N–OMe bond as internal oxidant

In 2010, Fagnou and co-workers utilized such conceptually new redox-neutral strategy for C–N bond formation of isoquinolones. In the presence of a catalytic amount of [Cp*RhCl₂]₂ and CsOAc, the cycloaddition of benzhydroxamic acid 2-51 and diphenylacetylene is achieved to furnish isoquinolone 2-52 in high yield (Scheme 2.24). The N–OMe bond is utilized as an internal oxidant for regeneration of Cp*Rh(III) to...
avoid the use of external oxidant. The first step of the mechanism involves a reversible ortho C–H bond activation, which is followed by alkyne insertion to generate 7-membered rhodacycle A. At this point, C–N bond formation and N–OMe bond cleavage occur to provide isoquinolone 2-52 and regenerate the Cp*Rh(III) catalyst (Scheme 2-24). It is worth to note that the reactions are highly regioselective towards unsymmetrical alkynes under these mild and copper free conditions.

A modified protocol implementing the N–OPiv bond as an internal oxidant promotes a wider scope of isoquinolone formation at room temperature with lower catalyst loading of only 0.5 mol % [Cp*RhCl]2.40 Similar approach can be applied for the coupling reactions of benzhydroxamic acid derivatives bearing an N–OPiv bond and alkenes41 or allenes42 to give 3,4-dihydroisoquinolines (Scheme 2-25). By using chiral cyclopentadienyl derivative as the ligand, Cramer and co-workers developed Rh(III)-catalyzed enantioselective synthesis of tetrahydroisoquinoliones from benzhydroxamic acids and alkenes via C–H bond functionalization (Scheme 2-26).43

![Scheme 2-25. Rh(III)-catalyzed synthesis of 3,4-dihydroisoquinolines](image)

![Scheme 2-26. An example of Rh(III)-catalyzed enantioselective synthesis of tetrahydroisoquinolinones](image)
By applying Rh(III)-catalyzed N–O bond cleavage redox-neutral process in an intramolecular manner, Park and co-workers developed Rh(III)-catalyzed intramolecular reaction of alkyne-tethered hydroxamic esters for the synthesis of isoquinolines with C-3 substituent bearing alcohol moiety. In this strategy, N–O bond is not only used as an internal oxidant but the oxygen atom of N–O bond is reserved as alcohol moiety in isoquinolines. It is worth to note that the transformation proceeds in a way to provide isoquinolones with reverse regioselectivity compared to the reported intermolecular version. This method is further applied for the total synthesis of (±)-septicine (Scheme 2-27).

![Scheme 2-27. Rh(III)-catalyzed synthesis of (±)-septicine](image)

In the effort to achieve an overall redox-neutral process, our group developed a redox [Cp*RhCl₂]₂–Cu(OAc)₂ bimetallic catalytic system such that the coupling of α-aryl vinyl azides and internal alkynes proceeded to form highly substituted isoquinolines (Scheme 2-28). The copper co-catalyst presumably plays multiple roles (1) to reduce the inner N–N bond of azide and generate an iminyl–Cu(II) species, and (2) to re-oxidize Cp*Rh(I) to the Cp*Rh(III) catalyst. We believed that iminyl–Cu(II) species undergoes transmetallation with Cp*Rh(III) to generate iminyl–Cp*Rh(III) species before further transformation.

![Scheme 2-28. An example of [Cp*RhCl₂]₂–Cu(OAc)₂ bimetallic catalytic system](image)
2.1.5 New redox-neutral approach with oximes

As discussed previously, the use of benzyhydroxamic acid derivatives (the attachment of an alkoxy or ester groups on the nitrogen of benzamides) as the precursor for the synthesis of isoquinolones has been successfully achieved under redox-neutral conditions where the N–O bond of benzyhydroxamic acid derivatives acts as an internal oxidant.

In that context, we are interested in exploring other nitrogen-containing directing groups bearing an N–O bond for such redox-neutral process. One of the potential candidates is oximes. Recently, Hartwig and co-workers revealed that Pd(0)-catalyzed synthesis of indole 2-54 from O-acetyl oxime 2-53 can be achieved under redox-neutral conditions where the reaction involves an initial oxidative addition of N–O bond of O-acetyl oxime 2-53 to Pd(0) (Scheme 2-29).46

Inspired by Hartwig’s work, we proposed a redox-neutral process which involves the synthesis of isoquinolines from O-acetyl oximes and alkynes using [Cp*RhCl₂]₂ as a catalyst without external oxidant (Scheme 2-30). In this case, oximes may serve as the directing group and the N–O bond of oximes works as internal oxidant to achieve catalytic turnover.
2.2 Results and discussion

2.2.1 Synthesis of O-acetyl oxime derivatives

As shown in Scheme 2-31, treatment of ketones with hydroxylamine in the presence of pyridine provides the corresponding oximes. Without any purification, the oximes were subjected for acetylation to give the respective aryl ketone O-acetyl oximes 2-1.

![Scheme 2-31. Synthesis of O-acetyl oximes 2-1 from ketones](image)

2.2.2 Optimization of reaction conditions

Based on our proposal shown in Scheme 2-30, we started to investigate the reactions of aryl O-acetyl oximes and alkynes using [Cp*RhCl₂]₂ as a catalyst. For optimization of reaction conditions, acetophenone O-acetyl oxime (2-1a) and diphenylacetylene (2-2a) were used as typical substrates of ketoxime and alkyne respectively (Table 2-1).

Even though no reaction was observed with only 2.5 mol % of [Cp*RhCl₂]₂ in MeOH (Table 2-1, entry 1), addition of metal acetate as a co-catalyst (30 mol %) resulted in the formation of isoquinoline 2-3aa in good yields at 60 °C (Table 2-1, entries 2 and 3). Both NaOAc and CsOAc gave comparable yields. When MeOH was replaced with other solvents such as t-BuOH and DMF, the yield of isoquinoline 2-3aa decreased dramatically to 14% and 4% respectively (Table 2-1, entries 4 and 5).
By changing R-substituent from acetyl to methyl protecting group, reaction became sluggish and affording isoquinoline 2-3aa in 13% yield with 64% recovery of O-methyl oxime 2-1a' even after 19 h (Table 2-1, entry 6). This indicates that the leaving group reactivity (as -OR group) is essential for isoquinoline formation. It is worth to note that Rh(I) catalysts such as Wilkinson's catalyst, RhCl(PPh₃)₃ did not provide any product for the present process.

Table 2-1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime</th>
<th>additive</th>
<th>solvent</th>
<th>conditions</th>
<th>yield of 2-3aa / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-1a</td>
<td>none</td>
<td>MeOH</td>
<td>60 °C, 7 h</td>
<td>0°</td>
</tr>
<tr>
<td>2</td>
<td>2-1a</td>
<td>NaOAc</td>
<td>MeOH</td>
<td>60 °C, 6 h</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>2-1a</td>
<td>CsOAc</td>
<td>MeOH</td>
<td>60 °C, 4 h</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>2-1a</td>
<td>CsOAc</td>
<td>t-BuOH</td>
<td>80 °C, 7 h</td>
<td>14°</td>
</tr>
<tr>
<td>5</td>
<td>2-1a</td>
<td>CsOAc</td>
<td>DMF</td>
<td>80 °C, 23 h</td>
<td>4°</td>
</tr>
<tr>
<td>6</td>
<td>2-1a'</td>
<td>NaOAc</td>
<td>MeOH</td>
<td>60 °C, 19 h</td>
<td>13°</td>
</tr>
</tbody>
</table>

a Reactions were carried out on the scale of 0.3 mmol of 2-1a and 2-2a in MeOH (0.2 M) under N₂ atmosphere. b Isolated yield. ° 1H NMR yield from the crude mixture. d 2-1a' was recovered in 64% yield.

2.2.3 Scope & limitations

2.2.3.1. Synthesis of isoquinolines from O-acetyl oximes and internal alkynes

By utilizing the optimized [Cp*RhCl₂]₂–NaOAc catalytic system (Table 2-1, entry 2), various aryl ketone O-acetyl oximes 2-1 and alkynes 2-2 were investigated (Table 2-2).
Table 2-2. Synthesis of isoquinolines from aryl ketone O-acetyl oximes and alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxime 2-1</th>
<th>Alkyne 2-2</th>
<th>Isoquinoline 2-3 / Yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-1a</td>
<td>2-2b (R$^3$ = Me, R$^4$ = Ph)</td>
<td>2-3ab: 72%</td>
</tr>
<tr>
<td>2</td>
<td>2-1a</td>
<td>2-2c (R$^3$ = CH$_2$OH, R$^4$ = Ph)</td>
<td>2-3ac: 42% ($9:1)^{c,d}$</td>
</tr>
<tr>
<td>3</td>
<td>2-1a</td>
<td>2-2d (R$^3$ = CH$_2$OTBS, R$^4$ = Ph)</td>
<td>2-3ad: 65% (14:1)$^d$</td>
</tr>
<tr>
<td>4</td>
<td>2-1a</td>
<td>2-2e (R$^3$ = n-Pr, R$^4$ = n-Pr)</td>
<td>2-3ae: 87%</td>
</tr>
<tr>
<td>5</td>
<td>2-1a</td>
<td>2-2f (R$^3$ = R$^4$ = CH$_2$OTBS)</td>
<td>2-3af: 73%</td>
</tr>
<tr>
<td>6</td>
<td>2-1b (R$^1$ = OMe)</td>
<td>2-2a</td>
<td>2-3ba: 87%</td>
</tr>
<tr>
<td>7</td>
<td>2-1c (R$^1$ = Ph)</td>
<td>2-2a</td>
<td>2-3ca: 92%</td>
</tr>
<tr>
<td>8</td>
<td>2-1d (R$^1$ = Br)</td>
<td>2-2a</td>
<td>2-3da: 94%</td>
</tr>
<tr>
<td>9</td>
<td>2-1e (R$^1$ = CF$_3$)</td>
<td>2-2a</td>
<td>2-3ea: 89%</td>
</tr>
<tr>
<td>10</td>
<td>2-1f (R$^1$ = OMe)</td>
<td>2-2a</td>
<td>2-3fa: 89%</td>
</tr>
<tr>
<td>11</td>
<td>2-1g (R$^1$ = Br)</td>
<td>2-2a</td>
<td>2-3ga: 82%</td>
</tr>
<tr>
<td>12</td>
<td>2-1h (R$^1$ = OMe)</td>
<td>2-2a</td>
<td>2-3ha: 58%</td>
</tr>
<tr>
<td>13</td>
<td>2-1i (R$^1$ = Br)</td>
<td>2-2a</td>
<td>2-3ia: 67%</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: [Cp*RhCl$_2$]$_2$ (2.5 mol%), NaOAc (30 mol%), MeOH, 60 °C, 4-10 h.

$^b$ Yield is based on the isolated product.
Table 2-2. Synthesis of isoquinolines from aryl ketone O-acetyl oximes and alkynes
(continue)

\[
\begin{array}{ccc}
\text{entry} & \text{oxime 2-1} & \text{alkyne 2-2} & \text{isoquinoline 2-3 / yield}^b \\
14 & \begin{array}{c}
N=OAc \\
\text{Ph}
\end{array} & \begin{array}{c}
R^2 = \text{Me} \\
\text{Ph}
\end{array} & \begin{array}{c}
2-3ja: 69\%
\end{array} \\
15 & 2-1k (R^2 = \text{Ph}) & 2-2a & 2-3ka: 98\% \\
16 & 2-1l (R^2 = \text{trans-CH} = \text{CPh}) & 2-2a & 2-3la: 95\% \\
17 & 2-1m (R^2 = \text{CO}_2\text{Me}) & 2-2a & 2-3ma: 91\% \\
18 & \begin{array}{c}
N=OAc \\
\text{Ph}
\end{array} & \begin{array}{c}
R^2 = \text{Ph} \\
\text{Ph}
\end{array} & \begin{array}{c}
2-3na: 76\%
\end{array}
\end{array}
\]

\(^a\) Reactions were carried out on the scale of 0.5 mmol of 2-1 and 0.6 mmol of 2-2 in MeOH (0.2 M) under N\(_2\) atmosphere. \(^b\) Isolated yield. \(^c\) Isolated as a mixture of 2 regioisomers and the regioselectivity was calculated based on \(^1\)H NMR. \(^d\) The structure of major isomer was described.

Based on the experimental results, the present process demonstrated wide substrate tolerance with internal alkynes (Table 2-2, entries 1-5). Insertion of unsymmetrical alkyne, 1-phenyl-1-propyne (2-2b) occurred regioselectively to give 4-methyl-3-phenylisoquinoline 2-3ab as a sole product (Table 2-2, entry 1). Similarly, 3-phenyl-2-propyn-1-ol (2-2c) afforded isoquinoline 2-3ac with high regioselectivity albeit in moderate yield (Table 2-2, entry 2). By protecting the hydroxy moiety of alkyne 2-2c with TBS group, the reaction was improved in terms of yield and regioselectivity (Table 2-2, entry 3). The reactions with dialkyl-substituted alkynes also proceeded smoothly (Table 2-2, entries 4 and 5).
Generally, both electron-donating and electron-withdrawing groups could be introduced as R^1-substituent on the benzene ring of acetophenone O-acetyl oximes 2-1. It is worth to note that even a C–Br bond or a C–CF_3 bond on benzene could be tolerated under the reaction conditions (Table 2-2, entries 8, 9, 11, and 13). In the case of meta-substituted acetophenone O-acetyl oximes 2-1h and 2-1i, two regioisomers were obtained in which the sterically less hindered C–H bond was cleaved preferentially (Table 2-2, entries 12 and 13). This approach also allowed the construction of thieno[2,3-c]pyridine structure in high yield (Table 2-2, entry 14).

To test the generality of R^2-substituent on aryl ketone O-acetyl oximes 2-1, phenyl and alkenyl groups or even an ester moiety were synthesized and subjected to the optimized conditions; the reactions proceeded to give the corresponding isoquinolines in excellent yields (Table 2-2, entries 15-17). In addition, α-tetralone O-acetyl oxime (2-1n) was successfully applied for preparing tricyclic isoquinoline 2-3na (Table 2-2, entry 18).

As shown, a wide scope of aryl ketone O-acetyl oximes 2-1 were found to be promising precursors for the present Rh(III)-catalyzed synthesis of isoquinolines with internal alkynes. However, when we treated 2-10 (syn:anti = 1:1) which possesses a bulky R^2-substituent (isopropyl group) under the standard conditions, the desired isoquinoline 2-30a was formed in 54% along with recovery of syn-isobutyrophenone oxime (syn-2-40) in 36% yield via deacetylation (Scheme 2-32). The result might suggest that only the anti-isomer is reacted.

![Scheme 2-32. Limitation of Rh(III)-catalyzed synthesis of isoquinoline from mixture of syn- and anti-ketoxime](image-url)
The phenomenon could be attributed to the stereochemical requirement of oxime where only the anti-isomer of 2-1o provides the correct geometry to direct the Cp*Rh(III) center in close proximity with ortho aryl C–H bond for C–H rhodation prior to the next transformation (Scheme 2-33). In contrast, the syn-isomer of 2-1o inhibits ortho aryl C–H bond activation.

Scheme 2-33. The stereochemical requirement for ortho C–H activation

As a result, this drawback hinders the synthesis of isoquinolines bearing bulky R^2-substituent from syn O-acetyl oximes under the present reaction conditions. One of the solutions is to fix the stereochemical requirement of oximes by using a cyclic analog of anti-O-acetyl oximes, 3-phenylisoxazol-5-ones 2-5 for similar transformation. On the other hand, a more general method will be discussed in Chapter 4 by using iminyl-metal species, which could derived from both anti- and syn-isomers of oximes, as the intermediate.

2.2.3.2. Synthesis of isoquinolines from isoxazolones and internal alkynes

3-Phenylisoxazol-5-ones 2-5 could be accessed from the corresponding β-keto esters by the reaction with hydroxylamine, where even two alkyl groups (R^5 and R^6) could easily be introduced at the α-position of 2-5 (Scheme 2-34).47
Fortunately, when 3-phenylisoxazol-5-one 2-5a and diphenylacetylene (2-2a) was subjected to the present reaction conditions (2.5 mol % [Cp*RhCl₂], 30 mol % NaOAc in MeOH, 60 °C), the reaction proceeded smoothly to afford 1-isopropylisoquinoline 2-6aa.

**Table 2-3. Synthesis of isoquinolines from 3-phenylisoxazol-5-ones and alkynes**

<table>
<thead>
<tr>
<th>entry</th>
<th>isoxazolone 2-5</th>
<th>alkyne 2-2</th>
<th>isoquinoline 2-6 / yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-5a</td>
<td>2-2a (R³ = R⁴ = Ph)</td>
<td>2-6aa (= 2-3aa): 91%</td>
</tr>
<tr>
<td>2</td>
<td>2-5a</td>
<td>2-2a (R³ = R⁴ = Ph)</td>
<td>2-6aa-d: 94% (93% D)</td>
</tr>
<tr>
<td>3</td>
<td>2-5a</td>
<td>2-2b (R³ = Me, R⁴ = Ph)</td>
<td>2-6ab: 56%</td>
</tr>
<tr>
<td>4</td>
<td>2-5a</td>
<td>2-2e (R³ = n-Pr, R⁴ = n-Pr)</td>
<td>2-6ae: 82%</td>
</tr>
<tr>
<td>5</td>
<td>2-5b</td>
<td>2-2a</td>
<td>2-6ba: 69%</td>
</tr>
<tr>
<td>6</td>
<td>2-5c</td>
<td>2-2a</td>
<td>2-6ca (= 2-3aa): 72%</td>
</tr>
</tbody>
</table>

Unless otherwise noted, the reactions were carried out on the scale of 0.5 mmol of 2-5 and 0.5 mmol of 2-2 in MeOH (0.2 M) under N₂ atmosphere. Isolated yield. The reaction was performed in MeOD. The reaction was conducted for 28 h and 2-5a was recovered in 38% yield.
in 91% yield via decarboxylation (Table 2-3, entry 1). Deuteration of the methine carbon of the isopropyl moiety was observed when the reaction was conducted in MeOD (Table 2-3, entry 2). In the case of unsymmetrical alkyne 2-2b, the insertion occurred regioselectively to give isoquinoline 2-6ab in 56% yield with recovery of 2-5a in 38% yield even after 28 h (Table 2-3, entry 3). High yield was observed for dipropyl-substituted alkyne 2-2e (Table 2-3, entry 4). In addition, mono- and none-substituted 3-phenylisoxazol-5-one 2-5b and 2-5c could also be utilized for this transformation to afford isoquinolines 2-6ba and 2-6ea (=2-3aa) in 69% and 72% respectively (Table 2-3, entries 5 and 6).

2.2.4 Mechanism insight

In order to understand the detailed mechanism of the present catalytic system, several reactions were performed as shown in Scheme 2-35. When O-acetyl oxime 2-1a was treated under the standard conditions in MeOD in the absence of alkynes, 33% of deacetylated oxime 2-4a-d with deuterium incorporation at ortho positions was observed (Scheme 2-35 (a)). The phenomenon might suggest that ortho C–H bond activation occurs and it is a reversible process.

In contrast, the reaction in MeOD in the presence of alkyne 2-2a afforded isoquinoline 2-3aa-d without deuterium incorporation at the C-8 position (Scheme 2-35 (b)). These results suggested that the catalytic cycle is initiated by C–H rhodation, followed by fast and irreversible alkyne insertion and C–N bond formation.

Interestingly, deuterium was incorporated into the methyl group of isoquinoline 2-3aa-d (Scheme 2-35 (b)). To investigate the possibility of deuterium/hydrogen exchange of isoquinoline 2-3aa under the reaction conditions, isoquinoline 2-3aa was treated under the standard conditions in MeOD; experimental result showed 99% recovery of
isoquinoline 2-3aa with no deuteration on methyl group (Scheme 2-35 (c)). These observations indicated that deuterium incorporation into methyl group of isoquinoline 2-3aa may occur during the catalytic ring formation process.

\[
\begin{align*}
\text{Scheme 2-35. Investigation of reaction mechanism--1}
\end{align*}
\]

Subsequently, ortho-alkenylketone 2-1p was synthesized from the corresponding ortho-alkenylketone, which was synthesized according to the reported procedure,\(^{48}\) by treatment with NH\(_2\)OH·HCl and pyridine in EtOH at 60 °C. 2-1p was employed to investigate the possibility of 6\(\pi\)-electrocyclization of ortho-alkenylated intermediate\(^{49,50}\) in the C–N bond-forming step. Treatment of 2-1p under the standard reaction conditions in the absence of alkynes resulted in only deacetylated oxime 2-4p without the formation of isoquinoline (Scheme 2-36 (a)). To resemble the same reaction conditions, ortho-alkenylloxime 2-1p was treated with alkyne 2-2e; only isoquinoline 2-3pe was formed as the only cyclized product (Scheme 2-36 (b)). Accordingly, 6\(\pi\)-electrocyclization is most likely ruled out from the possible reaction pathways.
Based on those mechanistic experimental results, possible catalytic cycle of aryl ketone $O$-acetyl oxime 2-1a and alkyne 2-2a is outlined in Scheme 2-37. The catalytic cycle is initiated by an ortho C–H bond activation of 2-1a with an assistance of the oxime $sp^2$ nitrogen to give aryl Cp*Rh(III) intermediate A, which undergoes insertion of alkynes 2-2a and followed by interaction with neighboring nitrogen to afford 7-membered rhodacyclic iminium cation intermediate B. Intermediate B may proceed with 2 possible pathways: (1) C–N bond reductive elimination to provide $N$-acetoxyisoquinolinium cation C and followed by reduction of the resulting Cp*Rh(I) species to afford isoquinoline 2-3aa along with regeneration of the Cp*Rh(III) catalyst (Scheme 2-37, path a); (2) direct formation of isoquinoline 2-3aa and Cp*Rh(III) species from rhodacycle B via a concerted redox process (Scheme 2-37, path b). The deuterium incorporation into the methyl moiety of isoquinoline 2-3aa under the standard reaction conditions in MeOD (see Scheme 2-35 (b)) strongly supports the presence of the rhodacyclic iminium cation B or isoquinolinium cation C which bears $\alpha$-protons with enough acidity for deuterium/hydrogen exchange in the reaction course. Furthermore, the deuterium/hydrogen exchange is possible only if the extrusion of Cp*Rh(III) species from intermediate B is the rate-determining step.
On the other hand, in the effort to understand the mechanism of Rh(III)-catalyzed synthesis of isoquinolones from hydroxamic acids with alkynes, Fagnou and Guimond also studied the mechanism for isoquinoline synthesis from oximes and alkynes. They found that the reaction of O-mesitoylacetophenone oxime with 4-octyne proceeds to provide the corresponding isoquinoline in 54% yield along with methyl mesitoate in 96% (Scheme 2-38). The only way to produce a quantitative amount of methyl mesitoate is via basic methanolysis of O-mesitoylacetophenone oxime, which will then convert to oxygen-free acetophenone oxime. The observation suggested that the oxygen-free oxime can be the active competent starting material. Similar experimental result is observed for simple oxygen-free acetophenone oxime. Therefore, they confirmed that oxygen-free oxime is the active starting material under their reaction conditions.

\[
\begin{align*}
\text{Scheme 2-37. Proposed catalytic cycle} \\
\text{Scheme 2-38. Observation of a methyl mesitoate as side-product}
\end{align*}
\]
However, we believed that the basic methanolysis of $O$-acetyl oximes under our mild basic conditions (with NaOAc) is unfavorable compared to the strongly basic conditions (with K$_2$CO$_3$) developed by Fagnou and Guimond. In addition, shorter reaction time of 6 h observed in the case of NaOAc revealed that the active starting material may possess higher reactivity compared to the model proposed by Fagnou and Guimond which required 16 h of reaction time (Scheme 2-39). Similarly, long reaction time of 16 h was also observed in Rh(III)-catalyzed synthesis of isoquinolines from oxygen-free arylketoximes reported by Li and coworkers.$^{52}$

![Scheme 2-39. Comparison of the effect of additive](attachment:scheme.png)

Therefore, we believe that the deacetylation of $O$-acetyl oxime via basic methanolysis does not proceed under our optimized reaction conditions. In our proposed catalytic cycle (Scheme 2-37), we also anticipated that the acetyl moiety of intermediate B is pivotal to facilitate the extrusion of Cp*Rh(III) species with the formation of isoquinoline via the internal coordination of the oxygen atom of the acetyl moiety to the Cp*Rh(III) of intermediate B.
2.3 Conclusion

A method of isoquinoline synthesis from aryl ketone O-acyloxime derivatives and internal alkynes has been developed using [Cp*RhCl₂]₂–NaOAc as the catalyst system. The catalytic system could accommodate a fairly broad substrate scope to provide isoquinolines in good to excellent yield. The present transformation was carried out by a redox-neutral sequence of ortho C–H rhodation, alkyne insertion and C–N bond formation in the putative 7-membered rhodaicyclic iminiun cation. It is worth to note that the N–O bond of oxime derivatives could work as an internal oxidant to maintain Rh(III)–Rh(I) catalytic cycle. However, the limitation of [Cp*RhCl₂]₂–NaOAc catalysis is that only the anti-isomers of oximes could be utilized under the optimized conditions (an improved version of the reaction will be discussed in Chapter 4).

2.4 References

3 Zhang, Q.; Tu, G.; Zhao, Y. Cheng, T. Tetrahedron 2002, 58, 6795.
7 Gensler, W. J. Org. Reactions 1951, 6, 191.


Chapter 3  Rhodium(III)-Catalyzed Synthesis of Pyridines from α,β-Unsaturated Ketoximes and Internal Alkynes

3.1  Introduction

3.1.1  Overview

Pyridine is a six-membered nitrogen heterocyclic aromatic compound. It has similar structure related to benzene whereby replacing one of the C-H bonds of benzene is replaced by a nitrogen atom gives pyridine.

Pyridine derivatives can be found in some vitamins and alkaloids. To serve as an example, nicotinamide (3-5) is a water-soluble vitamin which enhances the function of the digestive system, skin and nerves.\(^1\) With the few alkaloid-containing monocyclic pyridine derivatives, nicotine (3-6) is especially important because it is the active ingredient in cigarettes and other tobacco products. Besides, anabasine (3-7) and nicotyrine (3-8) are also important tobacco alkaloid-containing pyridine derivatives.

\[
\begin{align*}
\text{3-5} & : \quad \text{O} \quad \text{NH}_2 \\
\text{3-6} & : \quad \text{H} \quad \text{N} \quad \text{Me} \\
\text{3-7} & : \quad \text{H} \quad \text{N} \quad \text{H} \\
\text{3-8} & : \quad \text{N} \quad \text{Me}
\end{align*}
\]

Figure 3-1. Structure of nicotinamide and other tobacco alkaloids

Over the last few decades, pyridine derivatives have been discovered to be important motifs in many bioactive pharmaceutical compounds. Therefore, attention has been drawn to develop more pyridine-containing drugs in the pharmaceutical industry. To exemplify, isoniazide (3-9) is an antibiotic used to prevent and treat tuberculosis;\(^2\) ABT-594 (3-10) is an analgesic which appears to be more powerful than morphine, without the serious side effects;\(^3\) doxylamine (3-11) is the first generation antihistamine
used for short-term treatment of insomnia and also symptom of soft allergy and common cold.\(^4\)

![Pyridine-containing bioactive pharmaceutical compounds](image)

**Figure 3-2.** Pyridine-containing bioactive pharmaceutical compounds

### 3.1.2 Classical methods leading to pyridines

The importance of pyridine derivatives in pharmaceutical industry leads to the discovery of new approaches for the construction of multi-substituted pyridines. The following are a few examples of pyridine synthesis in the early stage of development.

One of the early examples is the Chichibabin pyridine synthesis.\(^5\) In a typical reaction, condensation of acetophenone with ammonia provides enamine 3-13 whereas aldol-condensation of acetophenone and benzaldehyde gives \(\alpha,\beta\)-unsaturated ketone 3-12. Michael addition of enamine 3-13 to \(\alpha,\beta\)-unsaturated ketone 3-12 and followed by cyclization affords pyridine 3-14 (Scheme 3-1).\(^6\) However, high reaction temperature is required and low yields (<40%) are observed in all cases thus it is not suitable for practical pyridine synthesis.

![Scheme 3-1. An example of the Chichibabin pyridine synthesis](image)

The first synthetically useful pyridine synthesis was discovered by Arthur Rudolf Hantzsch in 1881.\(^7\) The Hantzsch pyridine synthesis is a multi-component organic
reaction, typically, which utilizes acetoacetate 3-15, formaldehyde, and ammonium salt in a 2:1:1 ratio to construct 1,4-dihydropyridine 3-16 (Scheme 3-2). Further oxidation of 1,4-dihydropyridine by FeCl₂ or KMnO₄ provides pyridine 3-17 in an one-pot manner.

\[
\text{EtO}_2\text{C} + \text{H}_2\text{C} + \text{NH}_2\text{OAc} \xrightarrow{\text{NH}_4\text{OAc}, \text{H}_2\text{O}, \text{reflux}, <1 \text{ h}} \text{EtO}_2\text{C} + \text{Me} \xrightarrow{\text{FeCl}_3, \text{reflux}, 2 \text{ h}} \text{EtO}_2\text{C} + \text{Me}
\]

\text{Scheme 3-2. An example of the Hantzsch pyridine synthesis}

The Guareschi-Thorpe pyridine synthesis is closely related to the Hantzsch synthesis but it utilizes cyanoacetamide 3-19 as a coupling partner. This modification involves condensation of 1,3-diketone 3-18 and cyanoacetamide 3-19 to generate enamide 3-20 as an intermediate which is followed by facile intramolecular dehydrative condensation to afford pyridine 3-21 (Scheme 3-3).

\[
\text{CO}_2\text{Et} + \text{H}_2\text{C} \xrightarrow{\text{K}_2\text{CO}_3, \text{acetone}, 84\%} \text{CO}_2\text{Et} \xrightarrow{\text{H}_2\text{N}, \text{Me}} \text{CO}_2\text{Et} \xrightarrow{\text{Me}} \text{CO}_2\text{Et}
\]

\text{Scheme 3-3. An example of the Guareschi-Thorpe pyridine synthesis}

The Bohlmann-Rahtz reaction is a two-component coupling of acetylenic ketone 3-22 and enamine 3-23 to furnish pyridine 3-24 directly without an external oxidant (Scheme 3-4). The reaction mechanism involves Michael addition of enamine 3-23 to acetylenic ketone 3-22 where the mechanism is parallel with that of the Chichibabin protocol but with higher efficiency.

\[
\text{Me} + \text{Et} \xrightarrow{\text{AcOH, toluene}, 50 \text{ °C}, 85\%} \text{Me} \xrightarrow{\text{Et}, \text{CO}_2\text{Et}} \text{Me}
\]

\text{Scheme 3-4. An example of the Bohlmann-Rahtz reaction}
When Kröhnke compared the structure and reactivity of phenylacylpyridinium betains to 1,3-dicarbonyl compounds, he noticed that both of them have similar nucleophilic reactivity towards the Michael addition. As such, the reaction of phenylacylpyridinium betain 3-25 and α,β-unsaturated ketone 3-12 proceeds smoothly in the presence of AcOH and NH₄OAc to furnish pyridine 3-14, that is known as the Kröhnke pyridine synthesis (Scheme 3-5).¹⁰

![Scheme 3-5. An example of the Kröhnke pyridine synthesis](image)

### 3.1.3 Modern methods for pyridine synthesis

As discussed above, early synthetic methods of pyridine normally require harsh conditions and/or suffer from low yields. Due to the importance of the pyridine moieties in bioactive pharmaceutical drugs, the development of highly efficient and versatile methodologies for pyridine synthesis is of great concern in synthetic organic chemistry. Over the past few years, various new synthetic methods for pyridine construction have been invented especially from simple precursors using transition metals.

As an example, Ellman and co-workers revealed synthesis of highly substituted pyridines from α,β-unsaturated N-benzyl imines and alkynes via Rh(I)-catalyzed C–H bond activation.¹¹ The reaction is initiated by Rh(I)-catalyzed C–H functionalization of α,β-unsaturated N-benzyl imine 3-26 with alkyne 3-27 to generate the corresponding aza-triene, which undergo facile 6π-electrocyclization to give 1,2-dihydropyridine 3-28 (Scheme 3-6). Removal of benzyl moiety of 3-28 using Pd/C as the catalyst, and subsequent oxidation afford pyridine 3-29.
Scheme 3-6. An example of Rh(I)-catalyzed synthesis of pyridines from imines and alkynes via C–H activation

On the other hands, Liesbeskind and co-workers developed pyridine synthesis from alkenyl boronic acids and α,β-unsaturated oximes (Scheme 3-7). They designed the cascade reaction comprising (1) Cu(II)-catalyzed C–N cross coupling of alkenyl boronic acid 3-31 with, α,β-unsaturated oxime 3-30 to furnish 3-azatriene 3-32, (2) 6π-electrocyclization of 3-32 to generate the corresponding 3,4-dihydropyridine, (3) aerobic oxidation to yield pyridine 3-33.

Scheme 3-7. An example of pyridine synthesis from alkenyl boronic acids and ketoxime O-carboxylates

Alternatively, Davies and Manning disclosed one-pot synthesis of multi-substituted pyridines via a Rh(II)-carbenoid-induced ring-expansion of isoxazoles. The approach involves generation of ring-expansion adduct 3-36 from isoxazole 3-34 and α,β-unsaturated diazoacetate 3-35 via Rh(II)-carbenoid. Under reflux conditions in toluene, adduct 3-36 undergoes either (1) a [3,3]-sigmatropic rearrangement (Claisen rearrangement) to generate 3,4-dihydropyridine 3-38 directly or (2) a ring-opening electrocyclization to give azatriene 3-37 and subsequent 6π-electrocyclization to generate 3-38 (Scheme 3-8). 3-38 tautomerizes to 1,4-dihydropyridine 3-39, which is oxidized to pyridine 3-40 by treatment with DDQ at room temperature.
Besides, Filisti and co-workers showed that construction of pyridines can also be achieved by intermolecular cyclizations of $N$-propargylic $\beta$-enaminones using a catalytic amount of CuBr.\textsuperscript{15} The process is initiated by the coordination of CuBr to the alkynyl moiety of \ref{3-41} to facilitate the intramolecular nucleophilic addition of enamine to alkyne (Scheme 3-9). Further protonation and oxidation provides pyridine \ref{3-42}.

Another strategy for pyridine synthesis is one example reported by our group utilizing Pd(II)-catalyzed ring-expansion reactions of cyclic 2-azidoalcohols.\textsuperscript{16} In a typical reaction, they envisioned that alkoxy-Pd(II) species A, which is generated from 2-azidoalcohol \ref{3-43}, undergoes $\beta$-carbon elimination and elimination of a molecular dinitrogen to give alkylideneaminometal species B. Subsequent intramolecular nucleophilic addition of the iminyl-Pd(II) part to the carbonyl moiety leading to intermediate C; Further protonation and dehydration afford pyridine \ref{3-44} (Scheme 3-10).
In addition, our group has also revealed a versatile synthetic method of pyridine by Mn(III)-catalyzed reactions of cyclopropanols and vinyl azides. A wide range of di- or tri-substituted pyridines can be synthesized by using this method. In a typical reaction, the proposed mechanism involves the addition of the β-keto radical A, generated from cyclopropanol 3-46 via one-electron oxidation by Mn(III), to vinyl azide 3-45 to generate the iminyl radical B with elimination of a molecular dinitrogen (Scheme 3-11). After the formation of the iminyl-Mn(III) intermediate C, nucleophilic attack of which to carbonyl moiety affords alkoxy-Mn(III) intermediate D, and subsequent protonation, dehydration and oxidation to give pyridine 3-47.
Recently, Yoshikai and co-workers developed a modular pyridine synthesis from oximes and \(\alpha,\beta\)-unsaturated aldehydes through synergistic copper/iminium catalysis (Scheme 3-12). They strategically utilize Cu(I) as the catalyst where Cu(I) is used to reduce N–O bond of oxime 3-48 to form enaminyl-Cu(II) species A at the first step and the generated Cu(I) is used to oxidized dihydropyridine to give pyridine 3-50 at the last step. Therefore, the overall transformation is a redox-neutral process. Iminium salt B generated from \(\alpha,\beta\)-unsaturated aldehyde 3-49 and pyrrolidinium perchlorate, is highly reactive towards the Michael addition of enaminyl-Cu(II) species A.

![Scheme 3-12. An example of Cu(I)-catalyzed synthesis of pyridines from oximes and \(\alpha,\beta\)-unsaturated aldehydes](image)

### 3.1.4 Synthetic plan for pyridines using \([\text{Cp}^*\text{RhCl}_2]\)_2 as a catalyst

Even though diverse approaches have been developed towards synthesis of pyridine, there still remains a challenge to develop versatile methods for pyridine synthesis with high regioselectivity.

As discussed in Chapter 2, we have successfully utilized aryl ketone \(O\)-acetyl oximes and alkynes for the synthesis of isoquinolines via sequential \([\text{Cp}^*\text{RhCl}_2]\)_2-catalyzed \(aryl\, C–H\) bond activation, alkyne insertion and \(C–N\) bond formation. Based on
the finding, our attention has been drawn to use \([\text{Cp}^*\text{RhCl}_2]_2\) as the catalyst for vinyllic C–H bond activation using \(\alpha,\beta\)-unsaturated oximes as a substrate for the pyridine synthesis (Scheme 3-13).

\[
\text{R}^3 - \overset{\text{NOR}}{\text{R}} - \overset{\text{R}}{\text{R}}^2 + \overset{\text{R}^4}{\text{R}}^5 \rightarrow [\text{Cp}^*\text{RhCl}_2]_2
\]

Scheme 3-13. Proposed reaction of Rh(III)-catalyzed synthesis of pyridines from \(\alpha,\beta\)-unsaturated oximes and alkynes

3.2 Results and discussion

3.2.1 Synthesis of \(\alpha,\beta\)-unsaturated oximes

As shown in Scheme 3-14, the synthesis of \(\alpha,\beta\)-unsaturated oximes begins with aldol condensation between aldehydes and ketones to afford the corresponding \(\alpha,\beta\)-unsaturated ketones. Subsequent treatment of \(\alpha,\beta\)-unsaturated ketones with hydroxylamine provides \(\alpha,\beta\)-unsaturated oximes 3-1.

\[
\text{R}^3 - \overset{\text{OH}}{\text{R}}^2 \rightarrow \overset{\text{NH}_2\text{OH}+\text{HCl}}{\text{EtOH, 60 °C}} \text{pyridine} \rightarrow \overset{\text{N}}{\text{R}}^1
\]

Scheme 3-14. Synthesis of \(\alpha,\beta\)-unsaturated oximes–1

Commercially available (E)-4-phenylbut-3-en-2-one and (1E,4E)-1,5-diphenyl-1,4-pentadien-3-one were used directly for the synthesis of \(\alpha,\beta\)-unsaturated oximes 3-1a and 3-1i. Generally, \(\alpha,\beta\)-unsaturated ketones with \(\text{R}^2 = \text{H}\) were prepared by treating arylaldehydes and ketones with NaOH in ethanol (Scheme 3-15 (a)). The corresponding \(\alpha,\beta\)-unsaturated ketones was subjected to hydroxylamine without further purification to afford 3-1b to 3-1h and 3-1m. Three different methods were used to synthesize other
substituted α,β-unsaturated ketones (R² ≠ H) for the preparation of 3-1j, 3-1k and 3-1l as shown in Scheme 3-15 (b), (c) and (d).

\[ R^3\text{CH} + R^1\text{CH}_2\text{R}^1 \xrightarrow{\text{NaOH}} \xrightarrow{\text{EtOH}} R^3\text{CH} = \text{CHR}^1 \rightarrow 3-1b \text{ to } 3-1h \text{ and } 3-1m \]

\[ \text{PhH} + \text{MeOCH} \xrightarrow{\text{H}_2\text{SO}_4} \xrightarrow{\text{AcOH, rt, 60 } ^\circ\text{C}} \text{MeCH} \rightarrow 3-1j \]

\[ \text{Me} + \xrightarrow{\text{morpholine (cat.)}} \xrightarrow{\text{AcOH reflux, 2 days}} \text{Me} \rightarrow 3-1k \]

\[ \text{PhCH} + \xrightarrow{\text{AcOH, reflux, 2 days}} \xrightarrow{\text{morpholine (cat.)}} \xrightarrow{\text{AcOH reflux, 2 days}} \text{Me} \rightarrow 3-1l \]

**Scheme 3-15. Synthesis of α,β-unsaturated oximes–2**

### 3.2.2 Optimization of reaction conditions

According to our synthetic plan in Scheme 3-13, we started to screen the reaction conditions for the synthesis of pyridine 3-3aa with (E)-4-phenyl-3-butene-2-one oxime derivatives 3-1a and diphenyl acetylene (3-2a) (1.2 equiv) using 2.5 mol % of [Cp*RhCl₂]₂ and 30 mol % of metal carboxylates as an additive in MeOH (Table 3-1).

At the first trial, O-acetyl oxime 3-1a' and alkyne 3-2a was treated under the optimized reaction conditions as discussed in Chapter 2.2.2 (2.5 mol % [Cp*RhCl₂]₂, 30 mol % NaOAc in MeOH at 60 °C) but under an air atmosphere. As expected, the reaction proceeded to give the desired pyridine 3-3aa in 49% yield after 24 h (Table 3-1, entry 1). To investigate the counter ion effect of the acetate source, CsOAc was used instead of NaOAc, that improved the yield of 3-3aa to 62% (Table 3-1, entry 2).
changing acetate (CsOAc) to other carboxylates such as pivalate (CsOPiv), shorter reaction time and higher yield were observed (Table 3-1, entry 3). The reaction with Cu(OAc)$_2$ did not afford the desired pyridine 3-3aa but resulting in decomposition of O-acetyl oxime 3-1a', probably due to the Lewis acidity of Cu(OAc)$_2$ (Table 3-1, entry 4).

Table 3-1. Optimization of reaction conditions$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime 3-1</th>
<th>additive</th>
<th>time / h</th>
<th>yield of 3-3aa / %$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-1a'</td>
<td>NaOAc</td>
<td>24</td>
<td>49</td>
</tr>
<tr>
<td>2</td>
<td>3-1a'</td>
<td>CsOAc</td>
<td>24</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>3-1a'</td>
<td>CsOPiv</td>
<td>10</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>3-1a'</td>
<td>Cu(OAc)$_2$</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3-1a''</td>
<td>CsOPiv</td>
<td>19</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>3-1a</td>
<td>CsOPiv</td>
<td>7</td>
<td>79</td>
</tr>
<tr>
<td>7$^c$</td>
<td>3-1a</td>
<td>CsOPiv</td>
<td>24</td>
<td>78</td>
</tr>
<tr>
<td>8$^d$</td>
<td>3-1a</td>
<td>CsOPiv</td>
<td>24</td>
<td>86</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise stated, reactions were carried out on the scale of 0.3 mmol of 3-1a and 1.2 equiv of 3-2a in MeOH (0.2 M) under an air atmosphere. $^b$ Isolated yields. $^c$ The reaction was conducted under an N$_2$ atmosphere. $^d$ The reaction was conducted using 0.3 mmol of alkyne 3-2a and 1.5 equiv of oxime 3-1a, and the yield of 3-3aa was calculated based on alkyne 3-2a.

Using the $[\text{Cp}^*\text{RhCl}_2]_2$-CsOPiv catalytic system, the effect of the R-substituent on the N–O bond of oxime was next examined. Our first approach is to change O-acetyl oxime 3-1a' to O-pivalyl oxime 3-1a'', however, a bulky protecting group did not result in a higher yield of pyridine 3-3aa (Table 3-1, entry 5). On the other hand, the reaction of $\alpha,\beta$-unsaturated oxime 3-1a proceeded smoothly to give pyridine 3-3aa in 79% yield within 7 h under the present conditions (Table 3-1, entry 6). The reaction under a molecular nitrogen atmosphere provided comparable yield of pyridine 3-3aa, albeit in longer reaction time (Table 3-1, entry 7). This phenomenon suggested that the presence
of air (molecular oxygen) may have a crucial role to maintain and accelerate the catalytic turnover. By using 1.5 equiv of α,β-unsaturated oxime 3-1a with diphenyl acetylene (3-2a), pyridine 3-3aa was formed in 86% yield (based on acetylene 3-2a) but longer reaction time of 24 h was required (Table 3-1, entry 8).

As predicted, pyridine 3-3aa was formed via a 1 to 1 coupling of α,β-unsaturated oxime 3-1a and alkyne 3-2a. However, the formation of 2-naphthylpyridine 3-4aa (1 to 3 coupling of 3-1a and 3-2a) was observed as a minor side product (<10% yield) in most of the entries in Table 3-1. The naphthyl moiety of 3-4aa was probably constructed from 3-3aa via additional two C–H bond activations and an alkyne double insertion. In fact, treatment of 3-1a with excess amounts (5 equiv) of alkyne 3-2a under the present reaction conditions delivered 3-4aa in 56% yield after a long reaction time of 54 h along with 32% yield of pyridine 3-3aa (Scheme 3-16). In this case, molecular oxygen may be used as the terminal oxidant to achieve the catalytic turnover. Similar Rh(III)-catalyzed multiple C–H bond activations has been reported by Miura and co-workers involving the synthesis of 1-naphthylpyrazoles from 1-phenylazoles and alkynes (Scheme 3-17).19

![Scheme 3-16. Rh(III)-catalyzed synthesis of 2-naphthylpyridine](image)

![Scheme 3-17. An example of Rh(III)-catalyzed synthesis of 1-naphthylpyrazoles](image)

*CsH2Ph4 = 1,2,3,4-tetraphenyldicyclopentadiene
3.2.3 Scope & limitations

With the optimized reaction conditions (Table 3-1, entry 6) on hand, the generality of alkynes 3-2 was first investigated using α,β-unsaturated oxime 3-1a (Table 3-2).

For symmetrical diaryl alkynes 3-2 bearing methoxy, trimethylsilyl or even bromo substituent on aryl moiety, those reactions proceeded smoothly to afford the corresponding pyridines 3-3ab to 3-3ac in good yields (Table 3-2, entries 1-3). Similarly, dialkyl alkynes 3-2e and 3-2f also showed high reactivity under the present reaction conditions to provide pyridine 3-3ae and 3-3af respectively in high yields of 75% and 69% respectively (Table 3-2, entries 4 and 5). Regioselectivity was observed for insertion of unsymmetrical alkynes 3-2g to 3-2i, albeit in moderate selectivity (Table 3-2, entries 6-8).

Table 3-2. Scope of Internal alkynes

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne 3-2</th>
<th>R4</th>
<th>R5</th>
<th>time / h</th>
<th>yield of 3-3 / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-2b</td>
<td>4-MeOC6H4</td>
<td>4-MeOC6H4</td>
<td>24</td>
<td>3-3ab 61</td>
</tr>
<tr>
<td>2</td>
<td>3-2c</td>
<td>4-TMSC6H4</td>
<td>4-TMSC6H4</td>
<td>10</td>
<td>3-3ac 60°C</td>
</tr>
<tr>
<td>3</td>
<td>3-2d</td>
<td>3-BrC6H4</td>
<td>3-BrC6H4</td>
<td>10</td>
<td>3-3ad 77</td>
</tr>
<tr>
<td>4</td>
<td>3-2e</td>
<td>n-Pr</td>
<td>n-Pr</td>
<td>8</td>
<td>3-3ae 75</td>
</tr>
<tr>
<td>5</td>
<td>3-2f</td>
<td>CH2OTBS</td>
<td>CH2OTBS</td>
<td>30</td>
<td>3-3af 69</td>
</tr>
<tr>
<td>6</td>
<td>3-2g</td>
<td>Me</td>
<td>Ph</td>
<td>8</td>
<td>3-3ag 97 (1.5:1)d</td>
</tr>
<tr>
<td>7c</td>
<td>3-2h</td>
<td>CO2Et</td>
<td>Ph</td>
<td>24</td>
<td>3-3ah 45 (1.5:1)d</td>
</tr>
<tr>
<td>8</td>
<td>3-2i</td>
<td>4-MeOC6H4</td>
<td>4-F2CC6H4</td>
<td>24</td>
<td>3-3ai 87 (2.3:1)d</td>
</tr>
</tbody>
</table>

a Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of 3-1a and 1.2 equiv of 3-2 in MeOH (0.2 M) under air atmosphere. b Isolated yield. c Oxime 3-1a was recovered in 32% yield. d The structure of major isomer was described.
On the other hand, the scope and limitation of α,β-unsaturated oximes 3-1 were studied with alkyne 3-2a or 3-2e under the present reaction conditions (Table 3-3). The results showed that benzene ring bearing electron-donating groups such as methoxy and methyl moieties could be introduced as the R³-substituent on the β-carbon regardless of the position of the substituents (Table 3-3, entries 1-3). Even benzene bearing a bromo substituent could be tolerated (Table 3-3, entry 4).

Table 3-3. Scope of α,β-unsaturated oximes

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime 3-1</th>
<th>alkyne 3-2</th>
<th>time</th>
<th>pyridine 3-3 / yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-1b (R³ = 4-OH-C₆H₄)</td>
<td>3-2e</td>
<td>20 h</td>
<td>3-3be: 60%</td>
</tr>
<tr>
<td>2</td>
<td>3-1c (R³ = 2-OH-C₆H₄)</td>
<td>3-2e</td>
<td>30 h</td>
<td>3-3ce: 63%</td>
</tr>
<tr>
<td>3</td>
<td>3-1d (R³ = 3-Me-C₆H₄)</td>
<td>3-2a</td>
<td>30 h</td>
<td>3-3da: 68%</td>
</tr>
<tr>
<td>4</td>
<td>3-1e (R³ = 4-Br-C₆H₄)</td>
<td>3-2a</td>
<td>12 h</td>
<td>3-3ea: 87%</td>
</tr>
<tr>
<td>5</td>
<td>3-1f</td>
<td>3-2a</td>
<td>24 h</td>
<td>3-3fa: 87%</td>
</tr>
<tr>
<td>6</td>
<td>3-1f</td>
<td>3-2e</td>
<td>24 h</td>
<td>3-3fe: 77%</td>
</tr>
<tr>
<td>7</td>
<td>3-1g</td>
<td>3-2a</td>
<td>24 h</td>
<td>3-3ga: 74%</td>
</tr>
</tbody>
</table>
Table 3-3. Scope of α,β-unsaturated oximes (continue)\textsuperscript{a}

\[
\begin{array}{cccc}
\text{entry} & \text{oxime 3-1} & \text{alkyne 3-2} & \text{time} & \text{pyridine 3-3 / yield}\textsuperscript{b} \\
8 & \begin{array}{c}
\text{3-1h} \\
\text{3-1i} \\
\text{3-1j} \\
\text{3-1k} \\
\text{3-1l}
\end{array} & \begin{array}{c}
\text{3-2a} \\
\text{3-2a} \\
\text{3-2a} \\
\text{3-2a} \\
\text{3-2a}
\end{array} & \begin{array}{c}
24\ h \\
7\ h \\
7\ h \\
10\ h \\
2\ h
\end{array} & \begin{array}{c}
\begin{array}{c}
\text{3-3ha: 53\%} \\
\text{3-3ia: 81\%} \\
\text{3-3ja: 66\%} \\
\text{3-3ka: 68\%} \\
\text{3-3la: 88\%}
\end{array}
\end{array}
\end{array}
\]

\textsuperscript{a} Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of 3-1 and 1.2 equiv of 3-2 in MeOH (0.2 M) under an air atmosphere. \textsuperscript{b} Isolated yield. \textsuperscript{c} The reaction was conducted using 1 equiv of alkyne 3-2a.

Both 2-naphthyl and 1-naphthyl (more bulky) could be installed on the β-carbon to afford pyridine 3-3fa, 3-3fe and 3-3ga in high yields (Table 3-3, entries 5-7). Heteroaryl moiety such as thienyl group was intact in the transformation (Table 3-3, entry 8). The reaction of dibenzylideneacetone oxime (3-1i) with diphenyl acetylene (3-2a)
proceeded smoothly to give 6-stylylpyridine 3-3ia in 81% yield after 7 h (Table 3-3, entry 9). It is worth noting that pentasubstituted pyridines 3-3ja and 3-3ka could be synthesized in good yields (Table 3-3, entries 10 and 11).

It is surprising that when 3-benzyl-3-buten-2-one oxime (3-11; R^3 = H) was employed, the reaction took place in a shorter reaction time of 2 h, affording 2,3,5,6-tetrasubstituted pyridine 3-3la in 88% yield (Table 3-3, entry 12). The result suggested that a less steric bulky R^3-substituent on the β-carbon has a positive effect on the reactivity of α,β-unsaturated oxime 3-11.

As shown, the present process showed a wide substrate tolerance with α,β-unsaturated oxime derivatives 3-1. However, when the methyl moiety of α,β-unsaturated oxime 3-1a was replaced to the isopropyl moiety, the stereochemistry of the N–O bond of α,β-unsaturated oxime 3-1m became a mixture of syn- and anti-isomers in 1:1.2 ratio. The reaction of 3-1m under the present conditions afforded pyridine 3-3ma in 40% yield along with recovery of oxime syn-3-1m in 25% yield (Scheme 3-18). The observation is consistent with Scheme 2-32 in Chapter 2.2.3.1. However, the possibility of N–O bond isomerization under the reaction conditions is still cannot be ruled out.²⁰

Scheme 3-18. Limitation of Rh(III)-catalyzed synthesis of pyridine
3.2.4 Proposed mechanism

In accordance with the proposed mechanism of Rh(III)-catalyzed isoquinoline formation as described in Chapter 2.2.4, the reaction is speculated to proceed via a similar 7-membered rhodacyclic iminium cation intermediate B.

A proposed catalytic pathway of Rh(III)-catalyzed pyridine synthesis is outlined in Scheme 3-19. It commences with *vinyl* C–H bond activation of α,β-unsaturated oxime 3-1a with assistance of the directing group, oxime via sp² nitrogen atom to give 5-membered rhodacycle A, and followed by alkyne insertion of 3-2a to afford 7-membered rhodacyclic iminium cation intermediate B. The catalytic cycle is completed by C–N bond reductive elimination in a stepwise (Scheme 3-19, path a) or concerted manner (Scheme 3-19, path b) to regenerate Rh(III) species and release pyridine 3-3aa.

To further investigate the C–N bond reductive elimination, pyridine N-oxide could be synthesized and subjected to α,β-unsaturated oxime 3-1a and alkyne 3-2a under the standard reaction condition. If pyridine N-oxide could be converted to the corresponding pyridine, then there is a high possibility that the C–N bond reductive elimination is a stepwise reaction pathway involving pyridine N-oxide.
3.3 Conclusion

In summary, we have developed a versatile method for the synthesis of highly substituted pyridines from α,β-unsaturated oximes and internal alkynes using [Cp*RhCl₂]₂-CsOPiv as the catalytic system. The present catalytic reaction could tolerate a wide range of α,β-unsaturated oximes and alkynes bearing different functional groups. It is noteworthy that pentasubstituted pyridines could be synthesized in good yields.

During the course of this study, Rovis and co-workers also revealed Rh(III)-catalyzed synthesis of pyridines from α,β-unsaturated oximes and alkynes with almost the same approach (Scheme 3-20).²¹

\[
\begin{align*}
\text{Ph}=\text{Me} & \quad \text{Me} \\
\text{OH} & \\
n-\text{Bu} & \quad n-\text{Bu} \\
\text{TFA, 45 °C} & \quad 65% \\
\text{K}_2\text{CO}_3 & \quad (2 \text{ equiv}) \\
\text{[Cp*RhCl₂]₂ (2.5 mol %)} & \quad \text{Scheme 3-20. An example of Rh(III)-catalyzed synthesis of pyridines from oximes and alkynes}
\end{align*}
\]

3.4 References

1 Niren, N. M. Cutis 2006, 77, 11.


Chapter 4 Synthesis of Azaheterocycles from Aryl Ketone O-Acetyl Oximes and Internal Alkynes by Cu–Rh Bimetallic Relay Catalysts

4.1 Introduction

As shown in Chapter 2, a wide scope of aryl ketone O-acetyl oximes were found to be promising precursors for the Rh(III)-catalyzed synthesis of isoquinolines with internal alkynes. However, when 4-1a (syn:anti = 1:1) which possesses a bulky alkyl substituent (isopropyl moiety) was treated with alkyne 4-2a under the previous optimized reaction conditions (2.5 mol % [Cp*RhCl]_2, 30 mol % NaOAc, MeOH, 60 ºC), the desired isoquinoline 4-3aa was formed in 54% along with recovery of syn-isobutyrophenone oxime in 36% yield via deacetylation (Scheme 4-1). The result suggested that only the anti-isomer is reacted due to the stereochemical requirement of oximes for the coordination of Cp*Rh(III) center (see more detail in Chapter 2.2.3.1). As a result, the drawback hinders the use of syn-isomers of oximes for the synthesis of isoquinolines bearing bulky substituents.

Scheme 4-1. Limitation of Rh(III)-catalyzed synthesis of Isoquinoline from mixture of syn- and anti-ketoximes

One of the methods to solve the problem is to fix the stereochemistry of oximes by using a cyclic analog of anti-O-acetyl oximes, 3-phenylisoxazol-5-ones for the synthesis of isoquinolines bearing bulky substituents (Scheme 4-2), which has been
discussed in Chapter 2.2.3.2. However, this method required a multi-step synthesis of substituted 3-phenylisoxazol-5-ones from the corresponding β-keto esters.

\[
\begin{align*}
\text{Scheme 4-2. An example of synthesis of isoquinolines from 3-phenylisoxazol-5-ones and alkynes}
\end{align*}
\]

Therefore, we strived to develop a more general strategy that could be applied for both syn- and anti-isomers of oximes. One of the possibilities to achieve this goal is to use iminyl metal species, which could be derived from both syn- and anti-isomers of oximes, as the intermediate because it should be free to isomerize between syn- and anti-isomers and resolves the stereochemical requirement. The reactivity of various oxime-derived iminyl-metal species has been explored.

For the case of iminyl-Pd(II) species, Narasaka and co-workers reported Pd(0)-catalyzed amino-Heck reactions of alkenyl O-acyl oximes, where both of syn- and anti-isomers of oximes could be employed for the cyclization (Scheme 4-3).\(^1\) The proposed mechanism involves an initial oxidative addition of the N-O bonds of oximes to Pd(0) to afford iminyl-Pd(II) species A, which are facile toward intramolecular Heck reactions.

\[
\begin{align*}
\text{Scheme 4-3. An example of Pd(0)} & \text{-catalyzed amino-Heck reactions of alkenyl O-acyl oximes via iminyl-Pd(II) species}
\end{align*}
\]

On the other hand, Hartwig and co-workers isolated (E)-iminyl-Pd(II) complex A generated via oxidative addition of the N-O bond of O-pentafluorobenzoyloxime 4-10 to a Pd(0) complex, and characterized its structure by X-ray crystallographic analysis which
revealed that the bond angle of C=N–Pd(II) is about 120 degrees (Scheme 4-4). Further treatment of isolated complex A with 1 equiv of CsCO₃ in toluene at 150 °C affords indole 4-11 in 31% yield. In the case, isomerization of (E)-isomer of iminyl–Pd(II) complex A to (Z)-isomer should occur prior to the cyclization. Based on the experimental results from both Narasaka and Hartwig, iminyl–Pd(II) species should be free to isomerize between syn- and anti-isomers.

![Scheme 4-4. Synthesis of indole from isolated iminyl–Pd(II) species](image)

On the other hand, Liebeskind and co-workers reported Cu(I)/Cu(II)-catalyzed synthesis of N-substituted imines by N-imination of boronic acids with O-acyl oximes via iminyl–Cu(II) species. Both CuTc (copper(I) thiophene-2-carboxylate) and Cu(OAc)₂ are suitable for the transformation, where CuTc is used as the catalyst in most of the substrates. Separate treatments of syn- and anti-isomers of oxime 4-12 with boronic acid 4-13 in the presence of Cu(OAc)₂ as the catalyst result in the formation of N-aryl imines 4-14 (syn:anti = 1:2) in both cases (Scheme 4-5). These results implied that free isomerization between syn- and anti-isomers of the iminyl–Cu(II) species exists.

![Scheme 4-5. An example of Cu(II)-catalyzed N-imination of boronic acids with O-acyl oximes via iminyl–Cu(II) species](image)
Therefore, we intend to reduce the N–O bond of oximes as an initiation process by using lower valent transition metals \([M^n]\) such as Cu(I) and Pd(0) complexes to generate the corresponding iminyl–metal species (Scheme 4-6). If \([M^n]\) and \([\text{Cp}^*\text{RhCl}_2]\) work independently for two-electron reduction of aryl ketone O-acetyl oximes and C–H bond activation respectively in the same reaction system, the resulting iminyl–metal species may undergo transmetallation with \([\text{Cp}^*\text{Rh}(\text{III})]\) species to give iminyl–\([\text{Cp}^*\text{Rh}(\text{III})]\) intermediates, which is facile to undergo sequential ortho C–H rhodation, alkyne insertion and reductive elimination to afford isoquinolines.

![Scheme 4-6. Proposed reaction of syn- and anti-O-acetyl oximes with alkynes](image)

4.2 Results and discussion

4.2.1 Synthesis of O-acetyl oxime derivatives

Using a similar method as described in Scheme 2-31 in Chapter 2.2.1, aryl O-acetyl oximes 4-1 and heteroaryl O-acetyl oximes 4-4 were prepared from the corresponding ketones via treatment with hydroxylamine and acetic anhydride (Scheme 4-7). Aryl O-acetyl oximes 4-1a, 4-1d & 4-1e as well as heteroaryl O-acetyl oximes 4-4g & 4-4h were formed in a mixture of syn- and anti-isomers; 4-1b was generated in a pure syn-isomer; 4-1c, 4-4a to 4-4f and 4-4i were generated in pure anti-isomers.
anti-morpholino(phenyl)methanone O-acetyl oxime (4-1f) was prepared using a different method (Scheme 4-8). Treatment of benzaldehyde with hydroxylamine provided benzaldehyde oxime which was then reacted with N-chlorosuccinimide (NCS) and morpholine to generate anti-morpholino(phenyl)methanone oxime. Final acetylation with acetic anhydride yielded 4-1f.

![Scheme 4-7. Synthesis of O-acetyl oximes from ketones](image)

4.2.2 Optimization of reaction conditions

Based on our working hypothesis as shown in Scheme 4-6, the reaction of isobutyrophenone O-acetyl oxime (4-1a; syn:anti = 1:1) and diphenylacetylene (4-2a) was carried out to examine the effect of metal reductants such as Pd(0) and Cu(I) complexes in the presence of 2.5 mol % [Cp*RhCl]2 (Table 4-1). The initial investigation was conducted using Pd(dba)2 as an reductant and NaOAc as an acetate source in DMF, while a complex mixture was observed with the formation of the desired isoquinoline 4-3aa in 14% yield after 15 h (Table 4-1, entry 1). By changing the reductant from Pd(dba)2 to Pd(PPh3)4, no improvement was observed (Table 4-1, entry 2).
Table 4-1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>additive (mol %)</th>
<th>solvent</th>
<th>time</th>
<th>yield of 4-3aa / %b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(dba)₂ (20) + NaOAc (30)</td>
<td>DMF</td>
<td>15 h</td>
<td>14c</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄ (20) + NaOAc (30)</td>
<td>DMF</td>
<td>15 h</td>
<td>19c</td>
</tr>
<tr>
<td>3</td>
<td>CuOAc (10)</td>
<td>DMF</td>
<td>45 min</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>Cu(II)(OAc)₂ (10)</td>
<td>DMF</td>
<td>4 h</td>
<td>95</td>
</tr>
<tr>
<td>5d</td>
<td>Cu(II)(OAc)₂ (10)</td>
<td>DMF</td>
<td>24 h</td>
<td>20e</td>
</tr>
<tr>
<td>6</td>
<td>Cu(II)(OAc)₂ (10)</td>
<td>MeOH</td>
<td>1 h</td>
<td>80f</td>
</tr>
<tr>
<td>7</td>
<td>Cu(II)(OAc)₂ (10)</td>
<td>toluene</td>
<td>22 h</td>
<td>0g</td>
</tr>
</tbody>
</table>

a Reactions were carried out on the scale of 0.3 mmol of oxime 4-1a and 1.2 equiv of alkyne 4-2a in solvent (0.2 M) at 60 °C under N₂ atmosphere. b Isolated yield. c The reaction resulted in a complex mixture. d The reaction was conducted under an air atmosphere. e Oxime 4-1a was recovered in 40% yield. f Deacetylated oxime was formed in 15% yield. g Oxime 4-1a was recovered in 51% yield.

To our surprise, when 10 mol % of Cu(II)OAc was used as the reductant and also the acetate source, the reaction proceeded smoothly in DMF under a molecular nitrogen atmosphere to afford isoquinoline 4-3aa in 99% yield within 45 minutes (Table 4-1, entry 3); the result clearly showed that both syn- and anti-isomers of O-acetyl oxime 4-1a reacted in the presence of Cu(II)OAc as the reductant. It is worth to note that the use of Cu(II)(OAc)₂ instead of Cu(II)OAc provided 4-3aa in comparable yield, even though a longer reaction time (4 h) was required (Table 4-1, entry 4). In this case, Cu(I) species was believed to be the active catalyst as it might be generated *in situ* via reduction of Cu(II)(OAc)₂ by DMF. The speculation could be supported by observation of the sluggish reaction under an air atmosphere (Table 4-1, entry 5); implying that *in situ* generated Cu(I) species was oxidized to Cu(II) species in the presence of molecular oxygen and resulted in slow reaction rate with recovery of 4-1a in 40% yield even after 24 h.
Instead of using DMF as the solvent, the reaction with Cu$^{II}$(OAc)$_2$ in MeOH also proceeded to afford isoquinoline 4-3aa in 80% yield but along with the formation of deacetylated oxime in 15% yield (Table 4-1, entry 6). The use of solvent with no redox ability such as toluene resulted in the complete inhibition of the reaction (Table 4-1, entry 7).

When a control experiment was carried out with Cu$^{II}$(OAc)$_2$ but without [Cp*RhCl$_2$], no isoquinoline 4-3aa formation was observed. Therefore, the experimental results indicated that synergistic Cu–Rh cooperation should be indispensable for the present isoquinoline formation from syn- and anti-isomers of O-acetyl oximes. Even though the use of Cu'I(OAc) provided isoquinoline 4-3aa in higher yield with shorter reaction time, Cu$^{II}$(OAc)$_2$ was utilized as the co-catalyst for the ease of handling because Cu'I(OAc) is very sensitive to air, moisture, and light.

4.2.3 Scope & limitations

4.2.3.1. Synthesis of isoquinolines

By using the optimized [Cp*RhCl$_2$]$_2$–Cu(OAc)$_2$ catalytic system (Table 4-1, entry 4), the generality of aryl ketone O-acetyl oximes 4-1 and alkynes 4-2 were examined for the synthesis of isoquinolines (Table 4-2). Both methoxy- and bromo-substituted diaryl alkynes 4-2b and 4-2c reacted smoothly with isobutyrophenone O-acetyl oxime (4-1a; syn:anti = 1:1) to afford isoquinolines 4-3ab and 4-3ac in high yields respectively (Table 4-2, entries 1 and 2). Similarly, symmetrical dialkyl alkynes 4-2d and 4-2e also showed high reactivity under the present reaction conditions to provide corresponding isoquinolines in good yields (Table 4-2, entries 3 and 4).
Table 4-2. Synthesis of isoquinolines from syn- and/or anti-O-acetyl oximes and alkynes

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime 4-1 (syn:anti)</th>
<th>alkynes 4-2</th>
<th>isoquinoline 4-3 / yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-1a (1:1)</td>
<td>4-2b (R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = 4-OMe-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>4-3ab: 87%</td>
</tr>
<tr>
<td>2</td>
<td>4-1a (1:1)</td>
<td>4-2c (R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = 4-Br-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>4-3ac: 92%</td>
</tr>
<tr>
<td>3</td>
<td>4-1a (1:1)</td>
<td>4-2d (R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = n-Pr)</td>
<td>4-3ad: 78%</td>
</tr>
<tr>
<td>4</td>
<td>4-1a (1:1)</td>
<td>4-2e (R&lt;sup&gt;3&lt;/sup&gt; = R&lt;sup&gt;4&lt;/sup&gt; = CH&lt;sub&gt;2&lt;/sub&gt;OBS)</td>
<td>4-3ae: 79%</td>
</tr>
<tr>
<td>5</td>
<td>4-1a (1:1)</td>
<td>4-2f (R&lt;sup&gt;3&lt;/sup&gt; = Me, R&lt;sup&gt;4&lt;/sup&gt; = Ph)</td>
<td>4-3af: 93%</td>
</tr>
<tr>
<td>6</td>
<td>4-1a (1:1)</td>
<td>4-2g (R&lt;sup&gt;3&lt;/sup&gt; = CH&lt;sub&gt;2&lt;/sub&gt;OBS, R&lt;sup&gt;4&lt;/sup&gt; = Ph)</td>
<td>4-3ag: 98% (13:1)&lt;sup&gt;c,d&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>4-1a (1:1)</td>
<td>4-2h (R&lt;sup&gt;3&lt;/sup&gt; = CO&lt;sub&gt;2&lt;/sub&gt;Et, R&lt;sup&gt;4&lt;/sup&gt; = Ph)</td>
<td>4-3ah: 75% (1.7:1)&lt;sup&gt;d,a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>4-1a (1:1)</td>
<td>4-2i (R&lt;sup&gt;3&lt;/sup&gt; = n-hexyl, R&lt;sup&gt;4&lt;/sup&gt; = 2-thienyl</td>
<td>4-3ai: 81%</td>
</tr>
<tr>
<td>9</td>
<td>4-1b (syn)</td>
<td>Ph=ㅡ=Ph</td>
<td>4-2a: 99%</td>
</tr>
<tr>
<td>10</td>
<td>4-1c (anti)</td>
<td>4-2a</td>
<td>4-3ca: 94%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of oxime 4-1 and 1.2 equiv of alkyne 4-2 in DMF (0.2 M) at 60 °C for 4-10 h under N<sub>2</sub> atmosphere.

<sup>b</sup> Isolated yield.

<sup>c</sup> Isolated as a mixture of 2 regioisomers and the regioselectivity is based on <sup>1</sup>H NMR.

<sup>d</sup> The structure of major isomer was described.

<sup>e</sup> The reaction was conducted for 22 h.

Insertion of unsymmetrical alkyne, 1-phenyl-1-propyne (4-2f) occurred regioselectively to give one regioisomer, isoquinoline 4-3af in high yield (Table 4-2, entry 5); similar observation was achieved using alkyne 4-2i bearing 2-thienyl moiety (Table 4-2, entry 8). High regioselectivity was observed for alkyne 4-2g bearing...
trimethylsilyl moiety (Table 4-2, entry 6); in contrast, low regioselectivity was observed for ethyl 3-phenylpropionate (4-2h) (Table 4-2, entry 7).

It is worth noting that even the reaction of pure \textit{syn}-isomer, \textit{t}-butyl ketone \textit{O}-acetyl oxime 4-1b proceeded smoothly to afford the corresponding isoquinoline 4-3ba in excellent yield (Table 4-2, entry 9). For the case of pure \textit{anti}-isomer, 1,2-diphenylethanone \textit{O}-acetyl oxime (4-1c), isoquinoline 4-3ca was formed in 94% yield with benzyl moiety remained intact (Table 4-2, entry 10). These results showed that both \textit{syn}- and \textit{anti}-oximes could react independently under the present reaction conditions.

In the case of the reaction of 1,2,2-triphenylethanone \textit{O}-acetyl oxime (4-1d), isoquinoline 4-3da was formed selectively in 78% yield (Scheme 4-9 (a)), while Hartwig and co-workers reported that this kind of oximes can be utilized for the synthesis of indoles via Pd(0)-catalyzed intramolecular C–H amination (Scheme 4-9 (b)).

When cyclopropyl ketone \textit{O}-acetyl oxime 4-1e (\textit{syn:anti} = 1:2.2) was treated with diphenylacetylene (4-2a) under the present reaction conditions, cyclopropyl isoquinoline 4-3ea was formed in 57% yield along with the unexpected alkenyl isoquinoline 4-3ea' in 30% yield as an \textit{E,Z}-mixture of 6.5:1 (Scheme 4-10). Several experiments were performed to trace the formation of alkenyl isoquinoline 4-3ea'. First, independent...
treatment of cyclopropyl isoquinoline 4-3ea with or without alkyne 4-2a under the present reaction conditions showed no reactions in both cases, thus, the formation of alkenyl isoquinoline 4-3ea' is not due to the cyclopropyl ring-opening of isoquinoline 4-3ea. Secondly, the reactions of cyclopropyl ketone O-acetyl oxime 4-1e and alkyne 4-2a were conducted in the presence of D₂O or in DMF-d₇; the results showed no deuterium incorporation at the methyl vinyl part of 4-3ea' in both experiments. We are still not certain as to the reaction pathway of alkenyl isoquinoline 4-3ea' formation with the current experimental details.

To examine the reactivity of amidoxime, anti-isomer of aryl O-acetyl amidoxime 4-1f was subjected to the standard reaction conditions (2.5 mol % [Cp*RhCl₂]₂, 10 mol % Cu(OAc)₂ in DMF at 60 °C), while the reaction became sluggish to give isoquinoline 4-3fa in 19% yield only (Scheme 4-11). When the catalytic loading of [Cp*RhCl₂]₂ and Cu(OAc)₂ were increased to 5 mol % and 20 mol % respectively, the reaction proceeded to afford isoquinoline 4-3fa in 41% yield. Usage of 10 mol % of [Cp*RhCl₂]₂ and 40 mol % of Cu(OAc)₂ resulted in the formation of 4-3fa in 48% yield.
4.2.3.2. Synthesis of β-carbolines and other azaheterocycles

The successful transformation of aryl ketone O-acetyl oximes and alkynes to isoquinolines using this [Cp*RhCl₂]₂–Cu(OAc)₂ catalytic system probed us to examine the potential utility of heteroaryl ketone O-acetyl oximes for the synthesis of other azaheterocycles. The reaction of indolyl ketone O-acetyl oxime 4-4a (pure anti-isomer) with 1.5 equiv of diphenylacetylene (4-2a) with 2.5 mol % of [Cp*RhCl₂]₂ and 30 mol % of Cu(OAc)₂ in DMF at 60 °C resulted in the formation of β-carbolines 4-5aa in 82% yield (Table 4-3, entry 1), whereas the reaction under the previous [Cp*RhCl₂]₂–NaOAc catalytic system gave β-carbolines 4-5aa in 42% yield only along with the isolation of deacetylated oxime 4-6a in 25% yield (Scheme 4-12).

![Scheme 4-12. The reaction of indolyl ketone O-acetyl oxime and alkyne under previous [Cp*RhCl₂]₂–NaOAc catalytic system](image)

This finding prompted us to explore the generality of alkynes and indolyl ketone O-acetyl oxime derivatives for β-carbolines synthesis under the [Cp*RhCl₂]₂–Cu(OAc)₂ catalytic system. First of all, the reactivity of various alkynes were examined with indolyl ketone O-acetyl oxime 4-4a under the present conditions. The results showed that di(4-bromophenyl)acetylene (4-2c) proceeded smoothly to provide β-carbolines 4-5ac in 69% yield (Table 4-3, entry 3), while di(4-methoxyphenyl)acetylene (4-2b) give β-carbolines 4-5ab in low yield of 28% (Table 4-3, entry 2). Dialkyl alkyne, 4-octyne (4-2d) reacted smoothly to afford β-carbolines 4-5ad in 87% yield (Table 4-3, entry 4).
Insertion of unsymmetrical alkynes $4-2f$ and $4-2g$ proceeded albeit with lower regioselectivity (Table 4-3, entries 5 and 6) compared to that of the isoquinoline formation (see Table 4-2). In the case of methyl 3-phenylpropiolate ($4-2j$), $\beta$-carboline $4-5aj$ was formed in high yield of 71% with no control of regioselectivity (Table 4-3, entry 7).

To test the scope and limitation of $R^2$-substituent, indolyl ketone $O$-acetyl oximes $4-4$ bearing different functional groups were subjected to the present reaction conditions.

---

**Table 4-3. Synthesis of $\beta$-carbolines from $O$-acetyl oximes and alkynes**

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime 4-4</th>
<th>alkyne 4-2</th>
<th>$\beta$-carboline 4-5 / yield$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-4a (anti)</td>
<td>4-2a ($R^3 = R^4 = \text{Ph}$)</td>
<td>4-5aa: 82%</td>
</tr>
<tr>
<td>2</td>
<td>4-4a (anti)</td>
<td>4-2b ($R^3 = R^4 = 4-\text{OMe-C}_6\text{H}_4$)</td>
<td>4-5ab: 28%$^c$</td>
</tr>
<tr>
<td>3</td>
<td>4-4a (anti)</td>
<td>4-2c ($R^3 = R^4 = 4-\text{Br-C}_6\text{H}_4$)</td>
<td>4-5ac: 69%$^c$</td>
</tr>
<tr>
<td>4</td>
<td>4-4a (anti)</td>
<td>4-2d ($R^3 = R^4 = \text{n-Pr}$)</td>
<td>4-5ad: 87%</td>
</tr>
<tr>
<td>5</td>
<td>4-4a (anti)</td>
<td>4-2f ($R^3 = \text{Me, } R^4 = \text{Ph}$)</td>
<td>4-5af: 65% (5:1)$^d$</td>
</tr>
<tr>
<td>6</td>
<td>4-4a (anti)</td>
<td>4-2g ($R^3 = \text{CH}_2\text{OTBS, } R^4 = \text{Ph}$)</td>
<td>4-5ag: 50% (3:1)$^d$</td>
</tr>
<tr>
<td>7</td>
<td>4-4a (anti)</td>
<td>4-2j ($R^3 = \text{CO}_2\text{Me, } R^4 = \text{Ph}$)</td>
<td>4-5aj: 71% (1:1)$^d$</td>
</tr>
<tr>
<td>8</td>
<td>4-4b ($R^2 = \text{n-Bu, anti}$)</td>
<td>4-2d</td>
<td>4-5bd: 91%</td>
</tr>
<tr>
<td>9</td>
<td>4-4c ($R^2 = \text{CH}_2\text{CH}_2\text{CH} = \text{CH}_2, \text{anti}$)</td>
<td>4-2d</td>
<td>4-5cd: 36%$^{c,e}$</td>
</tr>
<tr>
<td>10</td>
<td>4-4d ($R^2 = \text{CO}_2\text{Et, anti}$)</td>
<td>4-2d</td>
<td>4-5dd: 60%$^c$</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of oxime 4-4 and 1.5 equiv of alkyne 4-2 in DMF (0.2 M) at 60 °C for 2−9 h under N₂ atmosphere. $^b$ Isolated yield. $^c$ The reaction was conducted using 5 mol % of [Cp*RhCl₂]. $^d$ The structure of the major isomer was described. $^e$ Deacetylated product of oxime 4-4c was observed in 16% yield.
Indolyl ketone O-acetyl oxime 4-4 bearing linear alkyl chain and ester moiety reacted smoothly to give β-carbolines 4-5bd and 4-5dd in 91% and 60% yield respectively (Table 4-3, entries 8 and 10). Even though O-acetyl oxime 4-4c bearing alkenyl moiety was tolerated under the reaction conditions, low yield was observed (Table 4-3, entry 9).

A wide scope of indolyl ketone O-acetyl oximes 4-4 was demonstrated. However, the reaction of indolyl carbaldehyde O-acetyl oxime (4-4e) with 4-octyne (4-2d) resulted in the formation of β-carboline 4-5ed in 40% yield only along with carbonitrile 4-7 in 51% yield (Scheme 4-13). The formation of carbonitrile 4-7 might be due to spontaneous elimination of AcOH from indolyl carbaldehyde O-acetyl oxime (4-4e) under the present conditions. Similar reaction pathway on the formation of carbonitriles from O-acetyl aldoxime has been reported.5

![Scheme 4-13. Limitation of using indolyl carbaldehyde O-acetyl oxime as the precursor](image)

In addition, other heteroaryl ketone O-acetyl oximes bearing benzofuranyl, furanyl, thieryl and pyrrolyl moieties demonstrated high reactivity toward 4-octyne (4-2d), providing the corresponding azaheterocycles in high yields (Table 4-4).
Table 4-4. Synthesis of other azaheterocycles from O-acetyl oximes and alkynes$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>oxime 4-4 (syn:anti)</th>
<th>azaheterocycles 4-5 / yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="4-4" /> 4-4f (anti)</td>
<td><img src="image" alt="4-5" /> 4-5fd: 86%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="4-4" /> 4-4g (1:20)</td>
<td><img src="image" alt="4-5" /> 4-5gd: 77%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="4-4" /> 4-4h (1:4)</td>
<td><img src="image" alt="4-5" /> 4-5hd: 81%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="4-4" /> 4-4i (anti)</td>
<td><img src="image" alt="4-5" /> 4-5id: 91%</td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of oxime 4-4 and 1.5 equiv of alkyne 4-2 in DMF (0.2 M) at 60 °C for 2–9 h under N$_2$ atmosphere. $^b$ Isolated yield.
4.2.4 Proposed mechanism

A proposed mechanism of \([\text{Cp}^*\text{RhCl}_2]_2-\text{Cu(OAc)}_2\) bimetallic catalytic system is outlined in Scheme 4-14. As an initiation process, \(\text{Cu}^{II}(\text{OAc})_2\) may be reduced by DMF to form \(\text{Cu}(I)\) species (Scheme 4-14, step (i)). The proposed initiation step is based on the experimental result where the use of \(\text{Cu}^{I}\text{OAc}\) results in higher yield and shorter reaction time compared to \(\text{Cu}^{II}(\text{OAc})_2\) (Table 4-1, entries 3 and 4).

There are two possible pathways for the generation of iminyl–Cu(II)/Cu(III) intermediate (Scheme 4-14, step (ii)). The first pathway is the direct generation of iminyl–Cu(III) intermediate \(A\) via oxidative addition of the N–O bond of \(O\)-acetyl oxime 4-1a. Alternate pathway is the formation of iminyI–Cu(II) intermediate \(A'\) via a 3-step process including (1) single electron reduction of \(O\)-acetyl oxime 4-1a by Cu(I) species; (2) homolytic N–O bond cleavage of anion radical; (3) further reduction by another Cu(I) species provides iminyl–Cu(II) intermediate \(A'\).

Intermediate \(A\) or \(A'\) undergoes transmetallation with \(\text{Cp}^*\text{Rh}(III)\) species and followed by ortho C–H bond activation and subsequent alkyne insertion to generate rhodacycle \(D\) (Scheme 4-14, step (iii)). C–N bond reductive elimination of rhodacycle \(D\) provides isoquinoline 4-3aa. To regenerate the active \(\text{Cp}^*\text{Rh}(III)\) and Cu(I) species, the final step involves a redox process between \(\text{Cp}^*\text{Rh}(I)\) and \(\text{Cu}(II)/\text{Cu}(III)\) (Scheme 4-14, step iv).

\[
\begin{align*}
\text{4-1a} & \quad \text{Cu}^{I}\text{OAc} (1.2 \text{ equiv}) \quad \text{DMF, 60 °C, 5 h} \quad \text{[Cu]} \quad \text{hydrolysis} \\
& \quad \text{isobutyrophenone} \\
\end{align*}
\]

Scheme 4-15. The formation of ketone via hydrolysis of iminyl-Cu(II)/(III) intermediate

To examine the proposed formation of iminyl–Cu(II)/(III) intermediate, \(O\)-acetyl oxime 4-1a was treated with 1.2 equiv of \(\text{Cu}^{I}\text{OAc}\) in DMF at 60 °C for 5 h (Scheme 4-14, step iv).
The corresponding isobutyrophenone, which could be formed via hydrolysis of iminyl–Cu(II)/Cu(III) species, was isolated in 27% yield.

\[(\text{i}) \quad \text{generation of Cu(I) species by reduction of Cu}^{II}(\text{OAc})_{2} \quad \text{with DMF} \]
\[
\begin{align*}
  \text{Cu}^{II}(\text{OAc})_{2} + \text{DMF} & \rightarrow [\text{Cu}^I] \\
\end{align*}
\]

\[(\text{ii}) \quad \text{reductive formation of iminyl–Cu intermediate from O-acetyloxime and Cu(I) species} \]

\[
\text{via oxidative addition}
\]
\[
\begin{align*}
  \text{4-1a} & \xrightarrow{[\text{Cu}^I]} \text{iminyl–Cu(III) intermediate A*} \\
  \text{oxime anion radical} & \rightarrow [\text{Cu}^{III}] - \text{OAc} \\
\end{align*}
\]

\[
\text{via one-electron reduction}
\]
\[
\begin{align*}
  \text{4-1a} & \xrightarrow{[\text{Cu}^I]} \text{iminyl–Cu(II) intermediate A} \\
\end{align*}
\]

\[(\text{iii}) \quad \text{transmetallation, ortho C–H rhodation, alkyne insertion, and C–N reductive elimination} \]

\[(\text{iv}) \quad \text{redox generation of Rh(III) and Cu(I) species} \]

\[
\begin{align*}
  \text{[Cp*Rh] + 2 [Cu]} & \rightarrow [\text{Cp*Rh}^{III}] + 2 [\text{Cu}] \\
  \text{[Cp*Rh] + [Cu]} & \rightarrow [\text{Cp*Rh}^{III}] + [\text{Cu}] \\
\end{align*}
\]

\[
\text{[Rh] = Rh(OAc)}_{n}
\]

Scheme 4-14. Proposed Mechanism
4.3 Application to 1,8-diazapyrene synthesis

Molecular structures with highly \( \pi \)-conjugated system such as oligomeric porphyrin derivatives\(^7\) have been demonstrated to possess large two-photon absorption (TPA) cross sections. However, the development of short synthetic routes for the synthesis of \( \pi \)-conjugated molecules possessing efficient two-photon-excited violet-blue emission has remained an important challenge.

In view of applying this method for the synthesis of planar \( \pi \)-conjugated 1,8-diazapyrene, 1,4-naphthoquinone \( O,O \)-diacetyl dioxime (4-8) was prepared from 1,4-naphthoquinone via hydroxylamination and acetylation (see Scheme 4-7). The reaction of \( O,O \)-diacetyl dioxime 4-8 and 2 equiv of internal alkynes with 5 mol % of [Cp*RhCl\(_2\)]\(_2\) and 20 mol % of Cu(OAc)\(_2\) in DMF at 60 °C resulted in the concurrent formation of two pyridine rings affording the corresponding 1,8-diazapyrenes 4-9 (Table 4-5). It is worth to note that this is the first example to construct 1,8-diazapyrene structures.

Both non- or bromo-substituted diaryl alkynes reacted smoothly with diacetyl dioxime 4-8 to afford 1,8-diazapyrenes 4-9a and 4-9c in high yields respectively (Table 4-5, entries 1 and 3), while methoxy-substituted diarylalkyne gave 1,8-diazapyrene in low yield (Table 4-5, entry 2). The reaction with 4-octyne (4-2d) gave 1,8-diazapyrene 4-9d in moderate yield only (Table 4-5, entry 4). In the reaction with 1-phenyl-1-propyne (4-2e), high regioselectivity was observed (Table 4-5, entry 5). In contrast, almost no regioselectivity was observed for unsymmetrical alkyne bearing ester moiety (Table 4-5, entry 6).

It is worth noting that the reaction of \( O,O \)-diacetyl dioxime 4-8 and 2 equiv of alkyne 4-2a under the previous [Cp*RhCl\(_2\)]\(_2\)-NaOAc catalytic system (2.5 mol % of [Cp*RhCl\(_2\)]\(_2\) and 30 mol % of NaOAc in MeOH at 60 °C) resulted in the decomposition of 4-8 without product formation.
Table 4-5. One step synthesis of 1,8-diazapyrenes from O,O-diacetyl dioxime of naphthoquinone and alkynes

<table>
<thead>
<tr>
<th>entry</th>
<th>alkyne 4-2</th>
<th>R^3</th>
<th>R^4</th>
<th>1,8-diazapyrene 4-9 / yield^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4-2a</td>
<td>Ph</td>
<td>Ph</td>
<td>4-9a: 77%</td>
</tr>
<tr>
<td>2</td>
<td>4-2b</td>
<td>4-OMe-C6H4</td>
<td>4-OMe-C6H4</td>
<td>4-9b: 34%</td>
</tr>
<tr>
<td>3</td>
<td>4-2c</td>
<td>4-Br-C6H4</td>
<td>4-Br-C6H4</td>
<td>4-9c: 71%</td>
</tr>
<tr>
<td>4</td>
<td>4-2d</td>
<td>n-Pr</td>
<td>n-Pr</td>
<td>4-9d: 33%</td>
</tr>
<tr>
<td>5</td>
<td>4-2f</td>
<td>Me</td>
<td>Ph</td>
<td>4-9f: 67% (7.4:1)^c,d</td>
</tr>
<tr>
<td>6</td>
<td>4-2h</td>
<td>CO2Et</td>
<td>Ph</td>
<td>4-9h: 59% (1:1.1)^d</td>
</tr>
</tbody>
</table>

^a Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of oxime 4-8 and 2 equiv of alkene 4-2 in DMF (0.2 M) at 60 °C under N2 atmosphere. ^b Isolated yield. ^c Isolated as a mixture of 2 regioisomers and the regioselectivity was calculated from 1H NMR. ^d The parenthesis showed the ratio of symmetrical 1,8-diazapyrene 4-9 to unsymmetrical 1,8-diazapyrene 4-9'.

To test the electronic properties of 1,8-diazapyrenes, 4-9a, 4-9c, 4-9d and 4-9f were subjected to TPA cross section measurement by pumping with femtosecond pulses. This is a collaboration work with Sun and co-workers who helps in photoluminescence (PL) and UV-Vis measurements. It was found that these 1,8-diazapyrenes 4-9 possess efficient two-photon-excited PL emission in the deep blue region, which can be easily observed by the naked eyes, as shown in Figure 4-1 (c). Figure 4-1 (b) logarithmically shows the PL integrated intensity versus the excitation power of 780 nm laser. All the plots have slopes near 2, which coincides with the requirement on two-photon-excited PL.

The measurement showed that TPA excited PL spectra for all of these 1,8-diazapyrenes 4-9 in THF (Figure 4-1 (a)) were essentially the same as their one-photon-excited PL spectra (Figure 4-2), implying that both one- and two-photon emissions were observed from the same excited state. Elongation of the π-conjugated length in 1,8-
diazapyrenes 4-9a and 4-9c led to the increase of TPA cross-sections without expense of the red shift of emission wavelength (Figure 4-1 (a)), probably due to the rigid planar structure of chromophores. It is worth to note that 2,3,6,7-tetra(4-bromo-phenyl)-1,8-diazapyrene (4-9c) has the largest TPA cross section.

Figure 4-1. (a) TPA excited PL spectra for 1,8-diazapyrenes 4-9; (b) Their PL Integrated Intensity vs power density at 780 nm. The log–log plots with slope values of around 2 indicate the nature of TPA in all of the compounds. (c) The Images of TPA excited PL emission for 1,8-diazapyrenes 4-9 under the excitation of 780 nm.

Figure 4-2. UV-Vis and one-photon-excited PL spectra of 1,8-diazapyrenes 4-9
4.4 Conclusion

We have developed a modified \([\text{Cp}^*\text{RhCl}_2]_2-\text{Cu(OAc)}_2\) bimetallic relay catalytic system for the synthesis of isoquinoline derivatives from readily available aryl ketone O-acetyl oximes and internal alkynes. In vivid contrast against the previous \([\text{Cp}^*\text{RhCl}_2]-\text{NaOAc}\) catalytic system (Chapter 2), both syn- and anti-isomers of O-acetyl oximes could be utilized and a wider substrate scopes could be applied under the present reaction conditions. Other azaheterocycles such as β-carbolines could also be synthesized using the present strategy. This method was further applied for the synthesis of planar π-conjugated 1,8-diazapyrenes which possess highly efficient two-photon-excited emission in the deep blue region by pumping with femtosecond pulses.

4.5 References

6 Step (i) in Scheme 4-14 was also proposed in the following report: Wang, Y.-F.; Toh, K. K.; Lee, J.-Y.; Chiba, S. Angew. Chem. Int. Ed. 2011, 50, 5927.


Chapter 5 A CuBr-Mediated Aerobic Reaction of 2-Alkynyl benzaldehydes and Primary Amines: Synthesis of 4-Bromoisoquinolones

5.1 Introduction

5.1.1 Overview

Isoquinolone (5-12) and quinolone (5-13) belong to a new class of azaheterocycles known as benzopyridinone where the structure consists of a benzene ring fused to a pyridinone.

![Figure 5-1. Benzopyridinone: Isoquinolone and quinolone](image)

The isoquinolone structure is one of the basic units found in many plant alkaloids. For example, alkaloid arolycoricidine (5-14), extracted from *Galanthus rizehensis* Stern, has been investigated for their effects on DNA topoisomerase reactions, which are known as the cellular targets of a number of chemotherapeutical drugs.\(^1\) Narciclasine (5-15) possesses potent inhibitory activity to human CYP3A4 cells, while its dihydro analogue, *trans*-dihydronarciclasine (5-16) is inactive. The biological studies revealed that the double bond is essential for inhibition action.\(^2\)

![Figure 5-2. Plant alkaloids with Isoquinolone as the basic unit](image)
Besides the biologically active plant alkaloids, isoquinolone-derived structures can also be found in pharmaceutical drugs. For example, indenoisoquinoline NSC314622 (5-17) and its derivatives both possess significant anti-cancer activity. Cytotoxicity analysis revealed that 5-17 is potential topoisomerase I poison and its DNA strand breaking-site is different from camptothecin (5-18).³

![Figure 5-3. Isoquinolone-derived pharmaceutical drugs](image)

5.1.2 Classical methods for the synthesis of isoquinolones

Even through isoquinolone derivatives present as the core structure in many biologically active compounds, there are only a few reports on the synthesis of isoquinolones in the early development. The pioneer research work has been reported by Mosby, in which phenyl isocyanate 5-19 undergoes intramolecular cyclization to give phenanthridone (5-20) by using AlCl₃ as a Lewis acid in chlorobenzene at room temperature (Scheme 5-1).⁴

![Scheme 5-1. AlCl₃-catalyzed synthesis of phenanthridone](image)

Later, Agawa and co-workers reported that the cyclization of vinyl isocyanate 5-21 bearing methylthio moiety under heating conditions proceeds to afford 2-
methy1thioisoquinolone (5-22) in quantitative yield even without Lewis acid (Scheme 5-2).

\[
\begin{align*}
\text{O=C-N} & \quad \text{neat} \\
\text{5-21} \quad & \quad 150^\circ \text{C, 2 h} \\
\text{quantitative} & \quad \rightarrow \\
\text{O} & \quad \text{5-22} \\
\text{N} & \quad \text{SMe} \\
\end{align*}
\]

**Scheme 5-2. Synthesis of 2-methylthioisoquinolone via thermolysis**

Direct intramolecular cyclization of the amide of nicotinamide 5-23 to the alkyne proceeds using sodium ethoxide as a base to provide 1,6-naphthyridinone 5-24 in high yield (Scheme 5-3). However, this approach is only limited to internal alkynes. As described in the same report, unsubstituted 1,6-naphthyridinone (5-27) can be synthesized from nicotinamide 5-25 by treatment with a catalytic amount of TsOH in benzene under reflux reaction conditions (Scheme 5-4). The reaction proceeds via an intramolecular condensation of the amide of 5-26 to the methyloxonium moiety under acidic condition.

\[
\begin{align*}
\text{MeO} & \quad \text{EtONa} \\
\text{5-23} \quad & \quad \text{EtOH, reflux, 3 h} \\
\text{88%} & \quad \rightarrow \\
\text{MeO} & \quad \text{5-24} \\
\text{N} & \quad \text{Ph} \\
\end{align*}
\]

**Scheme 5-3. Direct Intramolecular cyclization of 2-(phenylethynyl)nicotinamide**

\[
\begin{align*}
\text{MeO} & \quad \text{cat. TsOH} \\
\text{5-25} \quad & \quad \text{benzene, reflux, 8 h} \\
\text{55%} & \quad \rightarrow \\
\text{MeO} & \quad \text{5-26} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{O-Me} \\
\text{5-25} \quad & \quad \text{benzene, reflux, 8 h} \\
\text{55%} & \quad \rightarrow \\
\text{MeO} & \quad \text{5-26} \\
\end{align*}
\]

\[
\begin{align*}
\text{MeO} & \quad \text{O-Me} \\
\text{5-25} \quad & \quad \text{benzene, reflux, 8 h} \\
\text{55%} & \quad \rightarrow \\
\text{MeO} & \quad \text{5-26} \\
\end{align*}
\]

**Scheme 5-4. Synthesis of unsubstituted 1,6-naphthyridinone**

Another approach using Lewis acid-promoted Friedel-Craft-tyle cyclization has been applied for the construction of isoquinolone structure which forms the western hemisphere of Sch 56036. Sch 56036 is a polycyclic xanthone which exhibits high
activity against a number of fungal pathogens in antifungal testing. In that case, camphorsulfonic acid is used as the Lewis acid to facilitate Friedel-Crafts-type cyclization via activation of the diethoxymethyl moiety of 5-28 (Scheme 5-5). High temperature required for the cyclization also brought about O-demethylation to provide isoquinolone 5-29 without epimerization.

![Scheme 5-5. Construction of Isoquinolone structure of Sch 56036](image)

In another report, Overberger and Anselme showed that the conversion of 3-phenylisocoumarin to 3-phenylisoquinolone can be achieved using ethanol saturated with ammonia at 100 °C (Scheme 5-6). Similar methodology has been applied by Bach and co-workers for the total synthesis of (±)-fredericamycin A.

![Scheme 5-6. Conversion of Isocoumarin to Isoquinolone](image)
5.1.3 Modern routes in the synthesis of isoquinolones

The lack of efficient synthetic routes for isoquinolones probed researchers to discover new versatile methods to cope with the increasing trend of utilizing isoquinolone derivatives in pharmaceutical drugs. Therefore, numerous methodologies have been developed for the synthesis of isoquinolones over the last decade. Amongst, transition metal catalysis from simple precursors is one of the outstanding methods for isoquinolone synthesis.

In 2007, Pal and co-workers developed a simple transformation using Pd/C–Cu catalysis from 2-iodobenzoyl azides and terminal alkynes to 3-substituted isoquinolones. In a typical reaction, a Sonogashira coupling between 2-iodobenzoyl azide 5-30 and 1-octyne proceeds under Pd/C–Cu catalysis to generate 2-alkynylbenzoyl azide 5-31 in situ which readily undergo an intramolecular acetylenic Schmidt reaction under the present reaction conditions to afford isoquinolone 5-32 in high yield (Scheme 5-7).

![Scheme 5-7. An intramolecular acetylenic Schmidt reaction under Pd/C–Cu catalysis](image)

Using a different approach, Cheng and co-workers reported an efficient method for the synthesis of isoquinolones via Ni(II)-catalyzed annulation of 2-halobenzamides with alkynes. The reaction is most likely to start with the reduction of Ni(II) by zinc powder to the active Ni(0) species which is oxidatively added to 2-iodobenzamide (5-33) in the presence of Et$_3$N as a base to generate 5-membered ring nickelacycle A (Scheme 5-8). Subsequent alkyne insertion and reductive elimination afford isoquinolone 5-34 and regenerate the active Ni(0) species. The significance of this catalysis is reflected by its
application to the total synthesis of oxyavicine (Scheme 5-9), an alkaloid natural product which exhibits analgesic and anti-inflammatory effects in the biological evaluation\textsuperscript{12}. 

\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}

\textit{Scheme 5-8. An example of Ni(II)-catalyzed annihilation of 2-iodobenzamides with alkynes}

\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph}
\end{align*}

\textit{Scheme 5-9. Application of total synthesis of oxyavicine}

Kurahashi and co-workers reported that similar intermediate (5-membered ring nickelacycle A) can be generated from phthalimide using Ni(cod)\textsubscript{2} as a catalyst and PMe\textsubscript{3} (electron-rich phosphine) as a ligand.\textsuperscript{13} The reaction mechanism may involve the nucleophilic attack of electron-rich Ni(PMe\textsubscript{3})\textsubscript{n} to the amide moiety of phthalimide 5-35 and followed by subsequent decarbonylation to provide 5-membered ring nickelacycle A (Scheme 5-10). It is worth to note that the reaction results in low yield when R-substituent was replaced with an aryl moiety instead of 2-pyridinyl group and the reaction does not proceed with terminal alkynes such as 1-octyne and phenylacetylene.
Murakami and co-workers showed that similar Ni(cod)₂–PMe₃ catalytic system is applicable for the synthesis of isoquinolones from 1,2,3-benzotriazin-4(3H)-ones and alkynes (Scheme 5-11). In a typical reaction of 1,2,3-triazinone 5-36, the mechanism is proposed to involve the generation of 5-membered ring nickelacycle A via sequential oxidative addition of N–N bond to Ni(0) and extrusion of a molecular dinitrogen. In contrast to the above decarbonylative addition of phthalimides to alkynes, the present reaction conditions tolerate a wide range of alkynes such as terminal alkyne (1-octyne), boryl-substituted alkyne and silyl-substituted alkyne.

To shorten the synthetic route for starting materials, direct formation of isoquinolones from simple benzamide derivatives via C–H bond activation becomes an attractive strategy. As discussed in the previous chapters, transition metal-catalyzed isoquinolone synthesis via oxidative couplings of benzamides and alkynes has been developed by several research groups. For example, Ru(II)¹⁵ and Ni(0)¹⁶ (see Chapter 1 for more details) as well as Rh(III)¹⁷ (see Chapter 2 for more details) showed high reactivity towards isoquinolone synthesis.
Furthermore, Pd(II)-catalyzed approach has also been successfully applied for the synthesis of isoquinolones. Treatment of N-methoxy benzamide (5-37) and diphenylacetylene with Pd(OAc)$_2$ and NaI·2H$_2$O in DMF at 120 °C under an air atmosphere affords isoquinolone 5-38 in high yield (Scheme 5-12). The reaction intermediate, palladacycle A is proposed to be generated via N–H bond and C–H bond double activations. Oxygen is used as the terminal oxidant to regenerate the active Pd(II) species.

Scheme 5-12. An example of Pd(II)-catalyzed synthesis of isoquinolones from N-alkoxyl benzamides and alkynes

![Scheme 5-12](image)

5.1.4 Background of the reactivity of 2-alkynyl benzaldimines

Another fundamental strategy for the construction of azaheterocycles is through intramolecular annulations of alkynes with nitrogen nucleophiles. In particular, 2-alkynyl benzaldimines have shown to be promising precursors for preparation of substituted isoquinoline derivatives via electrophilic activations of alkynes under various types of the reaction conditions.

One of the approaches to achieve intramolecular annulations of alkynes involves the use of an external electrophile for alkyne activation. In that context, Larock and co-workers reported the synthesis of 3,4-disubstituted isoquinolines via electrophilic 6-endo-cyclization of N-tert-butyl-2-alkynyl benzaldimines with a variety of electrophiles under mild reaction conditions. Electrophiles such as I$_2$ (Scheme 5-13), ICl, PhSeCl, and
PhSCI have been successfully applied for the synthesis of 4-heterosubstituted isoquinolines. However, in some cases, 5-exo-cyclization products are dominant.

![Scheme 5-13. An example of isoquinoline synthesis via electrophilic ring closure of 2-alkynyl benzaldimines with iodine](image)

Another approach is to utilize Lewis acid as a catalyst for intramolecular annulations of 2-alkynyl benzaldimines to form isoquinolinium salts which can be further transformed to highly substituted isoquinolines. When CuI is used as the Lewis acidic catalyst, a simple cyclization of N-tert-butyl-2-alkynyl benzaldimine 5-39 proceeds to generate isoquinolinium–Cu(I) complex A, which is facile towards cleavage of tert-butyl group and protonation to afford isoquinoline 5-40 in quantitative yield (Scheme 5-14).

![Scheme 5-14. An example of Cu(I)-catalyzed cyclization of 2-alkynyl benzaldimines](image)

In the effort to functionalize the intermediate (isoquinolinium–metal complex) at the C-4 position, Larock’s group developed a sequential intramolecular annulations of alkynes and cross-couplings of organic halides using Pd(0) as a catalyst. In a typical reaction shown in Scheme 5-15, the design of the reaction involves initial oxidative addition of aryl iodide 5-41 to Pd(0) to form arylpalladium(II) iodide complex, which acts as a Lewis acid to activate the alkyne of 5-39 towards 6-endo-cyclization to generate isoquinolinium–Pd(II) complex A. Subsequent C–C bond reductive elimination and cleavage of tert-butyl group afford isoquinoline 5-42.
To explore the reactivity of the isoquinolinium–Pd(II) complex A in a Heck reaction, N-tert-buty1-2-alkynyl benzaldimine 5-39 is treated with styrene in the presence of PdBr₂ and CuCl₂ under an oxygen atmosphere. The reaction involves an intramolecular nucleophilic attack of imine nitrogen to alkyne, which is coordinated to Pd(II), to generate complex A and followed by a common Heck reaction to afford 4-styrylisooquinoline 5-43 (Scheme 5-16). It is worth noting that oxygen is used as the terminal oxidant to achieve catalytic turnover.

On the other hand, the C-1 position of isoquinolinium–metal complex can be functionalized via addition of a pronucleophile to the iminium moiety of the complex to furnish 1,2-dihydroisoquinoline. Yamamoto and co-workers achieved direct Mannich and nitro-Mannich reactions of 2-alkynyl benzaldimines using pronucleophiles such as nitromethane (Scheme 5-17), acetonitrile, acetone, or even terminal alkynes (phenylacetylene and 1-hexyne) in the presence of AgOTf as the Lewis acidic catalyst. The present process provides an alternative way for the construction of 1,2-dihydroisoquinolines without using activated imines as the precursor. The use of N-aryl
or \( N \)-alkyl group instead of \( N \)-tert-butyl group is important to stabilize the isoquinolinium–Ag(I) complexes A for nucleophilic attack. Further extension of the method to three-component reactions of 2-alkynylbenzaldehydes, amines, and ketones has been reported by Wu and co-workers.\(^{24}\)

\[
\begin{align*}
\text{AgOTf (3 mol %)} & \quad \text{CH}_2\text{Cl}_2, 80 \, ^\circ\text{C}, 6 \, \text{h} \\
\text{85\%} & \\
\end{align*}
\]

Scheme 5-17. An example of Ag(I)-catalyzed direct nitro-Mannich reaction of 2-alkynyl benzaldimines

\[
\begin{align*}
\text{AgOTf (10 mol %)} & \quad \text{DTBMP} \\
\text{72\%} & \\
\end{align*}
\]

Scheme 5-18. An example of Ag(I)-catalyzed cycloisomerizations/dipolar cycloadditions for the synthesis of pyrroloisoquinolines

Besides, Porco and co-workers developed an efficient catalytic system for the synthesis of pyrroloisoquinolines, which is the core structure of lamellarin natural products. In their approach, treatment of 2-alkynyl benzaldimine 5-44 with a catalytic amount of AgOTf affords isoquinolinium–Ag(I) complex A, which will be converted to azomethine ylide 5-47 via cycloisomerization (Scheme 5-18). At this point, the C-1
position of 5-47 can be functionalized with dimethylacetylene dicarboxylate (5-45) via [3+2] dipolar cycloaddition. Subsequent re-aromatization gives pyrroloisoquinoline 5-46. They believed that Ag(I)-catalyzed cycloisomerization to azomethine ylide 5-47 is the key step for the formation of pyrroloisoquinoline 5-46.

5.1.5 Study of 2-alkynyl benzaldehydes and amines under Cu–O$_2$ system

As shown above, Lewis acid-catalyzed intramolecular annulation of 2-alkynyl benzaldimines is a powerful strategy for the synthesis of highly substituted isoquinolines via functionalization of isoquinolinium–metal complexes. However, those methods normally require the preparation of benzaldimines via dehydrative condensation of benzaldehydes and primary amines where the process often suffers from low yield due to the instability of benzaldimines.

To address the drawback, we became interested in the direct transformation involving 2-alkynyl benzaldehydes and primary amines. Inspired by the previous successful application of Cu–O$_2$ system in functionalization of C–C unsaturated bonds, we envisioned new reactions between 2-alkynyl benzaldehydes and primary amines under Cu–O$_2$ system (Scheme 5-19). In that context, a different outcome is expected under the proposed oxidative conditions compare to Cu(I)-catalyzed synthesis of isoquinolines from 2-alkynyl benzaldimines as shown in Scheme 5-14.

![Scheme 5-19. A new synthetic approach under Cu–O$_2$ system](image-url)
5.2 Results and Discussion

5.2.1 Synthesis of 2-alkynyl benzaldehydes

2-Alkynyl benzaldehydes 5-1 were prepared by employing Sonogashira cross-coupling reactions (Scheme 5-20). Treatment of 2-bromobenzaldehyde derivatives and terminal alkynes with 2 mol % of PdCl$_2$(PPh$_3$)$_2$ and 1 mol % of CuI in Et$_3$N at 50 °C resulted in the formation of 5-1a, 5-1b, 5-1k to 5-1s and 5-1u & 5-1v in high yields.

\[
\begin{align*}
\text{R}^3&\text{Br} & \text{PdCl}_2(\text{PPh}_3)_2 (2 \text{ mol } \%) & \text{Et}_3\text{N}, 50 \degree \text{C}, 3-6 \text{ h} & \text{R}^2 \\
\text{H} & \text{CuI (1 mol } \%) & \text{C} & \rightarrow & \text{R}_2
\end{align*}
\]

Scheme 5-20. Synthesis of 2-alkynyl benzaldehydes–1

Similarly, 2-alkynyl benzaldehydes 5-1c to 5-1j and 5-1t which bearing R$_2$ = aryl moiety with different electronic properties could be synthesized by Sonogashira cross-couplings of 2-ethynylbenzaldehyde and aryl halides under the same reaction conditions (Scheme 5-21).

\[
\begin{align*}
\text{H} & \text{PdCl}_2(\text{PPh}_3)_2 (2 \text{ mol } \%) & \text{Et}_3\text{N}, 50 \degree \text{C}, 3-6 \text{ h} & \text{R}_2 \\
\text{H} & \text{CuI (1 mol } \%) & \text{C} & \rightarrow & \text{R}_2
\end{align*}
\]

Scheme 5-21. Synthesis of 2-alkynyl benzaldehydes–2

5.2.2 Optimization of reaction conditions

Based on our inspiration for a new synthetic route using 2-alkynyl benzaldehydes and amines under Cu–O$_2$ system as shown in Scheme 5-19, we began our investigation on the reaction of 2-(phenylethynyl)benzaldehyde (5-1a) and benzylamine (5-2a) using CuBr•SMe$_2$ as the initial catalyst under a molecular oxygen atmosphere (Table 5-1).
Table 5-1. Optimization of reaction conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>CuBr•SMe₂ (equiv)</th>
<th>additive (0.2 g)</th>
<th>solvent</th>
<th>time (h)</th>
<th>yield of 3aa (%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1⁰</td>
<td>0.5</td>
<td>—</td>
<td>toluene</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td>2⁰</td>
<td>2.2</td>
<td>—</td>
<td>toluene</td>
<td>22</td>
<td>29d</td>
</tr>
<tr>
<td>3⁰</td>
<td>2.2</td>
<td>SiO₂</td>
<td>toluene</td>
<td>1</td>
<td>34a</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>SiO₂</td>
<td>pyridine</td>
<td>4</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>2.2</td>
<td>SiO₂</td>
<td>toluene:pyridine = 5:1</td>
<td>6</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>SiO₂</td>
<td>CICH₂CH₂CH₂NPyridine = 5:1</td>
<td>3.5</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>2.2</td>
<td>SiO₂</td>
<td>benzene:pyridine = 5:1</td>
<td>4</td>
<td>77 (80)⁰</td>
</tr>
<tr>
<td>8</td>
<td>2.2</td>
<td>SiO₂</td>
<td>benzene:pyridine = 10:1</td>
<td>6</td>
<td>70</td>
</tr>
<tr>
<td>9</td>
<td>1.1</td>
<td>SiO₂</td>
<td>benzene:pyridine = 5:1</td>
<td>4</td>
<td>39⁰</td>
</tr>
<tr>
<td>10</td>
<td>0.2h</td>
<td>SiO₂</td>
<td>pyridine</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>11i</td>
<td>2.2</td>
<td>SiO₂</td>
<td>benzene:pyridine = 5:1</td>
<td>4</td>
<td>49⁰</td>
</tr>
<tr>
<td>12</td>
<td>2.2</td>
<td>SiO₂</td>
<td>benzene:Et₃N = 5:1</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>13j</td>
<td>2.2</td>
<td>SiO₂</td>
<td>benzene</td>
<td>5</td>
<td>0k</td>
</tr>
<tr>
<td>14j</td>
<td>2.2</td>
<td>SiO₂</td>
<td>benzene</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

⁰ Unless otherwise noted, the reactions were conducted using 0.3 mmol of 5-1a and 0.9 mmol of 5-2a (3 equiv) in solvent (3 mL, 0.1 M) in the presence of 0.2 g of SiO₂ at 80 °C under an O₂ atmosphere, where 0.3 mmol of 5-2a was added three times at every 1 h interval. Isolated yield. ¹ 1.1 equiv of 5-2a was used and 2.2 equiv of pyridine. ² 5-1a was recovered in 31% yield. ³ 4-Bromo-3-phenylisoquinoline (5-4) was isolated in 24%. ⁴ Parenthesis shows the yield of 5-3aa using 0.5 mmol of 5-1a with 0.3 g of SiO₂. ⁵ 1H NMR yield from the crude mixture. ⁶ 2 equiv of LiBr was added. ¹ CuBr₂ was used instead of CuBr•SMe₂. ¹ 2.2 equiv of DABCO was added. ² 3-Phenylisoquinoline (5-5) was isolated in 37% yield. ¹ 2.2 equiv of 2,2'-bipyridine was added.

To embark on the study, a mixture of 5-1a and 5-2a (1.1 equiv) was treated with 0.5 equiv of CuBr•SMe₂ and 2.2 equiv of pyridine in toluene at 80 °C under a molecular oxygen atmosphere. To our surprise, 4-bromoisoquinolone 5-3aa was isolated in 19% yield (Table 5-1, entry 1). The unprecedented 4-bromoisoquinolone formation suggested a new synthetic transformation involving C=N, C=Br and C=O bond formations from 2-alkynyl benzaldehyde and benzylamine under Cu–O₂ system; in contrast, isoquinolines
were generated from the previously reported methods as shown in Chapter 5.1.4. The initial finding prompted us to further optimize the reaction conditions with more than a stoichiometric amount of CuBr•SMe$_2$, which serves as the bromine source for the bromide incorporation.

When the amount of CuBr•SMe$_2$ was increased to 2.2 equiv under the same conditions, a slight increase in the yield of product 5-3aa to 29% was observed (Table 5-1, entry 2). It is worth noting that the reaction was accelerated by the addition of 0.2 g of SiO$_2$, however, 4-bromo-3-phenylisoquinoline (5-4) was also isolated in 24% yield (Table 5-1, entry 3). As reported by Anderson, SiO$_2$ has been used as an additive in an aerobic oxidative transformation of alkynes but the role of SiO$_2$ is still unclear. The yield of product 5-3aa was further improved to 56% by using pyridine as a solvent with the addition of 1 equiv of 5-2a three times at every 1 h interval (in total of 3 equiv of 5-2a was added) (Table 5-1, entry 4). The portionwise addition of benzylamine (5-2a) is to minimize the oxidative dimerization of benzylamine to $N$-benzylbenzaldimine, which was observed as a side reaction under the present reaction conditions. Similar oxidative dimerization of benzylamines has been also reported previously by Zeng and co-workers.

It was found that a co-solvent system including pyridine as the minor component was found to be efficient for this transformation (Table 5-1, entries 5-8). Among the solvent combinations, benzene–pyridine (5:1) solvent gave the best yield of 5-3aa in 77% (Table 5-1, entry 7). Usage of 1.1 equiv of CuBr•SMe$_2$ rendered the reaction sluggish, giving 5-3aa in 39% yield only (Table 5-1, entry 9). Moreover, the use of CuBr•SMe$_2$ as the catalyst and LiBr as an additional bromide source did not promote the reaction (Table 5-1, entry 10). The reaction with 2.2 equiv of CuBr$_2$ also worked well to provide 5-3aa, albeit in a lower yield of 49% (Table 5-1, entry 11).
The reactions using other tertiary amines such as triethylamine, DABCO, and 2,2'-bipyridine instead of pyridine did not afford product 5-3aa at all (Table 5-1, entries 12-14). No 4-bromoisoquinolone formation was observed under a molecular nitrogen atmosphere. These results suggested that the presence of pyridine and molecular oxygen plays important roles in this transformation.

5.2.3 Scope & limitations

With the optimized reaction conditions (Table 5-1, entry 7) in hand, the generality of primary amines 5-2 was first examined (Table 5-2). The results showed that several benzyl amines 5-2b to 5-2d bearing methoxy, methyl, and fluoro groups on the benzene ring were tolerated under the present reaction conditions to give the corresponding 4-bromoisoquinolones 5-3 in good yields (Table 5-2, entries 1-3).

Table 5-2. Scope of primary amines

<table>
<thead>
<tr>
<th>entry</th>
<th>amine 5-2</th>
<th>4-bromoisoquinolone 5-3 / yield&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-2b (R = 4-OMe-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>5-3ab: 64%</td>
</tr>
<tr>
<td>2</td>
<td>5-2c (R = 4-Me-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>5-3ac: 72%</td>
</tr>
<tr>
<td>3</td>
<td>5-2d (R = 4-F-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;)</td>
<td>5-3ad: 76%</td>
</tr>
<tr>
<td>4</td>
<td>5-2e (R = CH&lt;sub&gt;2&lt;/sub&gt;Ph)</td>
<td>5-3ae: 55% (51%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>5-2f (R = CHPh&lt;sub&gt;2&lt;/sub&gt;)</td>
<td>5-3af: 56% (42%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>5-2g (R = n-Bu)</td>
<td>5-3ag: 59%</td>
</tr>
<tr>
<td>7</td>
<td>5-2h (R = cyclo-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;11&lt;/sub&gt;)</td>
<td>5-3ah: 57% (53%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>5-2i (R = cyclo-C&lt;sub&gt;3&lt;/sub&gt;H&lt;sub&gt;10&lt;/sub&gt;)</td>
<td>5-3al: 57% (52%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
Table 5-2. Scope of primary amines (continue)

<table>
<thead>
<tr>
<th>entry</th>
<th>amine 5-2</th>
<th>4-bromoisoquinolone 5-3 / yield$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>H$_2$N$\bigcircledast$</td>
<td><img src="image" alt="5-3aj: 53%" /></td>
</tr>
<tr>
<td></td>
<td>5-2j</td>
<td><img src="image" alt="Ph Br" /></td>
</tr>
<tr>
<td>10</td>
<td>H$_2$N$\bigcircledast$OMe</td>
<td><img src="image" alt="5-3ak: 57%" /></td>
</tr>
<tr>
<td></td>
<td>5-2k</td>
<td><img src="image" alt="Ph Br" /></td>
</tr>
<tr>
<td>11</td>
<td>H$_2$N$\bigcircledast$Me</td>
<td><img src="image" alt="5-3al: 43% ; 5-6al: 17%" /></td>
</tr>
<tr>
<td></td>
<td>(40 wt % in H$_2$O)</td>
<td><img src="image" alt="Ph" /></td>
</tr>
</tbody>
</table>

$^a$ Unless otherwise noted, the reactions were carried out on the scale of 0.5 mmol of 5-1a and 1.5 mmol of 5-2 (3 equiv) at 80 °C under O$_2$ atmosphere where 0.5 mmol of 2 was added three times at every 1 h interval. $^b$ Isolated yield. $^o$ Parenthesis shows the yield of 5-3 when 1.2 equiv of amine 5-2 was used.

The reactions also proceeded smoothly with various alkyl amines 5-2e to 5-2k, which could possess linear and branched alkyl groups as well as cyclopropyl (for 5-2i), alkenyl (for 5-2j), and methoxy (for 5-2k) groups (Table 5-2, entries 4-10). When methyl amine (5-2l; 40 wt % in H$_2$O) was treated with 5-1a under the present reaction conditions, the corresponding 4-bromoisoquinolone 5-3al was formed in 43% yield along with 17% yield of protonated isoquinolone 5-6al (Table 5-2, entry 11).

In the case of ammonia (5-2m; 25 wt % in H$_2$O), no 4-bromoisoquinolone 5-3am was observed but 2-(phenylethynyl)benzonitrile (5-7) was formed in 32% yield (Scheme 5-22). Similar Cu(II)-catalyzed conversion of benzaldehyde to benzonitrile using NH$_3$ as
a nitrogen source and MeONa as a base under a molecular oxygen atmosphere in MeOH has been reported by Smit and co-workers.\textsuperscript{28} It is noted that aromatic amines (anilines) did not work at all.

![Scheme 5-22. Formation of benzonitrile from benzaldehyde]

The reaction of $\beta$-alanine ethyl ester hydrochloride salt (5-2n) with 5-1a under the standard reaction conditions, however, afforded 4-bromo-3-phenylisoquinoline (5-4) and 3-phenylisoquinoline (5-5) in 42% and 28% yields respectively, with no desired 4-bromoisoquinolone formation (Scheme 5-23 (a)). In this case, C-N bond cleavage is preferred over oxidation of the proposed intermediate (hemiaminal; see proposed mechanism in Scheme 5-27) and leading to isoquinoline formation. Similar reactivity was observed using propargylamine 5-2o and resulted in formation of 5-4 in 30% yield (Scheme 5-23 (b)).

![Scheme 5-23. Different reactivity of amines 5-2n and 5-2o]
Next, the substituent effect of 2-alkynylbenzaldehydes 5-1 was examined using benzylamine (5-2a) under the present conditions (Chart 5-1). Various aryl groups bearing electron-donating groups (methoxy and methyl moieties; for 5-3ba, 5-3ca, 5-3ga and 5-3ha) and halogen atoms (fluorine and bromine; for 5-3da and 5-3ia) could be tolerated as R²-substituent on the alkyne of 5-1 regardless of the arene substitution pattern to afford...
the corresponding 4-bromoisoquinolones 5-3 in good yields. However, aryl groups bearing electron-deficient moieties such as CO$_2$Et (for 5-3ea) and CF$_3$ (for 5-3fa) at R$^2$-substituent resulted in the formation of 4-bromoisoquinolones 5-3 in lower yields. Even the linear and cyclic alkyl groups (for 5-3ka to 5-3ma) could be installed as R$^2$-substituent.

As for the benzene ring of 2-alkynylbenzaldehydes 5-1, several electron-donating groups with different substitution pattern (for 5-3na to 5-3pa) as well as a fluorine atom (for 5-3qa) could be introduced as R$^3$-substituent. The replacement of benzene ring with heteroaryl motifs such as benzofuran (for 5-3ra) and pyridine (for 5-3sa) resulted in the same transformation, albeit in moderate yields. It is worth to note that treatment of 2-(phenylethynyl)nicotinaldehyde (5-1s) with benzylamine (5-2a) under the present conditions afforded 4-bromoisoquinoline 5-3sa in 43% yield along with the protonated isoquinolone 5-6sa in 38% yield.

**Chart 5-2. Limitation of 2-alkynylbenzaldehydes**

\[
\begin{align*}
\text{CuBr} & \cdot \text{SMe}_2 (2.2 \text{ equiv}) \\
\text{benzene-pyridine (5:1)} \\
\text{SiO}_2, 80^\circ \text{C} \\
\text{under O}_2 (1 \text{ atm})
\end{align*}
\]

\[
\begin{align*}
\text{5-1} & \quad \text{H} \\
\text{R}^2 & \\
\text{5-2a} & \quad \text{H}_2\text{N} \sim \text{Ph} \\
\text{5-3: 0\%}
\end{align*}
\]

\[
\begin{align*}
\text{5-1t} & \quad \text{5-1u} \\
\text{5-1v} & \quad \text{5-1v}
\end{align*}
\]

*a* Unless otherwise notes, the reactions were carried out on the scale of 0.5 mmol of 5-1 and 1.5 mmol of 5-2a (3 equiv) at 80°C under O$_2$ atmosphere where 0.5 mmol of 5-2a was added three times at every 1 h interval.

Even a wide range of 2-alkynylbenzaldehydes 5-1 were tolerated under the reaction conditions, 2-alkynylbenzaldehydes bearing 2-pyridinyl (5-1t) or trimethylsilyl...
(5-1u) moieties at R²-substituent as well as 2-(phenylethynyl)cyclohex-1-ene carbaldehyde (5-1v) were decomposed without the formation of 4-bromoisoquinolones 5-3 (Chart 5-2).

It was found that the treatment of 5-1a and 5-2a with CuCl and CuI separately under the same conditions without CuBr·SMe₂ resulted in the formation of 4-chloroisooquinolone 5-3aa’ and 4-iodoisooquinolone 5-3aa” in 23% and 39% respectively (Scheme 5-24).

\[
\begin{align*}
\text{Scheme 5-24. Synthesis of 4-chloroisooquinolone and 4-iodoisooquinolone from} \\
\text{CuCl and CuI respectively}
\end{align*}
\]

5.2.4 Mechanism insight

To elucidate the reaction mechanism for the formation of 4-bromoisoquinolone derivatives 5-3, several control experiments were conducted to understand the C–N, C=O and C–Br bond formations (Scheme 5-25 & Scheme 5-26). The reaction of 2-alkynyl N-benzylaldimine 5-8 under the standard reaction conditions furnished 4-bromoisoquinolone 5-3aa in 36% yield (Scheme 5-25 (a)), while cyclization of 2-alkynyl N-benzylamide 5-9 did not proceed at all (Scheme 5-25 (b)). These results suggested that the 6-endo-cyclization of the nitrogen atom onto the alkyne is most likely happened prior to the formation of C=O bond of the amide moiety. In fact, the reaction of benzaldehyde (5-10) and benzylamine (5-2a) under the present conditions gave N-benzylaldimine 5-11 in 116% yield (based on 5-10) without the formation of N-benzylbenzamide. The
chemical yield of over 100% revealed that 5-11 is not only derived from dehydrative condensation of 5-10 and 5-2a; however, 5-11 is also partly contributed from dimerization of 5-2a (Scheme 5-25 (c)). Similar oxidative dimerization of benzylamines has been reported previously by Lee and co-workers.26

![Chemical Structures and Reactions]

Previously, Stahl and co-workers reported a CuBr₂-catalyzed aerobic bromination of arenes in the presence of LiBr as a stoichiometric bromine atom source, where molecular bromine generated in situ via decomposition of CuBr₂ allowed the electrophilic bromination.29 To examine the possibility of in situ-generated molecular bromine as the bromine source, cyclooctene was treated with the present reaction conditions (2.2 equiv of CuBr₂·SMe₂ and SiO₂ in benzene–pyridine (5:1) under a molecular oxygen atmosphere) but electrophilic bromination product was not observed (Scheme 5-26 (a)). If the reaction involves generation of molecular bromine in solution, the reaction should turn red-brown in color; no such indication was observed in all of our cases. These observations suggested that molecular bromine is not likely to be involved as a precursor of...
bromonium cation for the electrophilic bromination in the synthesis of 4-bromoisoquinolones.

It is also noted that the vinylic C-H bromination of isoquinolone 5-6aa did not proceed under the present reaction conditions (Scheme 5-26 (b)). The result showed that the C-Br bond formation may occur directly during the process without going through isoquinolone 5-6 as the intermediate.

Based on the control experimental results, a proposed reaction pathway was outlined in Scheme 5-27. The nucleophilic addition of amine 5-2 to 2-alkynyl benzaldehyde 5-1 gives hemiaminal I, which undergoes the 6-endo-cyclization onto the electrophilically activated alkyne with [CuII]Br to give vinyl copper species II (Scheme 5-27, path a). In the present aerobic conditions, CuIIBr might be oxidized by molecular oxygen to CuIIIBr species, which may facilitate the isoquinolone formation.

Alternatively, hemiaminal I can undergo dehydrative condensation to provide aldime III, which is followed by 6-endo-cyclization to afford isoquinolinium salt IV (Scheme 5-27, path b). Addition of water to isoquinolinium salt IV gives the same intermediate, vinyl copper species II. Pathway b is most unlikely to be the reaction pathway because lower yield of 4-bromoisoquinolone 5-3aa was observed by using isolated aldime 5-8 as the starting material under the present aerobic conditions.
(Scheme 5-25 (a)). SiO₂ may play an important role to drive the equilibrium from aldimine III to hemiaminal I and lead to shorter reaction time and higher efficiency. From putative intermediate II, further C–Br bond reductive elimination and oxidation of the C–O bond under the Cu–O₂ system deliver 4-bromoisoquinolone 5-3. In this transformation, CuBr plays multiple roles as the promoter of C–N bond forming cyclization, the bromine carrier, and the oxidant for C=O bond formation.

\[
\text{Scheme 5-27. A proposed reaction mechanism}
\]

5.3 Conclusion

An unprecedented method for synthesis of 4-bromoisoquinolones has been developed using 2-alkynylbenzaldehydes and primary amines mediated by CuBr under a molecular oxygen atmosphere. In this transformation, CuBr plays multiple roles as the promoter of C–N bond forming cyclization, the bromine carrier, and the oxidant for C=O bond formation.
5.4 References


Chapter 6 Experimental

6.1 General

$^1$H NMR (400MHz) spectra [using $(CH_3)_4Si$ (for $^1$H, $\delta = 0.00$) as internal standard] and $^{13}$C NMR (100 MHz) spectra [using CDCl$_3$ (for $^{13}$C, $\delta = 77.00$) as internal standard] were recorded on a Bruker Avance 400 MHz spectrometers in CDCl$_3$. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and brs = broad singlet. IR spectra were recorded on a Shimazu IR Prestige-21 FT-IR Spectrometer. High-resolution mass spectra were obtained with a Finnigan MAT 95 XP mass spectrometer (Thermo Electron Corporation). X-ray crystallographic analyses were performed on a Bruker X8 APEX X-Ray Diffractometer. Melting points were uncorrected and were recorded on a Buchi B-54 melting point apparatus.

Flash column chromatography was performed using Merck silica gel 60 with distilled solvents. Methanol (MeOH) was distilled from magnesium and stored over MS 4 Å. Ethanol (EtOH) was distilled from sodium and stored over MS 4 Å. Commercially available anhydrous $N,N$-dimethylformamide (DMF, 99.8%), benzene (HPLC grade) and anhydrous pyridine (99.8%) were used directly for the reaction.
6.2 Experimental section of Chapter 2:

6.2.1 Synthesis of O-acyl oxime derivatives

6.2.1.1. Preparation of aryl ketone O-acetyl oximes: a typical procedure for synthesis of (E)-acetophenone O-acetyl oxime (2-1a).

![Chemical reaction]

To a solution of acetophenone (2.64 g, 22.0 mmol) and pyridine (5.0 mL, 61.8 mmol) in EtOH (10 mL) was added NH₂OH·HCl (2.29 g, 33.0 mmol) in one portion and the reaction mixture was stirred at 60 °C for 1 h. The reaction was quenched by adding water and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO₄. Volatile materials were removed *in vacuo* to give acetophenone oxime, which was used for the next acetylation without further purification.

The crude residue of acetophenone oxime obtained above was treated with Ac₂O (4.2 mL, 44.4 mmol) and a catalytic amount of DMAP (5 mg) in pyridine (10 mL) and the reaction mixture was stirred at room temperature for 1 h. After volatile materials were evaporated, the resulting residue was treated with water, and organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO₄. The solvents were removed under reduced pressure, giving white solid of crude acetophenone O-acetyl oxime. Further recrystallization was conducted from ethyl acetate-hexane to provide (E)-acetophenone O-acetyl oxime (2-1a) (2.43 g, 13.7 mmol) in 63% yield.
(E)-Acetophenone O-acetyl oxime (2-1a)

White solid; mp. 56-57 °C; IR (NaCl) 1763, 1616, 1445, 1368, 1310, 935 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.27 (3H, s), 2.39 (3H, s), 7.38-7.47 (3H, m), 7.74 (2H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.4, 19.8, 127.0, 128.5, 130.5, 134.8, 162.4, 169.0; ESI-HRMS: Found: m/z 178.0872. Calcd for C₁₀H₁₂NO₂: (M+H)⁺ 178.0868.

(E)-Acetophenone O-methyl oxime (2-1a')¹

 Prepared by treatment of acetophenone with MeONH₂·HCl in the presence of pyridine in EtOH, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 89% yield; Colorless oil; ¹H NMR (400 MHz, CDCl₃) δ 2.24 (3H, s), 4.01 (3H, s), 7.37-7.39 (3H, m), 7.65-7.68 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 12.6, 61.9, 126.0, 128.4, 129.0, 136.6, 154.6.

(E)-1-(4-Methoxyphenyl)ethanone O-acetyl oxime (2-1b)

 Prepared from 1-(4-methoxyphenyl)ethanone and purified by recrystallization from hexane-ethyl acetate (one time) in 79% yield; White solid; mp. 53-55 °C; IR (NaCl) 1761, 1605, 1514, 1321, 1256, 1179 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.28 (3H, s), 2.35 (3H, s), 3.83 (3H, s), 6.91 (2H, d, J = 8.8 Hz), 7.71 (2H, d, J = 8.8 Hz); ¹³C NMR

(100 MHz, CDCl₃) δ 14.1, 19.9, 55.3, 113.9, 127.1, 128.5, 161.5, 161.9, 169.1; ESI-HRMS: Found: m/z 208.0968. Calcd for C₁₁H₁₄NO₃: (M+H)⁺ 208.0974.

(E)-1-(Biphenyl-4-yl)ethanone O-acetyl oxime (2-1c)

Prepared from 1-(biphenyl-4-yl)ethanone and purified by recrystallization from hexane-ethyl acetate (twice) in 84% yield; White solid; mp. 93–95 °C; IR (NaCl) 3053, 1763, 1616, 1603, 1487, 1367, 1319 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.28 (3H, s), 2.42 (3H, s), 7.38 (1H, t, J = 7.3 Hz), 7.46 (2H, dd, J = 7.3, 7.5 Hz), 7.61 (1H, d, J = 7.5 Hz), 7.64 (1H, d, J = 8.5 Hz), 7.83 (1H, d, J = 8.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 19.8, 127.0, 127.1, 127.4, 127.8, 128.8, 133.5, 140.0, 143.3, 162.0, 168.9; ESI-HRMS: Found: m/z 254.1180. Calcd for C₁₆H₁₆NÖ₂: (M+H)⁺ 251.1181.

(E)-1-(4-Bromophenyl)ethanone O-acetyl oxime (2-1d)

Prepared from 1-(4-bromophenyl)ethanone and purified by recrystallization from hexane-ethyl acetate (twice) in 88% yield; White solid; mp. 95–97 °C; IR (NaCl) 1767, 1616, 1591, 1396, 1368, 1315, 1009 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.26 (3H, s), 2.36 (3H, s), 7.53 (2H, d, J = 8.8 Hz), 7.61 (2H, d, J = 8.5 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.2, 19.8, 125.1, 128.5, 131.8, 133.7, 161.4, 168.7; ESI-HRMS: Found: m/z 255.9978. Calcd for C₁₆H₁₁NO₂⁺Br: (M+H)⁺ 255.9973.
(E)-1-(4-(Trifluoromethyl)phenyl)ethanone O-acetyl oxime (2-1e)

Prepared from 1-(4-(trifluoromethyl)phenyl)ethanone and purified by recrystallization from hexane-ethyl acetate (one time) in 79% yield; White solid; mp. 42–44 °C; IR (NaCl) 1769, 1368, 1327, 1204, 1132, 1065 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.27 (3H, s), 2.41 (3H, s), 7.66 (2H, d, J = 8.0 Hz), 7.86 (2H, d, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 19.7, 123.8 (q, J = 270 Hz), 125.5 (q, J = 3.7 Hz), 127.3, 132.2 (q, J = 32.5 Hz), 138.3, 161.1, 168.5; ESI-HRMS: Found: m/z 246.0752. Calcd for C₁₁H₁₁NO₂F₃: (M+H)⁺ 246.0742.

(E)-1-(2-Methoxyphenyl)ethanone O-acetyl oxime (2-1f)

Prepared from 1-(2-methoxyphenyl)ethanone and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 70:30) in 38% yield; Colorless oil; IR (NaCl) 2940, 1767, 1616, 1599, 1493, 1366, 1246, 1204 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.24 (3H, s), 2.33 (3H, s), 3.83 (3H, s), 6.91 (1H, d, J = 8.4 Hz), 6.96 (1H, dd, J = 7.2, 7.6 Hz), 7.36 (1H, d, J = 7.6 Hz), 7.37-7.40 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 17.4, 19.8, 55.4, 110.9, 120.6, 125.2, 129.8, 131.1, 157.5, 164.8, 168.9; ESI-HRMS: Found: m/z 208.0982. Calcd for C₁₁H₁₄NO₃: (M+H)⁺ 208.0974.
(E)-1-(2-Bromophenyl)ethanone O-acetyl oxime (2-1g)

Prepared from 1-(2-bromophenyl)ethanone and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 85:15) in 66% yield; White solid; mp. 44–46 °C; IR (NaCl) 1767, 1474, 1433, 1368, 1317, 1254 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.24 (3H, s), 2.36 (3H, s), 7.23-7.27 (1H, m), 7.32-7.33 (2H, m), 7.57 (1H, d, J = 7.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 18.0, 19.6, 121.3, 127.4, 130.2, 130.7, 133.0, 137.2, 164.7, 168.5; ESI-HRMS: Found: m/z 255.9982. Calcd for C₁₀H₁₁NO₂Br: (M+H)⁺ 255.9973.

(E)-1-(3-Methoxyphenyl)ethanone O-acetyl oxime (2-1h)

Prepared from 1-(3-methoxyphenyl)ethanone and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) in 89% yield; Colorless oil; IR (NaCl) 2939, 2835, 1769, 1578, 1429, 1323, 1238, 1202 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.26 (3H, s), 2.36 (3H, s), 3.83 (3H, s), 6.96-6.99 (1H, m), 7.26-7.33 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ 14.5, 19.8, 55.3, 112.2, 116.3, 119.5, 129.5, 136.2, 159.6, 162.4, 168.9; ESI-HRMS: Found: m/z 208.0972. Calcd for C₁₁H₁₄NO₃: (M+H)⁺ 208.0974.
(E)-1-(3-Bromophenyl)ethanone O-acetyl oxime (2-1i)

\[
\begin{align*}
\text{Br} & \quad \text{N} \quad \text{OAc} \\
\text{Me} & \quad \text{N} \quad \text{OAc}
\end{align*}
\]

Prepared from 1-(3-bromophenyl)ethanone and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) in 99% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.26 (3H, s), 2.35 (3H, s), 7.27 (1H, dd, \(J = 7.8, 7.8\) Hz), 7.55 (1H, d, \(J = 7.8\) Hz), 7.65 (1H, d, \(J = 7.8\) Hz), 7.88 (1H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.3, 19.7, 122.7, 125.6, 129.9, 130.0, 133.5, 136.8, 161.1, 168.6.

(E)-1-(Thiophen-2-yl)ethanone O-acetyl oxime (2-1j)

\[
\begin{align*}
\text{S} & \quad \text{N} \quad \text{OAc} \\
\text{Me} & \quad \text{N} \quad \text{OAc}
\end{align*}
\]

Prepared from (E)-1-(thiophen-2-yl)ethanone oxime\(^3\) and purified by recrystallization from hexane-ethyl acetate (twice) in 89% yield; White solid; mp. 128–130 °C; IR (NaCl) 1763, 1601, 1529, 1368, 1306, 966 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.25 (3H, s), 2.40 (3H, s), 7.06 (1H, dd, \(J = 4.0, 5.2\) Hz), 7.41 (1H, d, \(J = 5.2\) Hz), 7.43 (1H, d, \(J = 4.0\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.4, 19.7, 127.2, 129.1, 129.2, 137.9, 157.7, 168.8; ESI-HRMS: Found: m/z 184.0435. Calcd for C\(_8\)H\(_{10}\)NO\(_2\)S: (M+H)\(^+\) 184.0432.

\(^2\) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* 2010, 12, 532.

\(^3\) Treatment of 1-(thiophen-2-yl)ethanone with hydroxylamine provided an mixture of syn- and anti-oxime in the ration of 1:0.3. Pure anti-oxime could be obtained by recrystallization of the mixture oxime from hexane-ethyl acetate. See: Spears, G. W.; Tsuji, K.; Tojo, T.; Nishimura, H.; Ogino, T. *Synth. Commun.* 2000, 30, 565.
Benzophenone O-acetyl oxime (2-1k)\textsuperscript{4}

\[
\begin{array}{c}
\text{N} \\
\text{OAc}
\end{array}
\]

Prepared from benzophenone and purified by recrystallization from hexane-ethyl acetate (one time) in 73\% yield; White solid; \( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta \) 2.11 (3H, s), 7.31-7.38 (4H, m), 7.43-7.49 (4H, m), 7.57-7.59 (2H, m); \( ^13\text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 19.7, 128.2, 128.4, 128.8, 129.0, 129.6, 130.9, 132.5, 134.8, 164.7, 168.8.

(1E,2E)-Chalcone O-acetyl oxime (2-1l)

\[
\begin{array}{c}
\text{N} \\
\text{OAc}
\end{array}
\]

Prepared from (1E,2E)-chalcone oxime\textsuperscript{4} and purified by recrystallization from hexane-ethyl acetate (twice) in 70\% yield; White solid; mp. 112–113 °C; IR (NaCl) 3061, 1765, 1618, 1447, 1368, 1342 cm\textsuperscript{-1}; \( ^1\text{H NMR (400 MHz, CDCl}_3 \) \( \delta \) 2.32 (3H, s), 6.85 (1H, d, \( J = \text{16.4 Hz} \)), 7.37-7.40 (3H, m), 7.43-7.52 (5H, m), 7.56-7.59 (3H, m); \( ^13\text{C NMR (100 MHz, CDCl}_3 \) \( \delta \) 19.8, 117.3, 127.8, 128.4, 128.8, 129.7, 130.0, 130.1, 133.1, 135.2, 143.2, 163.2, 168.8; ESI-HRMS: Found: m/z 266.1176. Calcd for C\textsubscript{17}H\textsubscript{16}N\textsubscript{2}O:\ (M+H\textsuperscript{+})\textsuperscript{5}

266.1181.


\textsuperscript{5} Treatment of trans-chalcone with hydroxylamine provided an \textit{syn-} and \textit{anti-}mixture of oxime in the ratio of 1:0.55. These isomers were separated by flash column chromatography and recrystallization. See: Ohwada, T.; Yamagata, N.; Shudo, K. \textit{J. Am. Chem. Soc.} \textbf{1991}, \textit{113}, 1364.
(Z)-Methyl 2-(acetoxyimino)-2-phenylacetate (2-1m)

\[
\begin{align*}
\text{CH}_2\text{CO}_2\text{Me} & \quad \text{N} \quad \text{OAc} \\
\end{align*}
\]

Prepared from methyl 2-oxo-2-phenylacetate and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 75:25) in 65% yield; Colorless oil; IR (NaCl) 2957, 1782, 1746, 1447, 1368, 1335, 1233, 1186 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.23 (3H, s), 3.99 (3H, s), 7.43 (2H, dd, \(J = 7.2, 7.6\) Hz), 7.51 (1H, t, \(J = 7.6\) Hz), 7.70 (2H, d, \(J = 7.2\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 19.5, 52.8, 127.4, 128.4, 129.0, 132.1, 156.9, 162.6, 167.4; ESI-HRMS: Found: m/z 222.0767. Calcd for C\(_{11}\)H\(_{12}\)NO\(_4\): (M+H\(^+\)) 222.0766.

(E)-3,4-Dihydronaphthalen-1(2H)-one O-acetyl oxime (2-1n)

\[
\begin{align*}
\text{N} \quad \text{OAc} \\
\end{align*}
\]

Prepared from \(\alpha\)-tetralone and purified by recrystallization from hexane-ethyl acetate (twice) in 83% yield; White solid; mp. 147–149 °C; IR (NaCl) 2945, 1761, 1368, 1321, 1003, 945, 926 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.89 (2H, tt, \(J = 6.4, 6.4\) Hz), 2.27 (3H, s), 2.79 (2H, t, \(J = 6.4\) Hz), 2.87 (2H, t, \(J = 6.4\) Hz), 7.17 (1H, d, \(J = 7.6\) Hz), 7.23 (1H, dd, \(J = 7.2, 7.6\) Hz), 7.34 (1H, dd, \(J = 7.2, 7.6\) Hz), 8.14 (1H, d, \(J = 7.6\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 19.9, 21.3, 25.6, 29.5, 125.6, 126.6, 128.7, 128.9, 130.7, 140.9, 161.3, 169.2; ESI-HRMS: Found: m/z 204.1021. Calcd for C\(_{12}\)H\(_{14}\)NO\(_2\): (M+H\(^+\)) 204.1025.
Isobutyrophenone O-acetyl oxime (2-1o)

\[
\text{\begin{align*}
\text{N} & \quad \text{Me} \\
\text{Me} & \quad \text{Me}
\end{align*}}
\]

\[
\text{sym:anti} = 1:1
\]

Colorless oil; IR (NaCl) 2970, 2934, 1626, 1466, 1445, 1366, 1206 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.17 (6\text{H} x 1, \text{d}, J = 6.8 \text{ Hz}), 1.22 (6\text{H} x 1, \text{d}, J = 7.2 \text{ Hz}), 1.95 (3\text{H} x 1, \text{s}), 2.23 (3\text{H} x 1, \text{s}), 2.99 (1\text{H} x 1, \text{septet}, J = 6.8 \text{ Hz}), 3.53 (1\text{H} x 1, \text{septet}, J = 7.2 \text{ Hz}), 7.13-7.16 (2\text{H} x 1, \text{m}), 7.34-7.45 (3\text{H} x 1+5\text{H} x 1, \text{m}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 19.49, 19.53, 19.77, 19.81, 29.9, 34.9, 126.7, 128.0, 128.1, 128.2, 128.7, 129.4, 132.9, 133.9, 168.79, 168.83, 171.6, 171.9; \text{ESI-HRMS: Found: m/z 206.1189. Calcd for C}_{12}\text{H}_{16}\text{NO}_2: (M+H)^+ 206.1181.}

\(\left(E\right)-1-(2-((\left(E\right)-1,2-\text{Diphenylvinyl})\text{phenyl})\text{ethanone O-acetyl oxime (2-1p)}}

\[
\text{\begin{align*}
\text{N} & \quad \text{Ph} \\
\text{Me} & \quad \text{Ph}
\end{align*}}
\]

Prepared from \(\left(E\right)-1-(2-(1,2-\text{diphenylvinyl})\text{phenyl})\text{ethanone}^6\) and purified by recrystallization from hexane-ethyl acetate (twice) in 70% yield; White solid; mp. 111–115 °C; IR (NaCl) 1765, 1491, 1443, 1368, 1317, 930 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.89 (3\text{H}, \text{s}), 2.01 (3\text{H}, \text{s}), 7.00-7.02 (3\text{H}, \text{m}), 7.11-7.15 (3\text{H}, \text{m}), 7.24-7.32 (5\text{H}, \text{m}), 7.36-7.43 (3\text{H}, \text{m}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 16.5, 19.9, 127.1, 127.4, 127.7, 128.0, 128.1, 128.3, 129.0, 129.2, 129.3, 129.8, 131.9, 136.3, 137.0, 139.2, 141.0, 142.5, 163.4, 170.7; \text{ESI-HRMS: Found: m/z 356.1653. Calcd for C}_{24}\text{H}_{22}\text{NO}_2: (M+H)^+ 356.1651.}

6.2.1.2. Preparation of 4,4-dimethyl-3-phenylisoxazol-5(4H)-one (2-5a)$^7$

\[
\begin{align*}
\text{O} & \quad \text{Me} \quad \text{Me} \quad \text{OEt} \quad \text{NH}_2\text{OH} + \text{HCl, KOH} \\
\text{H}_2\text{O}, 0^\circ\text{C} & \quad \rightarrow \\
\text{N-O} & \quad \text{Me} \quad \text{Me} \\
2-5a
\end{align*}
\]

To a stirred solution of NH$_2$OH·HCl (0.87 g, 12.5 mmol) in minimum amount of H$_2$O at 0°C was added 8 M of KOH (0.91 g, 22.8 mmol) in H$_2$O and ethyl 2,2-dimethyl-3-oxo-3-phenylpropanoate (2.50 g, 11.4 mmol) dropwise. The reaction mixture was allowed to stir at 0°C for 18 h. The reaction was quenched by 1 M aqueous HCl and the organic materials were extracted three times with CH$_2$Cl$_2$. The combined extracts were washed with sat. NaHCO$_3$ and dried over MgSO$_4$. Volatile materials were removed in vacuo and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 60:40) to give isoxazolone 2-5a in 66% yield.

4,4-Dimethyl-3-phenylisoxazol-5(4H)-one (2-5a)

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.62 (6H, s), 7.47-7.54 (3H, m), 7.76 (2H, d, $J$ = 8.0 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 23.0, 45.7, 126.9, 127.6, 129.2, 131.6, 169.7, 181.8.

---

6.2.1.3. Preparation of 3-phenylisoxazol-5-ones 2-5b and 2-5c: a typical procedure for the synthesis of 4,4-dimethyl-3-phenylisoxazol-5(4H)-one (2-5b)

![Chemical structure](image)

To a solution of ethyl benzyl benzoylacetate (2.00 g, 7.08 mmol) and pyridine (1.7 mL, 21.3 mmol) in EtOH (7 mL) was added NH$_2$OH·HCl (0.99 g, 14.2 mmol) in one portion and the reaction mixture was stirred at 60 °C for 18 h. The reaction was quenched by adding water and the organic materials were extracted three times with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO$_4$. Volatile materials were removed in vacuo and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 60:40) to give isoxazolone 2-5b in 39% yield.

4-Benzyl-3-phenylisoxazol-5(4H)-one (2-5b)$^8$

![Chemical structure](image)

a mixture of imine form and enamine form in 75 : 25 ratio

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.29 (0.75H$_{\text{imine}}$, dd, $J = 5.2, 14.0$ Hz), 3.37 (0.75H$_{\text{imine}}$, dd, $J = 4.8, 14.0$ Hz), 3.78 (0.5H$_{\text{enamine}}$, s), 4.15 (0.75H, dd, $J = 4.8, 5.2$ H), 6.87 (1.5H$_{\text{imine}}$, d, $J = 7.6$ Hz), 7.15-7.29 (3H, m), 7.76 (3.5H, m), 7.43-7.61 (5H, m); $^{13}$C NMR for imine form (100 MHz, CDCl$_3$) δ 34.6, 46.5, 126.9, 127.7, 128.6 (overlapped), 129.0, 129.3, 131.8, 134.2, 165.7, 177.5.

3-Phenylisoxazol-5(4H)-one (2-5c)\(^9\)

\[
\begin{array}{c}
\text{N} \\
\text{O-} \\
\text{O}
\end{array}
\]

Prepared from ethyl benzoylacetate and purified by recrystallization from hexane-ethyl acetate (twice) in 74% yield; White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.8 (2H, s), 7.46-7.57 (3H, m), 7.67-7.70 (2H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 34.0, 126.6, 127.6, 129.2, 132.2, 163.0, 174.7.

6.2.2 Rh (III)-catalyzed synthesis of isoquinolines: a typical procedure for the reaction of acetophenone \(O\)-acetyl oxime (2-1a) and diphenylacetylene (2-2a) (Table 2-1, entry 2).

![Reaction scheme](image)

To a MeOH solution (1.5 mL) of acetophenone \(O\)-acetyl oxime (2-1a) (53.2 mg, 0.30 mmol) and diphenylacetylene (2-2a) (64.2 mg, 0.36 mmol) were added \([\text{Cp}^*\text{RhCl}_2]\) (2.5 mol %) and NaOAc (30 mol %), and the reaction mixture was stirred at 60 °C under a nitrogen atmosphere for 6 h. After cooled to room temperature, the solvent was removed \textit{in vacuo}, and the resulting crude material was subjected to flash column chromatography (hexane : ethyl acetate = 8 : 92) to afford 1-methyl-3,4-diphenylisoquinoline (2-3aa) (73.5 mg, 0.248 mmol) in 82% yield.

1-Methyl-3,4-diphenylisoquinoline (2-3aa)\(^\text{10}\)

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.01 (3H, s), 7.16-7.26 (5H, m), 7.32-7.34 (5H, m), 7.58-7.61 (2H, m), 7.64-7.68 (1H, m). 8.20-8.23 (1H, m); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 22.7, 125.5, 126.1, 126.2, 126.5, 126.9, 127.1, 127.6, 128.2, 129.1, 129.9, 130.2, 131.4, 136.0, 137.6, 141.0, 149.4, 157.7.

1,4-Dimethyl-3-phenylisoquinoline (2-3ab)\(^\text{10}\)

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.60 (3H, s), 2.99 (3H, s), 7.39 (1H, t, \(J=7.2\) Hz), 7.47 (2H, dd, \(J=7.2, 7.6\) Hz), 7.57-7.63 (3H, m), 7.75 (1H, dd, \(J=7.6, 8.4\) Hz), 8.06 (1H, d, \(J=8.4\) Hz), 8.17 (1H, d, \(J=8.4\) Hz); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 15.4, 22.5, 122.2, 124.1, 126.1, 126.17, 126.24, 127.4, 128.1, 129.9 (overlapped), 136.3, 141.6, 150.7, 155.9.

(1-Methyl-3-phenylisoquinolin-4-yl)methanol (2-3ac)

Pure 2-3ac was obtained by recrystallization from hexane-ethyl acetate.

Yellow solid; mp. 161-163 °C; IR (NaCl) 3069, 2992, 1616, 1568, 1506, 1487, 1445, 1396 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.01 (3H, s), 5.03 (2H, s), 7.40-7.50 (3H, m), 7.62-7.82 (2H, m), 7.92-8.02 (2H, m), 8.23-8.32 (2H, m).

7.62-7.67 (3H, m), 7.79 (1H, ddd, J = 8.4, 6.8, 1.2 Hz), 8.20 (1H, d, J = 8.0 Hz), 8.30 (1H, d, J = 8.4 Hz); 13C NMR (100 MHz, CDCl₃) δ 22.7, 59.5, 124.1, 124.4, 126.1, 126.7, 128.0, 128.2, 129.7 (overlapped), 130.6, 135.8, 140.5, 151.8, 158.6; ESI-HRMS: Found: m/z 250.1234. Calcd for C₁₇H₁₆NO: (M+H)⁺ 250.1232.

4-((tert-Butyldimethylsilyloxy)methyl)-1-methyl-3-phenylisoquinoline (2-3ad)

Regioisomer (2-3ad-minor) was separated by flash column chromatography.

Pale yellow solid; mp. 84-87 °C; IR (NaCl) 2953, 2927, 1566, 1504, 1441, 1254, 1080, 1053 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.09 (6H, s), 0.91 (9H, s), 3.01 (3H, s), 4.99 (2H, s), 7.42-7.49 (3H, m), 7.61 (1H, dd, J = 8.0, 8.0 Hz), 7.71 (2H, d, J = 7.6 Hz), 7.76 (1H, dd, J = 8.0, 8.4 Hz), 8.17 (1H, d, J = 8.0 Hz), 8.25 (1H, d, J = 8.4 Hz); 13C NMR (100 MHz, CDCl₃) δ -5.33, 18.3, 22.7, 25.8, 60.1, 124.4, 124.9, 125.9, 126.4, 126.7, 127.9, 128.0, 129.9, 130.0, 136.2, 140.6, 151.4, 158.2; ESI-HRMS: Found: m/z 364.2105. Calcd for C₂₃H₃₀NOSi: (M+H)⁺ 364.2097.

3-((tert-Butyldimethylsilyloxy)methyl)-1-methyl-4-phenylisoquinoline (2-3ad-minor)

Pale yellow oil; IR (NaCl) 2951, 2928, 2855, 1566, 1462, 1393, 1254, 1080 cm⁻¹; (NaCl) cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ -0.06 (6H, s), 0.83 (9H, s), 3.03 (3H, s), 4.67 (2H, s),
7.33-7.36 (2H, m), 7.44-7.52 (4H, m), 7.53-7.58 (2H, m), 8.14-8.16 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ -5.25, 18.5, 22.4, 26.0, 65.5, 125.4, 126.2, 126.44, 126.48, 127.5, 128.2, 129.6, 130.3, 130.7, 136.0, 136.8, 148.6, 157.6; ESI-HRMS: Found: m/z 364.2097. Calcd for C$_{22}$H$_{30}$NOSi: (M+H)$^+$ 364.2097.

1-Methyl-3,4-dipropylisoquinoline (2-3ae)$^{10}$

![Image of 1-Methyl-3,4-dipropylisoquinoline (2-3ae)]

White solid; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.04 (3H, t, $J = 7.6$ Hz), 1.09 (3H, t, $J = 7.2$ Hz), 1.62-1.72 (2H, m), 1.73-1.83 (2H, m), 2.88-2.91 (2H, m), 2.92 (3H, s), 2.95-3.00 (2H, m), 7.48 (1H, dd, $J = 8.4$, 8.8 Hz), 7.65 (1H, dd, $J = 8.4$, 8.4 Hz), 7.96 (1H, d, $J = 8.8$ Hz), 8.08 (1H, d, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.4, 14.6, 22.3, 23.8, 24.2, 29.8, 37.4, 123.6, 125.2, 126.0, 126.1, 126.2, 129.4, 135.4, 151.6, 155.6.

3,4-Bis((tert-butyldimethylsilyloxy)methyl)-1-methylisoquinoline (2-3af)

![Image of 3,4-Bis((tert-butyldimethylsilyloxy)methyl)-1-methylisoquinoline (2-3af)]

White solid; mp. 63–65 °C; IR (NaCl) 2955, 2930, 1570, 1462, 1392, 1256, 1059, 837 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.10 (6H, s), 0.11 (6H, s), 0.90 (9H, s), 0.91 (9H, s), 2.94 (3H, s), 5.03 (2H, s), 5.26 (2H, s), 7.55 (1H, dd, $J = 8.0$, 8.4 Hz), 7.69 (1H, dd, $J = 8.0$, 8.4 Hz), 8.10 (1H, d, $J = 8.4$ Hz), 8.28 (1H, d, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ -5.15, -5.06, 18.30, 18.33, 22.4, 25.88, 25.93, 58.3, 66.3, 125.2, 125.7, 126.3, 126.7, 127.1, 129.5, 136.0, 149.5, 157.5; ESI-HRMS: Found: m/z 432.2756. Calcd for C$_{24}$H$_{42}$NO$_2$Si$_2$: (M+H)$^+$ 432.2754.
6-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3ba)\textsuperscript{10}

![Chemical Structure of 6-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3ba)]

White solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.02 (3H, s), 3.73 (3H, s), 6.92 (1H, d, \(J = 2.4\) Hz), 7.15-7.24 (6H, m), 7.30-7.36 (5H, m), 8.11 (1H, d, \(J = 9.2\) Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 22.7, 55.2, 104.5, 118.7, 121.9, 126.8, 127.1, 127.4, 127.5, 128.2, 128.6, 130.2, 131.3, 137.9, 138.0, 141.2, 150.1, 157.0, 160.5.

1-Methyl-3,4,6-triphenylisoquinoline (2-3ca)

![Chemical Structure of 1-Methyl-3,4,6-triphenylisoquinoline (2-3ca)]

White solid; mp. 177-179 °C; IR (NaCl) 3059, 2959, 1730, 1616, 1568, 1487, 1447, 1339 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.11 (3H, s), 7.18-7.28 (5H, m), 7.32-7.45 (6H, m), 7.57 (2H, d, \(J = 7.6\) Hz), 7.85 (1H, d, \(J = 9.2\) Hz), 7.86 (1H, s), 8.28 (1H, d, \(J = 9.2\) Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 22.7, 124.0, 125.2, 126.17, 126.19, 126.17, 126.19, 126.9, 127.2, 127.5, 127.6, 127.9, 128.2, 128.9, 129.4, 130.2, 131.4, 136.3, 137.5, 140.5, 141.0, 142.5, 150.0, 157.6; ESI-HRMS: Found: m/z 372.1754. Calcd for C\textsubscript{28}H\textsubscript{22}N: (M+H)\textsuperscript{+} 372.1752.
6-Bromo-1-methyl-3,4-diphenylisoquinoline (2-3da)

![Structure of 6-Bromo-1-methyl-3,4-diphenylisoquinoline](image)

White solid; mp. 193–195 °C; IR (NaCl) 3059, 2965, 1601, 1566, 1483, 1439, 1393, 1331, 1082 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.05 (3H, s), 7.17-7.21 (5H, m), 7.32-7.39 (5H, m), 7.67 (1H, dd, J = 2.0, 8.0 Hz), 7.80 (1H, d, J = 2.0 Hz), 8.06 (1H, d, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.7, 124.6, 125.0, 127.2, 127.3, 127.5, 127.6, 128.3, 128.4 (overlapped), 130.0, 130.2, 131.3, 136.9, 137.4, 140.6, 150.6, 157.8; ESI-HRMS: Found: m/z 374.0543. Calcd for C₂₂H₁₇N₇9Br: (M+H)+ 374.0544.

1-Methyl-3,4-diphenyl-6-(trifluoromethyl)isoquinoline (2-3ea)

![Structure of 1-Methyl-3,4-diphenyl-6-(trifluoromethyl)isoquinoline](image)

White solid; ¹H NMR (400 MHz, CDCl₃) δ 3.01 (3H, s), 7.19-7.24 (5H, m), 7.34-7.41 (5H, m), 7.76 (1H, d, J = 8.8 Hz), 7.98 (1H, s), 8.32 (1H, d, J = 8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.8, 122.2 (q, J = 3.0 Hz), 123.8 (q, J = 271 Hz), 123.9 (q, J = 5.0 Hz), 126.8, 127.0, 127.3, 127.66, 127.70, 128.5, 129.7, 130.2, 131.3, 131.5 (q, J = 33 Hz), 135.5, 136.5, 140.4, 150.9, 157.8.
8-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3fa)

\[
\text{Ph} \quad \text{N} \quad \text{Me} \quad \text{OMe}
\]

White solid; mp. 146–147 °C; IR (NaCl) 3061, 2965, 1610, 1572, 1551, 1456, 1433, 1389, 1263 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 3.22 (3H, s), 4.02 (3H, s), 6.90 (1H, d, J = 7.6 Hz), 7.15–7.22 (6H, m), 7.30–7.38 (5H, m), 7.44 (1H, dd, J = 7.6, 7.6 Hz); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 29.3, 55.5, 105.9, 118.4, 119.1, 126.9, 127.0, 127.5, 128.1, 128.3, 130.0, 130.2, 131.4, 138.2, 138.8, 140.9, 149.5, 157.5, 158.1; ESI-HRMS: Found: m/z 326.1543. Calcd for C\(_{23}\)H\(_{20}\)NO: (M+H\(^{+}\)) 326.1545.

8-Bromo-1-methyl-3,4-diphenylisoquinoline (2-3ga)

\[
\text{Ph} \quad \text{N} \quad \text{Me} \quad \text{Br}
\]

White solid; mp. 144–147 °C; IR (NaCl) 3061, 2978, 1543, 1499, 1435, 1385, 1356, 1339 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) δ 3.45 (3H, s), 7.17-7.21 (5H, m), 7.29 (1H, dd, J = 7.2, 8.4 Hz), 7.33–7.38 (5H, m), 7.61 (1H, d, J = 8.4 Hz), 7.91 (1H, d, J = 7.2 Hz); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 30.1, 120.1, 125.8, 126.6, 127.2, 127.4, 127.6, 128.4, 129.2, 129.4, 130.2, 131.4, 133.7, 137.6, 139.4, 140.3, 149.4, 157.4; ESI-HRMS: Found: m/z 374.0540. Calcd for C\(_{22}\)H\(_{17}\)N\(_{79}\)Br: (M+H\(^{+}\)) 374.0544.
7-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3ha)

Regioisomer (2-3ha') was separated by flash column chromatography.

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.04 (3H, s), 3.99 (3H, s), 7.13-7.26 (6H, m), 7.29-7.36 (5H, m), 7.39 (1H, d, \(J = 2.4\) Hz), 7.58 (1H, d, \(J = 9.2\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 22.8, 55.5, 103.5, 122.2, 126.7, 127.1, 127.3, 127.5, 128.0, 128.1, 129.2, 130.2, 131.3 (overlapped), 137.7, 141.0, 147.7, 156.0, 157.8.

5-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3ha')

White solid; mp. 147-149 °C; IR (NaCl) 3059, 2959, 1610, 1551, 1501, 1458, 1395, 1263 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.05 (3H, s), 3.41 (3H, s), 6.96 (1H, d, \(J = 7.6\) Hz), 7.01-7.18 (8H, m), 7.22-7.25 (2H, m), 7.53 (1H, dd, \(J = 7.6, 8.4\) Hz), 7.80 (1H, d, \(J = 8.4\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.3, 55.5, 110.0, 118.0, 125.6, 126.4 (overlapped), 127.1, 127.3, 127.4, 127.7, 127.9, 130.2, 130.3, 141.4, 141.6, 151.0, 156.8, 157.1; ESI-HRMS: Found: m/z 326.1546. Calcd for C\(_{23}\)H\(_{20}\)NO: (M+H)\(^+\) 326.1545.
7-Bromo-1-methyl-3,4-diphenylisoquinoline (2-3ia)

Regioisomer (2-3ia') was separated by flash column chromatography.

White solid; mp. 134–136 °C; IR (NaCl) 3061, 2961, 1553, 1497, 1443, 1383, 1358 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.04 (3H, s), 7.17-7.22 (5H, m), 7.33-7.38 (5H, m), 7.53 (1H, d, J = 9.2 Hz), 7.64 (1H, dd, J = 2.0, 9.2 Hz), 8.34 (1H, d, J = 2.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.7, 120.5, 127.1, 127.3, 127.4, 127.7, 127.9, 128.2, 128.3, 129.1, 130.2, 131.3, 133.2, 134.7, 137.0, 140.6, 149.9, 156.8; ESI-HRMS: Found: m/z 374.0545. Calcd for C₂₂H₁₇N₇⁹Br: (M+H)+ 374.0544.

5-Bromo-1-methyl-3,4-diphenylisoquinoline (2-3ia')

White solid; mp. 166–168 °C; IR (NaCl) 3059, 2963, 1601, 1558, 1543, 1497, 1447, 1389 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.07 (3H, s), 7.11-7.22 (10H, m), 7.42 (1H, dd, J = 7.6, 8.4 Hz), 7.98 (1H, d, J = 7.6 Hz), 8.24 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 23.5, 120.2, 126.0, 126.7, 126.9, 127.1, 127.2, 127.3, 128.2, 128.8, 129.9, 132.5, 133.2, 138.0, 138.1, 141.4, 152.9, 158.0; ESI-HRMS: Found: m/z 374.0544. Calcd for C₂₂H₁₇N₇⁹Br: (M+H)+ 374.0544.
7-Methyl-4,5-diphenylthieno[2,3-c]pyridine (2-3ja)\(^8\)

![Image of 7-Methyl-4,5-diphenylthieno[2,3-c]pyridine](image)

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.91 (3H, s), 7.18-7.25 (6H, m), 7.29-7.37 (5H, m), 7.61 (1H, d, \(J = 5.2\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 23.7, 124.2, 127.0, 127.1, 127.7, 128.18, 128.23, 130.3, 130.5, 130.9, 134.2, 138.3, 140.5, 145.7, 150.9, 151.4.

1,3,4-Triphenylisoquinoline (2-3ka)\(^8\)

![Image of 1,3,4-Triphenylisoquinoline](image)

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.17-7.22 (3H, m), 7.30-7.32 (2H, m), 7.34-7.44 (5H, m), 7.45-7.62 (5H, m), 7.73 (1H, d, \(J = 8.4\) Hz), 7.83 (1H, d, \(J = 6.8\) Hz), 8.19 (1H, d, \(J = 8.4\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 125.4, 126.0, 126.6, 127.0, 127.3, 127.50, 127.53, 128.3 (overlapped), 128.5, 129.8, 129.9, 130.2, 130.4, 131.3, 137.0, 137.6, 139.8, 140.9, 149.6, 159.8.

(\(E\))-3,4-Diphenyl-1-styrylisoquinoline (2-3la)

![Image of (\(E\))-3,4-Diphenyl-1-styrylisoquinoline](image)

White solid; mp. 172–174 °C; IR (NaCl) 3061, 1632, 1539, 1503, 1449, 1385, 1339 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20-7.27 (5H, m), 7.31-7.48 (8H, m), 7.56-7.62 (2H, m),
7.69-7.73 (3H, m), 8.08 (1H, d, J = 15.6 Hz), 8.14 (1H, d, J = 15.6 Hz), 8.45 (1H, d, J = 8.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 122.9, 124.3, 125.4, 126.3, 126.6, 127.1, 127.2, 127.47, 127.51, 128.3, 128.5, 128.7, 129.78, 129.83, 130.5, 131.4, 136.1, 136.8, 137.1, 137.7, 141.1, 149.8, 153.4; ESI-HRMS: Found: m/z 384.1753. Calcd for C$_{29}$H$_{22}$N: (M+H)$^+$ 384.1752.

**Methyl 3,4-diphenyisoquinoline-1-carboxylate (2-3ma)**

![Methyl 3,4-diphenyisoquinoline-1-carboxylate](image)

White solid; mp. 157–159 ºC; IR (NaCl) 3059, 2953, 1724, 1549, 1502, 1439, 1362, 1256 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.11 (3H, s), 7.18-7.25 (5H, m), 7.35-7.41 (5H, m), 7.62-7.73 (3H, m), 8.71-8.74 (1H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 53.0, 125.2, 126.0, 126.2, 127.4, 127.68, 127.71, 128.0, 128.4, 130.4, 130.5, 131.0, 133.9, 136.8, 137.0, 139.9, 148.4, 149.6, 166.7; ESI-HRMS: Found: m/z 340.1337. Calcd for C$_{23}$H$_{18}$NO$_2$: (M+H)$^+$ 340.1338.

**2,3-Diphenyl-8,9-dihydro-7H-benzo[de]quinoline (2-3na)**

![2,3-Diphenyl-8,9-dihydro-7H-benzo[de]quinoline](image)

White solid; mp. 151–153 ºC; IR (NaCl) 3061, 2947, 1607, 1580, 1557, 1443, 1389, 1375 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.28 (2H, tt, $J = 6.0$, 6.4 Hz), 3.20 (2H, t, $J = 6.0$ Hz), 3.38 (2H, t, $J = 6.4$ Hz), 7.15-7.23 (5H, m), 7.31-7.37 (6H, m), 7.45-7.51 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 23.4, 30.7, 34.8, 123.5, 123.9, 124.7, 126.8, 127.0, 127.6,
128.1, 129.0, 129.9, 130.2, 131.4, 136.2, 137.8, 138.5, 141.1, 149.5, 159.3; ESI-HRMS: 
Found: m/z 322.1594. Calcd for C₂₄H₂₀N: (M+H)⁺ 322.1596.

1-Isopropyl-3,4-diphenylisoquinoline (2-3oa)

![Chemical structure of 1-Isopropyl-3,4-diphenylisoquinoline](image)

White solid; mp. 142–145 °C; IR (NaCl) 3061, 2967, 1551, 1504, 1389, 1323, 1009 cm⁻¹; 
¹H NMR (400 MHz, CDCl₃) δ 1.53 (6H, d, J = 6.8 Hz), 4.03 (1H, septet, J = 6.8 Hz), 7.17-7.22 (3H, m), 7.23-7.25 (2H, m), 7.34-7.40 (3H, m), 7.43-7.46 (2H, m), 7.53-7.60 (2H, m), 7.66-7.68 (1H, m), 8.29-8.31 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 31.3, 124.5, 124.8, 126.2, 126.5, 126.8, 127.1, 127.4, 128.3, 128.4, 129.3, 130.6, 131.4, 136.5, 138.1, 141.3, 148.6, 165.0; ESI-HRMS: Found: m/z 324.1748. Calcd for C₂₄H₂₂N: (M+H)⁺ 324.1752.

(E)-8-(1,2-Diphenylvinyl)-1-methyl-3,4-dipropylisoquinoline (2-3pe)

![Chemical structure of (E)-8-(1,2-Diphenylvinyl)-1-methyl-3,4-dipropylisoquinoline](image)

Yellow oil; IR (NaCl) 2959, 2930, 1597, 1560, 1493, 1445, 1375, 1217 cm⁻¹; ¹H NMR 
(400 MHz, CDCl₃) δ 1.04 (3H, t, J = 7.6 Hz), 1.15 (3H, t, J = 7.2 Hz), 1.72-1.81 (4H, m), 2.81 (3H, s), 2.85-2.89 (2H, m), 3.01-3.05 (2H, m), 6.93-6.95 (2H, m), 7.04-7.07 (3H, m), 7.21-7.29 (8H, m), 7.50 (1H, dd, J = 7.2, 8.8 Hz), 8.03 (1H, dd, J = 0.8, 8.8 Hz); ¹³C 
NMR (100 MHz, CDCl₃) δ 14.5, 14.7, 23.5, 24.1, 26.7, 30.3, 37.5, 123.7, 126.0, 126.3, 126.6, 126.9, 127.6, 128.1, 128.2, 128.5, 129.2, 129.5, 129.6, 137.0, 137.4, 138.7, 142.6,
143.9, 151.6, 155.6; ESI-HRMS: Found: m/z 406.2535. Calcd for C_{30}H_{32}N: (M+H)^+ 406.2535.

\[(E)-1-(2-((E)-1,2\text{-}diphenylvinyl)phenyl)ethanone\text{ oxime (2-4p)}\]

\[
\begin{center}
\text{\includegraphics[width=0.2\textwidth]{image}}
\end{center}
\]

White solid; mp. 133–135 °C; IR (NaCl) 1599, 1491, 1443, 1366, 924 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.77 (3H, s), 6.96 (1H, s), 7.01 (2H, dd, \(J = 1.6, 7.6\) Hz), 7.10-7.15 (3H, m), 7.21–7.37 (9H, m); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.5, 126.9, 127.3, 127.4, 127.8, 128.0, 128.2, 128.9 (overlapped), 129.0, 129.3, 131.7, 137.1, 138.0, 138.9, 141.5, 142.8, 157.0; ESI-HRMS: Found: m/z 315.1544. Calcd for C\(_{22}\)H\(_{20}\)NO: (M+H)^+ 314.1545.

\[1\text{-Isopropyl-4-methyl-3-phenylisoquinoline (2-6ab)}\]

\[
\begin{center}
\text{\includegraphics[width=0.2\textwidth]{image}}
\end{center}
\]

White solid; mp. 92–94 °C; IR (NaCl) 3059, 2967, 1613, 1562, 1506, 1389. 1323 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.47 (6H, d, \(J = 6.8\) Hz), 2.66 (3H, s), 3.95 (1H, septet, \(J = 6.8\) Hz), 7.40 (1H, tt, \(J = 1.2, 7.2\) Hz), 7.48 (2H, dd, \(J = 7.2, 7.2\) Hz), 7.59 (1H, \(J = 8.0, 8.4\) Hz), 7.66–7.74 (3H, m), 8.08 (1H, \(d, J = 8.4\) Hz), 8.27 (1H, \(d, J = 8.4\) Hz); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 15.7, 22.3, 31.1, 121.4, 124.4, 124.8, 125.1, 126.0, 127.3, 127.8, 129.3, 130.3, 136.8, 142.0, 150.2, 163.2; ESI-HRMS: Found: m/z 262.1596. Calcd for C\(_{19}\)H\(_{20}\)N: (M+H)^+ 262.1596.
1-Isopropyl-3,4-dipropylisoquinoline (2-6ae)

\[
\begin{array}{c}
\text{n-Pr} \\
\text{N} \\
\text{Ph} \\
\text{Me} \\
\text{Me}
\end{array}
\]

Colorless oil; IR (NaCl) 3071, 2959, 2930, 1614, 1566, 1456, 1389, 1379, 1003 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.03 (3H, t, \(J = 7.2\) Hz), 1.10 (3H, t, \(J = 7.2\) Hz), 1.42 (6H, d, \(J = 6.8\) Hz), 1.68 (2H, tt, \(J = 7.2, 7.6\) Hz), 1.86 (2H, tt, \(J = 7.2, 7.6\) Hz), 2.93 (2H, t, \(J = 7.6\) Hz), 2.98 (2H, t, \(J = 7.6\) Hz), 3.89 (1H, septet, \(J = 6.8\) Hz), 7.47 (1H, dd, \(J = 7.6, 8.4\) Hz), 7.62 (1H, dd, \(J = 7.6, 8.4\) Hz), 7.98 (1H, d, \(J = 8.4\) Hz), 8.18 (1H, d, \(J = 8.4\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.3, 14.7, 22.3, 23.0, 24.0, 29.8, 30.8, 37.1, 123.8, 124.5, 124.9, 125.0, 125.4, 128.8, 135.7, 151.5, 162.7; ESI-HRMS: Found: m/z 256.2065. Calcd for C\(_{18}\)H\(_{20}\)N: (M+H)\(^+\) 256.2065.

1-Phenethyl-3,4-diphenylisoquinoline (2-6ba)

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{Ph} \\
\text{Ph}
\end{array}
\]

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.30-3.34 (2H, m), 3.71-3.75 (2H, m), 7.17-7.25 (6H, m), 7.32-7.39 (9H, m), 7.57-7.61 (2H, m), 7.67-7.69 (1H, m), 8.24-8.27 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 35.3, 37.2, 124.9, 125.5, 126.0, 126.4, 126.6, 126.9, 127.1, 127.5, 128.2, 128.4, 128.5, 129.2, 129.7, 130.4, 131.4, 136.3, 137.7, 141.0, 142.1, 149.2, 160.0.
6.3 Experimental section of Chapter 3:

6.3.1 Synthesis of α,β-unsaturated oxime derivatives

6.3.1.1 Preparation of α,β-unsaturated oximes 3-1a and 3-1i: a typical procedure for synthesis of (2E,3E)-4-phenylbut-3-en-2-one oxime (3-1a).

\[
\begin{array}{c}
\text{Ph} \quad \text{C=O} \\
\text{Me} \\
\text{EtOH, 60 °C} \\
\text{NH}_2\text{OH·HCl} \\
\text{pyridine} \\
\rightarrow \\
\text{Ph} \quad \text{C=O} \\
\text{Me} \\
\text{N} \quad \text{O} \\
\text{3-1a}
\end{array}
\]

To a solution of (E)-4-phenylbut-3-en-2-one (3.0 g, 20.5 mmol) and pyridine (4.1 mL, 51.3 mmol) in EtOH (20 mL) was added NH₂OH·HCl (2.14 g, 30.8 mmol) in one portion and the reaction mixture was stirred at 60 °C for 1 h. The reaction was quenched by adding water and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO₄. Volatile materials were removed \textit{in vacuo} and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) to give (2E,3E)-4-phenylbut-3-en-2-one oxime (3-1a) in quantitative yield.

\textit{(2E,3E)-4-Phenylbut-3-en-2-one oxime (3-1a)}\textsuperscript{11}

White solid; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 2.16 (3H, t, \(J = 0.8\) Hz), 6.86 (1H, dt, \(J = 16.4, 1.6\) Hz), 6.91 (1H, d, \(J = 16.4\) Hz), 7.28 (1H, t, \(J = 7.2\) Hz), 7.35 (2H, dd, \(J = 7.2, 7.6\) Hz), 7.47 (2H, d, \(J = 7.6\) Hz); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 9.7, 125.7, 126.9, 128.4, 128.7, 133.4, 136.3, 156.8.

(2E,3E)-4-Phenylbut-3-en-2-one O-acetyl oxime (3-1a')12

\[ \text{Prepared by treatment of 3-1a with Ac_2O (2 equiv) in the presence of DMAP (5 mg) in pyridine, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 82% yield; White solid; }^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ 2.23 (6H, s), 7.01 (1H, d, } J = 16.4 \text{ Hz), 7.08 (1H, d, } J = 16.4 \text{ Hz), 7.30-7.39 (3H, m), 7.46-7.50 (2H, m); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta \text{ 11.6, 19.7, 124.3, 127.2, 128.9, 129.2, 135.5, 137.4, 162.3, 168.4.} \]

(2E,3E)-4-Phenylbut-3-en-2-one O-pivaloyl oxime (3-1a'')

\[ \text{Prepared by treatment of 3-1a with PivOH (1.2 equiv) in the presence of DCC (1.5 equiv) and DMAP (5 mol %) in CH}_2\text{Cl}_2\text{, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 80% yield; White solid; }^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta \text{ 1.33 (9H, s), 2.23 (3H, s), 7.04 (1H, d, } J = 16.8 \text{ Hz), 7.08 (1H, d, } J = 16.8 \text{ Hz), 7.30-7.40 (3H, m), 7.49 (2H, d, } J = 8.0 \text{ Hz); }^{13}\text{C NMR (100 MHz, CDCl}_3\text{) } \delta \text{ 11.6, 27.3, 38.8, 124.5, 127.2, 128.9, 129.2, 135.6, 137.2, 162.8, 175.0.} \]

(1E,4E)-1,5-Diphenylpenta-1,4-dien-3-one oxime (3-1i)13

\[ \text{Prepared from (1E,4E)-1,5-diphenyl-1,4-pentadien-3-one and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 33% yield; White solid; }^1\text{H NMR} \]

(400 MHz, Acetone-d$_6$) $\delta$ 7.06 (1H, dd, $J = 16.4, 0.8$ Hz), 7.20 (1H, d, $J = 16.4$ Hz), 7.28-7.33 (2H, m), 7.34-7.44 (5H, m), 7.49 (1H, dd, $J = 16.8, 0.8$ Hz), 7.61 (2H, d, $J = 7.6$ Hz), 7.66 (2H, d, $J = 7.6$ Hz); $^{13}$C NMR (100 MHz, Acetone-d$_6$) $\delta$ 117.0, 122.9, 126.9, 127.2, 128.1, 128.69, 128.74, 128.8, 133.0, 135.9, 136.8, 137.0, 153.2.

6.3.1.2. Preparation of $\alpha,\beta$-unsaturated oximes 3-1b to 3-1h and 3-1m: a typical procedure for synthesis of (2E,3E)-4-(4-methoxyphenyl)but-3-en-2-one oxime (3-1b).

![Diagram of chemical reaction]

To a stirred solution of 4-methoxybenzaldehyde (1.36 g, 10 mmol) and acetone (5.2 mL, 4.06 g, 70 mmol) in EtOH (10 mL) was added dropwise an aqueous solution of NaOH (5% in H$_2$O, 25 mL) and the reaction mixture stirred for 2 h (monitored by TLC). The reaction was quenched with H$_2$O and neutralized with 3 M HCl. The residue was extracted with ethyl acetate and the combined organic layers were washed with brine and dried with MgSO$_4$. After removal of the solvent, the white crystal was used for the next hydroxylamination without further purification. The experimental procedure is same as Chapter 6.3.1.1. The corresponding (2E,3E)-4-(4-methoxyphenyl)but-3-en-2-one oxime (3-1b) was obtained in 56% yield (2 steps).

(2E,3E)-4-(4-Methoxyphenyl)but-3-en-2-one oxime (3-1b)$^{14}$

White solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.12 (3H, s), 3.83 (3H, s), 6.70 (1H, d, $J = 16.4$ Hz), 6.85 (1H, d, $J = 16.4$ Hz), 6.89 (2H, d, $J = 8.8$ Hz), 7.41 (2H, d, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 9.6, 55.3, 114.2, 123.6, 128.2, 129.1, 132.9, 156.9, 159.9.

(2E,3E)-4-(2-Methoxyphenyl)but-3-en-2-one oxime (3-1c)

\[
\begin{array}{c}
\text{OMe} \\
\text{OH} \\
\text{Me}
\end{array}
\]

Prepared from 2-methoxybenzaldehyde and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 47% yield; White solid; mp. 126–128 °C; IR (NaCl) 3271, 1597, 1489, 1466, 1435, 1242, 1026 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.17 (3H, s), 3.88 (3H, s), 6.85-6.90 (2H, m), 6.95 (1H, t, \(J = 7.2\) Hz), 7.25-7.30 (2H, m), 7.54 (1H, d, \(J = 8.0\) Hz); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.7, 55.5, 110.9, 120.8, 125.3, 126.0, 126.7, 128.1, 129.5, 156.9, 157.4; ESI-HRMS: Found: m/z 192.1025. Calcd for C\(_{11}\)H\(_9\)NO\(_2\): (M+H\(^+\)) 192.1025.

(2E,3E)-4-(m-Tolyl)but-3-en-2-one oxime (3-1d)\(^{14}\)

\[
\begin{array}{c}
\text{Me} \\
\text{OH} \\
\text{Me}
\end{array}
\]

Prepared from 3-methylbenzaldehyde and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 52% yield; White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.15 (3H, d, \(J = 4.8\) Hz), 2.36 (3H, s), 6.84-6.93 (2H, m), 7.10 (1H, d, \(J = 6.4\) Hz), 7.22-7.30 (3H, m), 9.25 (1H, brs); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.7, 21.4, 124.1, 125.5, 127.5, 128.6, 129.3, 133.6, 136.2, 138.3, 156.8.
(2E,3E)-4-(4-Bromophenyl)but-3-en-2-one oxime (3-1e)

\[
\text{Br} \quad \text{OH} \\
\begin{array}{c}
\text{Me} \\
\end{array}
\]

Prepared from 4-bromobenzaldehyde and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 47% yield; White solid; mp. 143–145 °C; IR (NaCl) 3264, 1489, 1396, 1373, 1072 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 2.14 (3H, s), 6.82 (2H, s), 7.33 (2H, dt, \(J=8.4, 2.0\) Hz), 7.47 (2H, dt, \(J=8.4, 2.0\) Hz), 8.97 (1H, brs); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 9.6, 122.3, 126.5, 128.3, 131.9, 132.1, 135.2, 156.6; ESI-HRMS: Found: m/z 240.0027. Calcd for C\(_{10}\)H\(_{11}\)NO\(_7\)Br: (M+H\(^{+}\)) 240.0024.

(2E,3E)-4-(Naphthalen-2-yl)but-3-en-2-one oxime (3-1f)

\[
\text{Me} \\
\begin{array}{c}
\text{N} \quad \text{OH} \\
\end{array}
\]

Prepared from 2-naphthaldehyde and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 35% yield; White solid; mp. 152–154 °C; IR (NaCl) 3464, 3256, 3194, 1589, 1512, 1366, 1018 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta \) 2.20 (3H, s), 6.98 (1H, d, \(J=16.4\) Hz), 7.08 (1H, d, \(J=16.4\) Hz), 7.46-7.50 (2H, m), 7.67 (1H, dd, \(J=8.8, 1.6\) Hz), 7.80-7.84 (4H, m), 8.80 (1H, brs); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta \) 9.7, 123.4, 126.1, 126.3, 126.5, 127.4, 127.7, 128.1, 128.5, 133.36, 133.43, 133.5, 133.8, 156.9; ESI-HRMS: Found: m/z 212.1077. Calcd for C\(_{14}\)H\(_{14}\)NO: (M+H\(^{+}\)) 212.1075.
(2E,3E)-4-(Naphthalen-1-yl)but-3-en-2-one oxime (3-1g)

![Naphthalen-1-yl oxime](image)

Prepared from 1-naphthaldehyde and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 36% yield; White solid; mp. 144–146 °C; IR (NaCl) 3264, 1512, 1396, 1373, 1350, 1304, 841 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.30 (3H, s), 6.97 (1H, d, J = 16.4 Hz), 7.47-7.59 (3H, m), 7.72 (1H, d, J = 10.4 Hz), 7.74 (1H, s), 7.84 (1H, d, J = 8.4 Hz), 7.89 (1H, d, J = 7.6 Hz), 8.17 (1H, d, J = 8.0 Hz), 9.82 (1H, brs); ¹³C NMR (100 MHz, CDCl₃) δ 10.0, 123.4, 124.0, 125.6, 125.9, 126.3, 128.5, 128.7, 128.8, 130.3, 131.1, 133.6, 133.7, 156.9; ESI-HRMS: Found: m/z 212.1072. Caled for C₁₄H₁₄NO: (M+H)+ 212.1075.

(2E,3E)-4-(Thiophen-2-yl)but-3-en-2-one oxime (3-1h)

![Thiophen-2-yl oxime](image)

Prepared by employing slightly modified procedure of the aldol-condensation. To a solution of thiophene-2-carbaldehyde (2.24 g, 20 mmol) and acetone (4 mL) in 2 mL of H₂O was added 0.5 mL of 10% aqueous NaOH over a period of 15 min. The corresponding oxime was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 35% yield; Yellow solid; mp. 115–117 °C; IR (NaCl) 3264, 1620, 1427, 1373, 1304, 1288, 702 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.10 (3H, s), 6.65 (1H, d, J = 16.0 Hz), 7.00-7.04 (2H, m), 7.09 (1H, d, J = 3.2 Hz), 7.24 (1H, d, J = 5.2 Hz), 8.00 (1H, brs); ¹³C NMR (100 MHz, CDCl₃) δ 9.6, 125.2, 125.7, 126.3, 127.2, 127.7, 141.8, 156.4; ESI-HRMS: Found: m/z 168.0480. Caled for C₉H₁₀NOS: (M+H)+ 168.0483.
(1E)-4-Methyl-1-phenylpent-1-en-3-one oxime (3-1m)

```
Ph
\(=\)
Me
\(=\)
Me

\textit{anti: syn} = 1:1.2
```

Prepared by employing slightly modified procedure of the aldol-condensation. MeOH was used instead of EtOH and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 34% yield; White solid; mp. 68–78 °C; IR (NaCl) 3264, 2970, 2932, 1628, 1335, 972, 694 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.23 (6H x0.55, d, \(J = 7.2\) Hz), 1.26 (6H x0.45, d, \(J = 7.2\) Hz), 3.04 (IH x0.45, sept, \(J = 7.2\) Hz), 3.52 (1H x0.55, sept, \(J = 7.2\) Hz), 6.63 (1H x0.55, d, \(J = 16.4\) Hz), 7.02 (1H x0.45, d, \(J = 16.4\) Hz), 7.06 (1H x0.55, d, \(J = 16.4\) Hz), 7.23-7.40 (3H x0.45+3H x0.55, m), 7.42-7.50 (1H x0.45+2H x0.55, m), 7.54 (2H x0.45, d, \(J = 6.8\) Hz), 9.53 (1H x0.45+1H x0.55, brs); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 19.1, 21.1, 25.9, 29.7, 115.9, 121.8, 126.9, 127.4, 128.3, 128.66, 128.71, 128.9, 133.1, 135.6, 136.45, 136.51, 159.9, 162.8; ESI-HRMS: Found: m/z 190.1229. Calcd for C\(_{12}\)H\(_{16}\)NO: (M+H)\(^+\) 190.1232.

### 6.3.1.3. Preparation of \(\alpha,\beta\)-unsaturated oxime 3-1j

```
\[
\text{PhCHO} + \text{Me} = \text{Me} \xrightarrow{\text{H}_2\text{SO}_4} \xrightarrow{\text{AcOH, rt, 60 °C}} \text{Ph} = \text{Me} \xrightarrow{\text{NH}_2\text{OH}+\text{HCl, pyridine, EtOH, 60 °C}} \text{Ph} = \text{Me}
\]
```

To a stirred solution of benzaldehyde (2.7 g, 25 mmol) and 2-butanone (4.5 mL, 3.6 g, 50 mmol) in acetic acid (20 mL) was added slowly concentrated H\(_2\)SO\(_4\) (2.4 g) at room temperature. The reaction was allowed to stirred for 20 h and then quenched with H\(_2\)O and neutralized with 25% aqueous NaOH. The residue was extracted with ethyl
acetate and the combined organic layers were washed with aqueous NaHCO₃, brine and dried with MgSO₄. After removal of the solvent, the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) to give the corresponding α,β-unsaturated ketone in 96% yield. The α,β-unsaturated ketone was then subjected to hydroxylamination according to the experimental procedure in Chapter 6.3.1.1. and (2E,3E)-3-methyl-4-phenylbut-3-en-2-one oxime (3-1j) was obtained in 65% yield.

(2E,3E)-3-Methyl-4-phenylbut-3-en-2-one oxime (3-1j)

White solid; mp. 99–101 °C; IR (NaCl) 3287, 2924, 1489, 1443, 1373, 1026, 926 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.09 (3H, s), 2.19 (3H, s), 6.94 (1H, s), 7.26 (1H, dd, J = 7.2, 7.2 Hz), 7.31 (2H, d, J = 7.2 Hz), 7.36 (2H, dd, J = 8.0, 7.2 Hz), 9.82 (1H, brs); ¹³C NMR (100 MHz, CDCl₃) δ 10.3, 14.2, 127.1, 128.2, 129.3, 131.2, 134.4, 137.1, 158.0; ESI-HRMS: Found: m/z 176.1081. Calcd for C₁₁H₁₄NO: (M+H)+ 176.1075.

6.3.1.4. Preparation of α,β-unsaturated oxime 3-1k

Trifluoroacetic anhydride (38.9 mL, 280 mmol) was added directly to the acetic acid (4.0 mL, 69.9 mmol) and the reaction mixture was stirred at room temperature for 10 min. To the reaction mixture at 0 °C was added 85% phosphoric acid (8.56 g, 69.9 mmol) and followed by cyclohexene (7.1 mL, 69.9 mmol). Then, the reaction mixture allowed stirring at room temperature for 2 h. The reaction was then quenched with water and the organic materials were extracted twice with CH₂Cl₂. The combined extracts were
washed with 30% aqueous NaOH and brine, and dried over MgSO₄. Volatile materials were removed \emph{in vacuo}. The residue was purified by silica gel column chromatography (hexanes-ethyl acetate = 95:5) to afford 1-(cyclohex-1-en-1-yl)ethanone in 35% yield. 1-(Cyclohex-1-en-1-yl)ethanone was then subjected to hydroxylamination according to the experimental procedure in Chapter 6.3.1.1. and \( (E)-1-(\text{Cyclohex-1-en-1-yl})\text{ethanone oxime (3-1k)} \) was obtained in 76% yield.

\( (E)-1-(\text{Cyclohex-1-en-1-yl})\text{ethanone oxime (3-1k)} \)

White solid; \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 1.57-1.69 (4H, m), 2.02 (3H, s), 2.16-2.21 (2H, m), 2.26-2.29 (2H, m), 6.20 (1H, \( t, J = 4.0 \text{ Hz} \)), 9.60 (1H, brs); \(^13\)C NMR (100 MHz, CDCl₃) \( \delta \) 9.7, 22.0, 22.4, 24.3, 26.0, 130.0, 134.4, 156.8.

6.3.1.5. Preparation of \( \alpha,\beta \)-unsaturated oxime 3-11

To a stirred solution of formaldehyde (4.8 g, 60 mmol) and a catalytic amount of morpholine (3-5 drops) was added a solution of benzylacetone (3.0 g, 20 mmol) in acetic acid (18 mL). The resulting reaction mixture was refluxed for 2 days and cooled to room temperature and neutralized with 0.1 M aqueous NaOH. The residue was extracted with ethyl acetate and the combined organic layers were washed with aqueous NaHCO₃, brine and dried with MgSO₄. After removal of the solvent, the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) to give the corresponding \( \alpha,\beta \)-unsaturated ketone in 13% yield. The \( \alpha,\beta \)-unsaturated ketone was then subjected to hydroxylamination according to the experimental procedure in Chapter
6.3.1.1. and (2E,3E)-3-methyl-4-phenylbut-3-en-2-one oxime (3-1I) was obtained in 91% yield.

**(E)-3-Benzylbut-3-en-2-one oxime (3-1I)**

White solid; mp. 120–122 °C; IR (NaCl) 3287, 2916, 1620, 1605, 1373, 1018 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 2.06 (3H, s), 3.66 (2H, s), 5.10 (1H, s), 5.53 (1H, s), 7.17-7.21 (3H, m), 7.25-7.30 (2H, m), 8.71 (IH, brs); ¹³C NMR (100 MHz, CDCl₃) δ 10.4, 38.1, 118.5, 126.0, 128.2, 129.1, 139.5, 144.5, 156.2; ESI-HRMS: Found: m/z 176.1082.

Calcd for C₁₁H₁₄NO: (M+H⁺) 176.1075.

6.3.2 Rh (III)-catalyzed synthesis of pyridines: a typical procedure for the reaction of (2E,3E)-4-phenylbut-3-en-2-one oxime (3-1a) and diphenylacetylene (3-2a) (Table 3-1, entry 6).

To a MeOH solution (2.5 mL) of (2E,3E)-4-phenylbut-3-en-2-one oxime (3-1a) (80.5 mg, 0.50 mmol) and diphenylacetylene (3-2a) (106.9 mg, 0.60 mmol) were added [Cp*RhCl₂]₂ (7.7 mg, 0.0125 mmol) and CsΟPiv (35.1 mg, 0.15 mmol), and the reaction mixture was stirred at 60 °C under air for 7 h. After cooled to room temperature, the solvent was removed *in vacuo*, and the resulting crude material was subjected to flash column chromatography (hexane:ethyl acetate = 90:10) to afford 6-methyl-2,3,4-triphenylpyridine (3-3aa) (126.4 mg, 0.393 mmol) in 79% yield.
6-Methyl-2,3,4-triphenylpyridine (3-3aa)

White solid; mp. 128–129 °C; IR (NaCl) 3024, 2955, 1574, 1535, 1489, 1443, 1373 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.72 (3H, s), 6.86-6.89 (2H, m), 7.02-7.10 (5H, m), 7.18-7.23 (7H, m), 7.27-7.29 (2H, m); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 123.2, 126.3, 127.1, 127.2, 127.5, 127.6, 127.8, 129.2, 129.8, 131.4, 131.5, 137.9, 139.6, 140.9, 149.9, 156.9, 157.8; ESI-HRMS: Found: m/z 322.1600. Calcd for C₂₄H₂₀N: (M+H)+ 322.1596.

2,3-Bis(4-methoxyphenyl)-6-methyl-4-phenylpyridine (3-3ab)

![Chemical structure](image)

Colorless crystal; mp. 154–155 °C; IR (NaCl) 2940, 2839, 1605, 1512, 1288, 1180, 1034 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.66 (3H, s), 3.71 (3H, s), 3.76 (3H, s), 6.59 (2H, dt, J = 8.8, 2.4 Hz), 6.72 (2H, dt, J = 8.8, 1.6 Hz), 6.75 (2H, dt, J = 8.8, 2.4 Hz), 7.03-7.08 (2H, m), 7.14 (1H, s), 7.18-7.22 (5H, m); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 55.0, 55.2, 113.1, 113.2, 122.9, 127.0, 127.8, 129.2, 130.3, 130.8, 131.2, 132.5, 133.6, 139.9, 150.1, 156.5, 157.5, 158.0, 158.7; ESI-HRMS: Found: m/z 382.1807. Calcd for C₂₆H₂₄NO₂: (M+H)+ 382.1807.
6-Methyl-4-phenyl-2,3-bis(4-(trimethylsilyl)phenyl)pyridine (3-3ac)

White solid; mp. 164–165 °C; IR (NaCl) 2955, 2893, 1582, 1427, 1250, 1111, 849 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) δ 0.17 (9H, s), 0.19 (9H, s), 2.68 (3H, s), 6.83 (2H, d, J = 7.6 Hz), 7.05-7.08 (2H, m), 7.15-7.22 (8H, m), 7.30 (2H, d, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ -1.2 (overlapped), 24.4, 123.1, 127.2, 127.8, 129.0, 129.3, 130.7, 131.6, 132.4, 132.5, 138.1, 138.2, 139.0, 139.7, 141.3, 149.8, 156.8, 157.9; ESI-HRMS: Found: m/z 466.2388. Caled for C₃₀H₃₆N₅Si₂: (M+H)+ 466.2386.

2,3-Bis(3-bromophenyl)-6-methyl-4-phenylpyridine (3-3ad)

Colorless crystal; mp. 128–129 °C; IR (NaCl) 2963, 1582, 1558, 1535, 1474, 887 cm⁻¹;
¹H NMR (400 MHz, CDCl₃) δ 2.69 (3H, s), 6.78 (1H, dt, J = 8.0, 1.2 Hz), 6.93 (1H, t, J = 8.0 Hz), 6.99-7.07 (5H, m), 7.21-7.25 (5H, m), 7.34 (1H, dt, J = 7.2, 1.6 Hz), 7.55 (1H, t, J = 1.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 121.7, 122.0, 123.7, 127.6, 128.0, 128.4, 129.07, 129.13, 129.2, 129.8, 130.0, 130.2, 130.5, 132.9, 134.2, 138.8, 139.6, 142.4, 150.2, 156.0, 157.6; ESI-HRMS: Found: m/z 479.9789. Caled for C₂₄H₁₈N⁷⁹Br⁸¹Br: (M+H)+ 479.9786.
6-Methyl-4-phenyl-2,3-dipropylpyridine (3-3ae)

\[
\begin{align*}
\text{Yellow oil; IR (NaCl) 2955, 2932, 2870, 1589, 1543, 1497, 1450, 1381 cm}^{-1} ; \\
^1\text{H NMR (400 MHz, CDCl}_3) & \delta 0.77 (3H, t, J = 7.2 Hz), 1.05 (3H, t, J = 7.2 Hz), 1.37 (2H, tq, J = 8.0, 7.2 Hz), 1.77 (2H, tq, J = 8.0, 7.2 Hz), 2.50 (2H, t, J = 8.0 Hz), 2.50 (3H, s), 2.79 (2H, t, J = 8.0 Hz), 6.80 (1H, s), 7.23-7.26 (2H, m), 7.36-7.42 (3H, m); \\
^{13}\text{C NMR (100 MHz, CDCl}_3) & \delta 14.3, 14.4, 23.8, 24.0, 24.3, 30.6, 37.5, 122.1, 127.3, 128.0, 128.4, 129.9, 140.6, 150.4, 154.2, 160.3; \\
\text{ESI-HRMS: Found: m/z 254.1902. Calcd for C}_{18}H_{24}N: (M+H)^+ 254.1909.}
\end{align*}
\]

2,3-Bis(tert-butyldimethylsiloxymethyl)-6-methyl-4-phenylpyridine (3-3af)

\[
\begin{align*}
\text{White solid; mp. 85–87 °C; IR (NaCl) 2955, 2932, 2855, 1589, 1466, 1258, 1065, 841 cm}^{-1} ; \\
^1\text{H NMR (400 MHz, CDCl}_3) & \delta -0.03 (6H, s), 0.10 (6H, s), 0.86 (9H, s), 0.90 (9H, s), 2.56 (3H, s), 4.70 (2H, s), 4.98 (2H, s), 7.00 (1H, s), 7.38-7.42 (5H, m); \\
^{13}\text{C NMR (100 MHz, CDCl}_3) & \delta -5.5, -5.0, 18.3, 18.4, 24.1, 25.8, 25.9, 58.1, 66.1, 123.4, 127.9, 128.1, 128.6, 129.0, 139.2, 151.1, 156.2, 159.1; \\
\text{ESI-HRMS: Found: m/z 458.2914. Calcd for C}_{26}H_{44}NO_2Si_2: (M+H)^+ 458.2911.}
\end{align*}
\]
3,6-Dimethyl-2,4-diphenylpyridine (3-3ag)

Regioisomer (3-3ag-minor) was separated by flash column chromatography.

White solid; mp. 65–67 °C; IR (NaCl) 2955, 1589, 1551, 1489, 1450, 1420, 1381 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.13 (3H, m), 2.59 (3H, m), 7.02 (1H, s), 7.34-7.47 (8H, m), 7.51-7.54 (2H, m); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 17.5, 24.1, 122.8, 125.1, 127.65, 127.68, 128.1, 128.3, 128.7, 129.0, 140.1, 141.4, 151.0, 154.8, 159.2; ESI-HRMS: Found: m/z 260.1437. Calcd for C\(_{19}\)H\(_{18}\)N: (M+H\(^+\)) 260.1439.

2,6-Dimethyl-3,4-diphenylpyridine (3-3ag-minor)

White solid; mp. 105–106 °C; IR (NaCl) 2940, 1589, 1543, 1443, 1381, 1011, 872 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.39 (3H, s), 2.61 (3H, s), 7.03-7.06 (5H, m), 7.14-7.17 (3H, m), 7.19-7.25 (3H, m); \(^1\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 121.7, 126.7, 127.1, 127.7, 128.0, 129.1, 130.3, 132.3, 138.4, 139.5, 149.1, 156.1, 156.2; ESI-HRMS: Found: m/z 260.1435. Calcd for C\(_{19}\)H\(_{18}\)N: (M+H\(^+\)) 260.1439.
Ethyl 2,4-diphenyl-6-methylpyridine-3-carboxylate (3-3ah)\textsuperscript{15}

![Chemical structure of Ethyl 2,4-diphenyl-6-methylpyridine-3-carboxylate](image)

Regioisomer (3-3ah-minor) was separated by flash column chromatography.

Colourless solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 0.84 (3H, t, \(J = 7.2\) Hz), 2.67 (3H, s), 3.92 (2H, q, \(J = 7.2\) Hz), 7.16 (1H, s), 7.39-7.43 (8H, m), 7.60-7.62 (2H, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 13.4, 24.6, 61.2, 122.3, 125.9, 128.0, 128.3, 128.4, 128.46 (overlapped), 128.55, 138.4, 139.9, 148.8, 156.5, 158.9, 168.7.

Ethyl 3,4-diphenyl-6-methylpyridine-2-carboxylate (3-3ah-minor)

![Chemical structure of Ethyl 3,4-diphenyl-6-methylpyridine-2-carboxylate](image)

Yellow oil; IR (NaCl) 2986, 1736, 1589, 1450, 1381, 1342, 1273 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 0.95 (3H, t, \(J = 7.2\) Hz), 2.68 (3H, s), 4.08 (2H, q, \(J = 7.2\) Hz), 7.04-7.08 (4H, m), 7.19-7.23 (6H, m), 7.30 (1H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 13.6, 24.1, 61.4, 125.7, 127.3, 127.7, 127.9, 128.0, 129.2, 129.9, 131.5, 136.4, 138.2, 150.0 150.8, 157.4, 167.6; ESI-HRMS: Found: m/z 318.1496. Calcd for C\textsubscript{21}H\textsubscript{20}N\textsubscript{2}O\textsubscript{2}: (M+H)\textsuperscript{+} 318.1494.

3-(4-Methoxyphenyl)-6-methyl-4-phenyl-2-(4-(trifluoromethyl)phenyl)pyridine (3-3ai)

Regioisomer (3-3ai-minor) was separated by flash column chromatography.

Colorless oil; IR (NaCl) 2963, 2839, 1612, 1574, 1512, 1250, 1165 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.67 (3H, s), 3.70 (3H, s), 6.59 (2H, dt, \(J = 8.8, 2.0\) Hz), 6.74 (2H, dt, \(J = 8.8, 2.0\) Hz), 7.05-7.08 (2H, m), 7.20-7.23 (4H, m), 7.39 (2H, d, \(J = 8.4\) Hz), 7.45 (2H, d, \(J = 8.4\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.3, 55.0, 113.4, 123.9, 124.2 (\(J_{CF} = 170.3\) Hz), 124.6 (\(J_{CF} = 6.7\) Hz), 127.3, 127.9, 129.1 (\(J_{CF} = 32.0\) Hz), 129.2, 129.4, 130.2, 131.4, 132.4, 139.4, 144.8, 150.3, 156.4, 157.0, 158.3; ESI-HRMS: Found: m/z 420.1575. Calcd for C\(_{26}\)H\(_{19}\)NO\(_1\)F\(_3\): (M+H)\(^+\) 420.1575.

2-(4-Methoxyphenyl)-6-methyl-4-phenyl-3-(4-(trifluoromethyl)phenyl)pyridine (3-3ai-minor)

White solid; mp. 138–140 °C; IR (NaCl) 2963, 2839, 1612, 1589, 1512, 1327, 1126 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.68 (3H, s), 3.75 (3H, s), 6.72 (2H, dt, \(J = 8.8, 2.0\) Hz), 6.97-7.02 (4H, m), 7.15 (2H, dt, \(J = 8.8, 2.0\) Hz), 7.18-7.21 (4H, m), 7.30 (2H, d, \(J = 8.0\) Hz), 7.40 (2H, d, \(J = 8.0\) Hz), 7.57-7.61 (2H, m), 7.66 (2H, d, \(J = 8.0\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.6, 55.0, 113.4, 123.9, 124.2 (\(J_{CF} = 170.3\) Hz), 124.6 (\(J_{CF} = 6.7\) Hz), 127.3, 127.9, 129.1 (\(J_{CF} = 32.0\) Hz), 129.2, 129.4, 130.2, 131.4, 132.4, 139.4, 144.8, 150.3, 156.4, 157.0, 158.3; ESI-HRMS: Found: m/z 420.1575. Calcd for C\(_{26}\)H\(_{19}\)NO\(_1\)F\(_3\): (M+H)\(^+\) 420.1575.
Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.5, 55.2, 113.3, 122.9, 124.1 ($J_C$-$F$ = 270.3 Hz),
124.6 ($J_C$-$F$ = 3.7 Hz), 127.5, 128.0, 128.4 ($J_C$-$F$ = 32.2 Hz), 129.2, 129.9, 131.2, 131.8,
132.9, 139.2, 142.3, 150.0, 157.3, 157.5, 159.1; ESI-HRMS: Found: m/z 420.1575. Caled
for C$_{26}$H$_{31}$NO$^{19}$F$_3$: (M+H)$^+$ 420.1575.

4-(4-Methoxyphenyl)-6-methyl-2,3-dipropylpyridine (3-3be)

[Diagram of 4-(4-Methoxyphenyl)-6-methyl-2,3-dipropylpyridine (3-3be)]

Colorless oil; IR (NaCl) 2963, 2932, 1612, 1512, 1466, 1288, 1250, 1034 cm$^{-1}$; $^1$H NMR
(400 MHz, CDCl$_3$) δ 0.79 (3H, t, $J$ = 7.2 Hz), 1.04 (3H, t, $J$ = 7.2 Hz), 1.37 (2H, tq, $J$ =
8.4, 7.2 Hz), 1.76 (2H, tq, $J$ = 8.4, 7.2 Hz), 2.49 (3H, s), 2.52 (2H, t, $J$ = 8.4 Hz), 2.78
(2H, t, $J$ = 8.4 Hz), 3.86 (3H, s), 6.78 (1H, s), 6.94 (2H, d, $J$ = 8.8 Hz), 7.18 (2H, d, $J$ =
8.8 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.37, 14.43, 23.8, 24.0, 24.3, 30.6, 37.5, 55.2,
113.5, 122.3, 129.6, 130.2, 133.0, 150.1, 154.2, 158.9, 160.2; ESI-HRMS: Found: m/z
284.2015. Calcd for C$_{19}$H$_{26}$NO: (M+H)$^+$ 284.2014.

4-(2-Methoxyphenyl)-6-methyl-2,3-dipropylpyridine (3-3ce)

[Diagram of 4-(2-Methoxyphenyl)-6-methyl-2,3-dipropylpyridine (3-3ce)]

Colorless oil; IR (NaCl) 2955, 2870, 1605, 1589, 1551, 1497, 1435, 1242 cm$^{-1}$; $^1$H NMR
(400 MHz, CDCl$_3$) δ 0.73 (3H, t, $J$ = 7.2 Hz), 1.04 (3H, t, $J$ = 7.2 Hz), 1.20-1.40 (2H, m),
1.78 (2H, tq, $J$ = 8.8, 7.2 Hz), 2.27-2.50 (2H, m), 2.49 (3H, s), 2.78 (2H, t, $J$ = 8.8 Hz),
3.74 (3H, s), 6.76 (1H, s), 6.95 (1H, d, $J$ = 8.4 Hz), 6.99 (1H, dd, $J$ = 7.6, 7.2 Hz), 7.07
(1H, dd, $J$ = 7.6, 2.0 Hz), 7.35 (1H, ddd, $J$ = 7.6, 7.2, 1.6 Hz); $^{13}$C NMR (100 MHz,
CDCl$_3$ δ 14.4 (overlapped), 23.7, 23.8, 24.0, 31.1, 37.5, 55.3, 110.6, 120.3, 122.4, 129.0, 129.3, 130.4, 147.3, 154.1, 155.9, 159.7; ESI-HRMS: Found: m/z 284.2012. Calcd for C$_{19}$H$_{26}$NO: (M+H)$^+$ 284.2041.

6-Methyl-2,3-diphenyl-4-(m-tolyl)pyridine (3-3da)

![Chemical structure of 6-Methyl-2,3-diphenyl-4-(m-tolyl)pyridine](image)

White solid; mp. 100–102°C; IR (NaCl) 2955, 1589, 1535, 1489, 1443, 1427 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 2.22 (3H, s), 2.69 (3H, s), 6.81 (1H, d, $J = 7.2$ Hz), 6.83-6.88 (2H, m), 6.91 (1H, s), 6.98-7.08 (5H, m), 7.13-7.18 (3H, m), 7.20 (1H, s), 7.22-7.28 (2H, m); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 21.3, 24.4, 123.2, 126.3, 126.4, 127.1, 127.5, 127.56, 127.60, 127.9, 129.9, 130.0, 131.6, 131.6, 137.4, 138.0, 139.5, 141.0, 150.0, 156.8, 157.8; ESI-HRMS: Found: m/z 336.1750. Calcd for C$_{25}$H$_{22}$N: (M+H)$^+$ 336.1752.

4-(4-Bromophenyl)-6-methyl-2,3-diphenylpyridine (3-3ea)

![Chemical structure of 4-(4-Bromophenyl)-6-methyl-2,3-diphenylpyridine](image)

Colorless crystal; mp. 162–164°C; IR (NaCl) 2963, 1589, 1574, 1489, 1420, 1373 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 2.68 (3H, s), 6.84 (2H, d, $J = 7.2$ Hz), 6.92 (2H, d, $J = 8.4$ Hz), 7.01-7.10 (3H, m), 7.13-7.20 (4H, m), 7.21-7.27 (2H, m), 7.30 (2H, d, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 24.4, 121.6, 122.9, 126.6, 127.2, 127.6, 127.8, 129.8, 130.9, 131.0, 131.31,131.34, 137.5, 138.5, 140.7, 148.6, 157.0, 158.0; ESI-HRMS: Found: m/z 400.0699. Calcd for C$_{24}$H$_{19}$N$^{79}$Br: (M+H)$^+$ 400.0701.
6-Methyl-4-(naphthalen-2-yl)-2,3-diphenylpyridine (3-3fa)

\[
\begin{array}{c}
\text{Ph} \\
\text{N} \\
\text{Me}
\end{array}
\]

White solid; mp. 159–160 °C; IR (NaCl) 3055, 2955, 1574, 1535, 1504, 1443, 856 cm\(^{-1}\); 
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.70 (3H, s), 6.89 (2H, dd, \(J = 8.0, 1.6\) Hz), 6.95-7.05 (4H, m), 7.16-7.19 (3H, m), 7.26-7.29 (2H, m), 7.31 (1H, s), 7.43-7.47 (2H, m), 7.57 (1H, d, \(J = 8.4\) Hz), 7.70 (1H, s), 7.72-7.77 (2H, m); 
\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.5, 123.5, 126.1, 126.2, 126.4, 127.1, 127.2 (overlapped), 127.57, 126.61, 127.7, 128.0, 128.4, 129.9, 131.5, 131.7, 132.3, 133.0, 137.3, 137.8, 141.0, 149.8, 157.0, 158.0; ESI-HRMS: Found: m/z 372.1752. Calcd for C\(_{28}\)H\(_{22}\)N: (M+H)\(^+\) 372.1752.

6-Methyl-4-(naphthalen-2-yl)-2,3-dipropylpyridine (3-3fe)

\[
\begin{array}{c}
n-\text{Pr} \\
n-\text{Pr} \\
\text{Me}
\end{array}
\]

Yellow oil; IR (NaCl) 2955, 2932, 2870, 1589, 1551, 1505, 1466, 1450 cm\(^{-1}\); 
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.74 (3H, t, \(J = 7.2\) Hz), 1.06 (3H, t, \(J = 7.2\) Hz), 1.40 (2H, tq, \(J = 8.0, 7.1\) Hz), 1.80 (2H, tq, \(J = 8.0, 7.2\) Hz), 2.53 (3H, s), 2.55 (2H, t, \(J = 8.4\) Hz), 2.82 (2H, t, \(J = 8.0\) Hz), 6.88 (1H, s), 7.38 (1H, dd, \(J = 8.4, 1.6\) Hz), 7.50–7.55 (2H, m), 7.71 (1H, s), 7.84-7.90 (3H, m); 
\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.3, 14.4, 23.8, 24.0, 24.4, 30.7, 37.5, 122.3, 126.1, 126.4, 126.8, 127.3, 127.6, 127.7, 128.0, 130.1, 132.4, 133.0, 138.2, 150.3, 154.3, 160.4; ESI-HRMS: Found: m/z 304.2068. Calcd for C\(_{22}\)H\(_{26}\)N: (M+H)\(^+\) 304.2065.
6-Methyl-4-(naphthalen-1-yl)-2,3-diphenylpyridine (3-3ga)

White solid; mp. 122–124 °C; IR (NaCl) 3009, 2963, 1589, 1574, 1535, 1443, 1420, 802 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.70 (3H, s), 6.73–6.85 (5H, m), 7.07 (1H, d, J = 6.8 Hz), 7.14–7.18 (3H, m), 7.20 (1H, s), 7.26 (1H, t, J = 7.6 Hz), 7.31–7.35 (2H, m), 7.35–7.43 (2H, m), 7.67 (2H, dd, J = 9.2, 8.8 Hz), 7.77 (1H, dd, J = 7.2, 2.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 124.1, 124.7, 125.6, 125.9, 126.0, 126.2, 127.16, 127.23, 127.3, 127.59, 127.65, 128.1, 129.9, 130.6, 131.4, 133.0, 133.2, 137.2, 137.8, 140.9, 149.0, 156.4, 157.8; ESI-HRMS: Found: m/z 372.1752. Calcd for C₂₅H₂₂N: (M+H)⁺ 372.1752.

6-Methyl-2,3-diphenyl-4-(thiophen-2-yl)pyridine (3-3ha)

White solid; mp. 161–163 °C; IR (NaCl) 2963, 1582, 1535, 1443, 1420 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.68 (3H, s), 6.71 (1H, dd, J = 3.6, 1.2 Hz), 6.85 (1H, dd, J = 4.8, 3.6 Hz), 7.00 (2H, dd, J = 8.0, 2.0 Hz), 7.12–7.18 (6H, m), 7.21–7.25 (3H, m), 7.36 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 24.4, 122.2, 126.9, 127.08, 127.09, 127.1, 127.5, 128.0, 128.1, 129.7, 130.9, 131.3, 137.9, 140.8, 140.9, 142.3, 157.1, 158.4; ESI-HRMS: Found: m/z 328.1163. Calcd for C₂₅H₁₈NS: (M+H)⁺ 328.1160.
(E)-2,3,4-Triphenyl-6-styrylpyridine (3-3ia)

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Ph} \\
\text{N} \\
\text{Ph} \\
\end{array}
\]

White solid; mp. 184–186 °C; IR (NaCl) 3063, 2970, 1574, 1528, 1497, 1443, 1381, 972 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.88 (2H, dd, \(J = 7.6, 1.6\) Hz), 7.01-7.07 (3H, m), 7.08-7.13 (2H, m), 7.17-7.24 (6H, m), 7.26-7.40 (6H, m), 7.47 (1H, s), 7.60 (2H, d, \(J = 7.6\) Hz), 7.72 (1H, d, \(J = 16.4\) Hz); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 121.6, 126.5, 127.1, 127.30, 127.35, 127.56, 127.61, 127.9, 128.1, 128.2, 128.7, 129.2, 130.0, 131.4, 132.9, 133.0, 136.8, 137.8, 139.6, 140.9, 150.2, 154.2, 158.2; ESI-HRMS: Found: m/z 410.1905. Calcd for C\(_{31}\)H\(_{24}\)N: (M+H\(^{+}\)) 410.1909.

2,3-Dimethyl-4,5,6-triphenylpyridine (3-3ja)

\[
\begin{array}{c}
\text{Ph} \\
\text{Ph} \\
\text{Me} \\
\text{N} \\
\text{Me} \\
\end{array}
\]

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.10 (3H, s), 2.69 (3H, s), 6.75-6.82 (2H, m), 6.91-6.97 (5H, m), 7.11-7.22 (6H, m), 7.23-7.29(2H, m); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.8, 23.6, 125.9, 126.7, 126.9, 127.2, 127.5, 127.7, 128.0, 129.4, 129.9, 131.2, 132.8, 138.7, 138.9, 141.1, 149.8, 154.3, 156.1.

1-Methyl-3,4-diphenyl-5,6,7,8-tetrahydroisoquinoline (3-3ka)

![Chemical structure of 1-Methyl-3,4-diphenyl-5,6,7,8-tetrahydroisoquinoline](image)

White solid; mp. 142–144 °C; IR (NaCl) 3055, 2940, 2862, 1558, 1427, 1412, 1335 cm⁻¹;

\(^1\)H NMR (400 MHz, CDCl₃) δ 1.66-1.71 (2H, m), 1.82-1.87 (2H, m), 2.44 (2H, t, \(J = 6.4\) Hz), 2.56 (3H, s), 2.74 (2H, t, \(J = 6.4\) Hz), 7.01-7.07 (2H, m), 7.08-7.16 (3H, m), 7.17-7.27 (5H, m); \(^13\)C NMR (100 MHz, CDCl₃) δ 22.4, 22.51, 22.54, 26.6, 28.8, 126.6, 126.7, 127.4, 128.0, 129.3, 129.8, 130.4, 133.3, 138.7, 141.1, 144.7, 153.4, 155.7; ESI-HRMS: Found: m/z 300.1753. Calcd for C₂₂H₂₂N: (M+H)⁺ 300.1752.

3-Benzyl-2-methyl-5,6-diphenylpyridine (3-3la)\(^{17}\)

![Chemical structure of 3-Benzyl-2-methyl-5,6-diphenylpyridine](image)

White solid; \(^1\)H NMR (400 MHz, CDCl₃) δ 2.59 (3H, s), 4.06 (2H, s), 7.12-7.14 (2H, m), 7.19-7.24 (9H, m), 7.29-7.36 (4H, m), 7.42 (1H, s); \(^13\)C NMR (100 MHz, CDCl₃) δ 22.5, 38.5, 126.4, 126.8, 127.4, 127.8, 128.2, 128.6, 128.7, 129.6, 129.9, 132.5, 133.5, 139.1, 139.7, 140.0, 140.2, 154.3, 155.9.

6-Isopropyl-2,3,4-triphenylpyridine (3-3ma)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{Me}
\end{align*}
\]

White solid; mp. 134–136 °C; IR (NaCl) 2963, 2870, 1582, 1566, 1535, 1489, 1381 cm\(^{-1}\); \(\text{^1H NMR (400 MHz, CDCl}_3\) \(\delta 1.41 (6\text{H}, \text{d}, J = 7.2 \text{ Hz}), 3.22 (1\text{H}, \text{sept}, J = 7.2 \text{Hz}), 6.86 (2\text{H}, d, J = 6.4 \text{Hz}), 6.99-7.10 (5\text{H}, m), 7.13-7.23 (7\text{H}, m), 7.25-7.31 (2\text{H}, m); \text{^13C NMR (100 MHz, CDCl}_3\) \(\delta 22.7, 36.3, 120.1, 126.3, 127.08, 127.10, 127.5, 127.6, 127.8, 129.3, 130.0, 131.5, 131.7, 138.1, 140.1, 141.1, 150.0, 157.2, 165.9; \text{ESI-HRMS: Found: m/z 350.1905. Calcd for C}_{26}\text{H}_{24}\text{N}: (M+H)\text{^+} 350.1909.}
\]

\((1E,3Z)-4\text{-Methyl-1-phenylpent-1-en-3-one oxime (syn-3-1m)}\)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Me} & \quad \text{Me}
\end{align*}
\]

White solid; mp. 110–114 °C; IR (NaCl) 3264, 2970, 2932, 2870, 1489, 1450, 1381, 941 cm\(^{-1}\); \(\text{^1H NMR (400 MHz, CDCl}_3\) \(\delta 1.26 (6\text{H}, d, J = 6.8 \text{ Hz}), 3.04 (1\text{H}, \text{sept}, J = 6.8 \text{Hz}), 7.01 (1\text{H}, d, J = 16.8 \text{Hz}), 7.32 (1\text{H}, d, J = 7.2 \text{Hz}), 7.37 (2\text{H}, dd, J = 7.2, 7.2 \text{Hz}), 7.46 (1\text{H}, d, J = 16.8 \text{Hz}), 7.54 (2\text{H}, d, J = 7.2 \text{Hz}), 9.28 (1\text{H}, \text{brs}); \text{^13C NMR (100 MHz, CDCl}_3\) \(\delta 21.1, 29.6, 115.9, 127.4, 128.7, 128.9, 135.5, 136.5, 159.9; \text{ESI-HRMS: Found: m/z 190.1240. Calcd for C}_{12}\text{H}_{16}\text{NO}: (M+H)\text{^+} 190.1232.}\)
6-Methyl-3,4-diphenyl-2-(5,6,7,8-tetraphenylnaphthalen-1-yl)pyridine (3-4aa)

White solid; mp. 128-130 °C; IR (NaCl) 3055, 3024, 2932, 1582, 1535, 1497, 1443, 1381, 1366 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.42 (3H, s), 6.51 (1H, d, J = 7.2 Hz), 6.61-6.66 (4H, m), 6.71-6.85 (10H, m), 6.85-7.00 (5H, m), 7.01-7.10 (4H, m), 7.12-7.18 (5H, m), 7.21-7.28 (3H, m), 7.37 (1H, d, J = 6.8 Hz), 7.43 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.0, 122.5, 124.3, 124.9, 125.1, 125.3, 125.5, 126.1, 126.2, 126.30, 126.32, 126.4, 126.6, 127.0, 127.1, 127.2, 127.5, 127.8, 129.1, 130.6, 130.7, 130.90, 130.94, 131.0, 131.17, 131.20, 131.22, 131.26, 131.34, 133.1, 133.7, 137.2, 137.6, 137.9, 138.2, 139.0, 139.86, 139.89, 140.1, 140.57, 140.62, 140.7, 148.2, 155.7, 159.6; ESI-HRMS: Found: m/z 676.3000. Calcd for C₅₂H₃₈N: (M+H)⁺ 676.3004.
6.4 Experimental section of Chapter 4:

6.4.1 Synthesis of O-acetyl oxime derivatives

6.4.1.1. Preparation of aryl ketone O-acetyl oximes: a typical procedure for synthesis of isobutyrophenone O-acetyl oxime (4-1a).

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{NH}_2\text{OH-HCl, pyridine, EtOH, 60 °C} \\
\text{Me} & \quad \text{Ac}_2\text{O, cat. DMAP, pyridine, rt} \\
\text{Me} & \quad \text{N}^+\text{OAc} \\
\text{4-1a (syn:anti = 1:1)}
\end{align*}
\]

To a solution of isobutyrophenone (0.9 g, 6.1 mmol) and pyridine (1.4 mL, 9.2 mmol) in EtOH (6 mL) was added NH$_2$OH-HCl (0.64 g, 17.1 mmol) in one portion and the reaction mixture was stirred at 60 °C for 2 h. The reaction was quenched by adding water and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO$_4$. Volatile materials were removed \textit{in vacuo} to give acetophenone oxime, which was used for the next acetylation without further purification.

The crude residue of acetophenone oxime obtained above was treated with Ac$_2$O (1.2 mL, 12.2 mmol) and a catalytic amount of DMAP (5 mg) in pyridine (3 mL) and the reaction mixture was stirred at room temperature for 1 h. After volatile materials were evaporated, the resulting residue was treated with water, and organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO$_4$. The solvents were removed under reduced pressure and the crude was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) to yield O-acetyl oxime 4-1a in 97% yield.
Isobutyrophenone O-acetyl oxime (4-1a)\textsuperscript{18}

Colorless oil; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{\delta} 1.17 (6H \times 1, d, \textit{J} = 6.8 Hz), 1.22 (6H \times 1, d, \textit{J} = 7.2 Hz), 1.95 (3H \times 1, s), 2.23 (3H \times 1, s), 2.99 (1H \times 1, septet, \textit{J} = 6.8 Hz), 3.53 (1H \times 1, septet, \textit{J} = 7.2 Hz), 7.13-7.16 (2H \times 1, m), 7.34-7.45 (3H \times 1+5H \times 1, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \textit{\delta} 19.49, 19.53, 19.77, 19.81, 29.9, 34.9, 126.7, 128.0, 128.1, 128.2, 128.7, 129.4, 132.9, 133.9, 168.79, 168.83, 171.6, 171.9.

(Z)-2,2-Dimethylpropiophenone O-acetyl oxime (4-1b)

Prepared from 2,2-dimethylpropiophenone and purified by recrystallization from hexane-ethyl acetate (two times) in 84\% yield; White solid; mp. 74–75 °C; IR (NaCl) 2974, 2934, 1753, 1622, 1479, 1443, 1366 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{\delta} 1.24 (9H, s), 1.89 (3H, s), 7.01-7.04 (2H, m), 7.34-7.41 (3H, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \textit{\delta} 19.6, 28.0, 38.3, 126.6, 127.8, 128.1, 133.2, 168.9, 174.8; ESI-HRMS: Found: m/z 220.1340. Calcd for C\textsubscript{13}H\textsubscript{18}NO\textsubscript{2}: (M+H)+ 220.1338.

(E)-1,2-Diphenylethanone O-acetyl oxime (4-1c)

Prepared from 1,2-diphenylethanone and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) in 87\% yield; White solid; mp. 47–48 °C; IR (NaCl) 3063, 3015, 1767, 1601, 1495, 1445, 1366, 1321 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textit{\delta} 2.23 (3H, s), 4.24 (2H, s), 7.18-7.23 (3H, m), 7.26-7.30 (2H, m), 7.35-7.44 (3H, m), 7.74

\textsuperscript{18} Compound 4-1a is same as compound 2-10 in Chapter 2.
(2H, d, J = 7.6 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 19.8, 34.3, 126.7, 127.5, 128.3, 128.6, 128.8, 130.6, 134.0, 135.3, 163.7, 168.7; ESI-HRMS: Found: m/z 254.1179. Calcd for C\textsubscript{16}H\textsubscript{16}NO\textsubscript{2}: (M+H\textsuperscript{+}) 254.1181.

\textbf{1,2,2-Triphenylethanone O-acetyl oxime (4-1d)}

![Structure of 1,2,2-Triphenylethanone O-acetyl oxime (4-1d)]

\(\text{syn:anti} = 2:1\)

Prepared from 1,2,2-triphenylethanone\textsuperscript{19} and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) (65% yield); Colorless oil; IR (NaCl) 3061, 3026, 1769, 1599, 1495, 1366, 1200, 1001 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.86 (3H\times0.5, s), 1.98 (3H\times1, s), 5.44 (1H\times1, s), 6.01 (1H\times0.5, s), 7.03-7.05 (2H\times1, m), 7.19 (2H\times1, d, \(J = 7.2\) Hz), 7.24-7.34 (11H\times1+13H\times0.5, m), 7.48-7.52 (2H\times0.5, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 19.2, 19.7, 53.5, 57.9, 127.0, 127.2, 127.4, 128.0, 128.3, 128.4, 128.5, 128.6, 129.0, 129.2, 129.4, 130.0, 133.4, 134.9, 138.6, 138.7, 166.6, 167.6, 167.9, 169.1; ESI-HRMS: Found: m/z 330.1497. Calcd for C\textsubscript{22}H\textsubscript{20}NO\textsubscript{2}: (M+H\textsuperscript{+}) 330.1494.

\textbf{Cyclopropyl(phenyl)methanone O-acetyl oxime (4-1e)}

![Structure of Cyclopropyl(phenyl)methanone O-acetyl oxime (4-1e)]

\(\text{syn:anti} = 1:2.2\)

Prepared from cyclopropyl(phenyl)methanone and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) in quantitative yield; Colorless oil; IR (NaCl) 3017, 1769, 1759, 1601, 1493, 1366, 1207 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 0.68-0.72 (2H\times1, m), 0.84-0.89 (2H\times0.46, m), 0.90-0.95 (2H\times0.46, m), 0.98-1.03 (2H\times1, m), 1.81-2.84 (3H\times0.46, m), 2.01-2.1 (2H\times1, m), 2.21-2.27 (2H\times0.46, m), 2.59 (1H\times0.46, m), 4.36 (1H\times1, s), 7.04-7.07 (2H\times0.46, m), 7.16-7.17 (2H\times1, m), 7.23-7.33 (11H\times1+13H\times0.5, m), 7.47-7.52 (2H\times0.5, m); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 19.2, 19.7, 53.5, 57.9, 127.0, 127.2, 127.4, 128.0, 128.3, 128.4, 128.5, 128.6, 129.0, 129.2, 129.4, 130.0, 133.4, 134.9, 138.6, 138.7, 166.6, 167.6, 167.9, 169.1; ESI-HRMS: Found: m/z 330.1497. Calcd for C\textsubscript{22}H\textsubscript{20}NO\textsubscript{2}: (M+H\textsuperscript{+}) 330.1494.

(E)-1-(Benzofuran-2-yl)ethanone O-acetyl oxime (4-4f)

\[
\begin{align*}
\text{Prepared from 1-(benzofuran-2-yl)ethanone and purified by recrystallization from hexane-ethyl acetate (one time) (68% yield); White solid; mp. 101-102 \, ^\circ C; IR (NaCl) 1773, 1607, 1560, 1449, 1368, 1306 \, \text{cm}^{-1}; ^1\text{H NMR (400 MHz, CDCl}_3) & \delta 2.29 (3\, H, s), \\
& 2.42 (3\, H, s), 7.25-7.29 (2\, H, m), 7.38 (1\, H, ddd, J = 1.2, 7.2, 8.4 \, \text{Hz}), 7.56 (1\, H, dd, J = 0.8, 8.4 \, \text{Hz}), 7.62 (1\, H, d, J = 7.6 \, \text{Hz}); ^13\text{C NMR (100 MHz, CDCl}_3) & \delta 13.3, 19.6, 109.8, 112.0, 121.8, 123.4, 126.6, 127.5, 149.9, 154.3, 155.5, 168.2; ESI-HRMS: Found: m/z 218.0811. Calcd for C\textsubscript{12}H\textsubscript{12}N\textsubscript{0}O\textsubscript{3}: (M+H\sp{+})^\sp{\ast} 218.0817.
\end{align*}
\]

1-(Furan-2-yl)ethanone O-acetyl oxime (4-4g)

\[
\begin{align*}
\text{Prepared from 1-(furan-2-yl)ethanone and purified by recrystallization from hexane-ethyl acetate (two times) (70% yield); White solid; mp. 99-100 \, ^\circ C; IR (NaCl) 1771, 1609, 1481, 1393, 1368, 1325 \, \text{cm}^{-1}; ^1\text{H NMR (400 MHz, CDCl}_3) & \delta 2.25 (3\, H\times 1, s), 2.28 (3\, H\times 0.05), 2.31 (3\, H\times 1, s), 2.41 (3\, H\times 0.05), 6.49 (1\, H\times 1, dd, J = 1.8, 3.6 \, Hz), 6.59 (1\, H\times 0.05, dd, J = 1.6, 3.6 \, Hz), 6.91 (1\, H\times 1, dd, J = 0.4, 3.6 \, Hz), 7.35 (1\, H\times 0.05, dd, J = 0.4, 3.6 \, Hz), 7.54 (1\, H\times 1, dd, J = 0.6, 1.8 \, Hz); ^13\text{C NMR (100 MHz, CDCl}_3) & \delta 13.1, 19.6,
\end{align*}
\]
111.7, 113.2, 145.0, 148.3, 153.8, 168.4; ESI-HRMS: Found: m/z 168.0656. Calcd for C₈H₁₀NO₃: (M+H)⁺ 168.0661.

1-(Thiophen-2-yl)ethanone O-acetyl oxime (4-4h)

![Chemical structure of 1-(Thiophen-2-yl)ethanone O-acetyl oxime (4-4h)]

Prepared from 1-(thiophen-2-yl)ethanone and purified by recrystallization from hexane-ethyl acetate (two times) (85% yield); White solid; mp. 115–117 °C; IR (NaCl) 1763, 1603, 1526, 1431, 1368, 1306, 968 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.26 (3H, s), 2.33 (3H×0.75, s), 2.40 (3H×1, s), 2.51 (3H×0.75, s), 7.07 (1H×1, dd, J = 4.0, 5.2 Hz), 7.16 (1H×0.25, dd, J = 3.6, 5.2 Hz), 7.42 (1H×1, dd, J = 1.0, 5.0 Hz), 7.44 (1H×1, dd, J = 1.0, 3.8 Hz), 7.58 (1H×0.25, dd, J = 1.2, 4.0 Hz), 7.67 (1H×0.25, dd, J = 1.2, 5.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 19.7, 19.92, 19.94, 126.2, 127.2, 129.0, 129.1, 131.7, 132.2, 132.7, 137.8, 153.3, 157.6, 167.6, 168.7; ESI-HRMS: Found: m/z 184.0435. Calcd for C₈H₁₀NO₃S: (M+H)⁺ 184.0432.

(E)-1-(1-Tosyl-1H-pyrrol-2-yl)ethanone O-acetyl oxime (4-4i)

![Chemical structure of (E)-1-(1-Tosyl-1H-pyrrol-2-yl)ethanone O-acetyl oxime (4-4i)]

Prepared from 1-(1-tosyl-1H-pyrrol-2-yl)ethanone²⁰ and purified by recrystallization from hexane-ethyl acetate (two times) (68% yield); White solid; mp. 113–115 °C; IR (NaCl) 1767, 1597, 1368, 1263, 1175, 1148 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.24 (3H, s), 2.38 (6H, s), 6.25 (1H, t, J = 3.2 Hz), 6.40 (1H, dd, J = 1.6, 3.2 Hz), 7.27 (1H, dd, J = 1.6, 3.2 Hz), 7.28 (2H, d, J = 8.4 Hz), 7.77 (2H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃)

δ 19.2, 19.6, 21.6, 113.1, 117.9, 125.4, 127.5, 129.7, 129.8, 135.2, 145.3, 158.9, 168.1;

ESI-HRMS: Found: m/z 321.0904. Calcd for C_{19}H_{17}N_{2}O_{4}: (M+H)^+ 321.0909.

(1E,4E)-Naphthalene-1,4-dione O,O-diacetyl dioxime (4-8)

\[
\begin{array}{c}
\text{N}\\
\text{OAc}
\end{array}
\begin{array}{c}
\text{N}\\
\text{OAc}
\end{array}
\]

Prepared from naphthalene-1,4-dione and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 60:40) in 30% yield; Reddish brown solid; mp. 146–148 °C;

IR (NaCl) 1773, 1620, 1574, 1539, 1520, 1368, 1188, 939 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 2.36 (6H, s), 7.55 (2H, s), 7.56 (2H, dd, \(J = 3.6, 6.4\) Hz), 8.37 (2H, dd, \(J = 3.6, 6.0\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) δ 19.8, 122.2, 124.3, 128.5, 130.9, 150.8, 168.2;

ESI-HRMS: Found: m/z 273.0884. Calcd for C_{14}H_{13}N_{2}O_{4}: (M+H)^+ 273.0875.

6.4.1.2. Preparation of (Z)-morpholino(phenyl)methanone O-acetyl oxime (4-1f)

\[
\begin{array}{c}
\text{N}\\
\text{OAc}
\end{array}
\begin{array}{c}
\text{N}\\
\text{OAc}
\end{array}
\]

To a solution of benzaldehyde (5.0 g, 47.0 mmol) and pyridine (11.2 mL, 131.6 mmol) in EtOH (40 mL) was added NH\(_2\)OH•HCl (5.07 g, 70.5 mmol) in one portion and the reaction mixture was stirred at 60 °C for 2 h. The reaction was quenched by adding water and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO\(_4\). Volatile
materials were removed *in vacuo* to give benzaldehyde oxime, which was used for the next step without further purification.

To a stirred solution of the crude residue of benzaldehyde oxime (1.0 g, 8.3 mmol) in 8 mL of DMF at 0 °C was added *N*-chlorosuccinimide (1.21 g, 9.1 mmol) in portion. The reaction was allowed to stir at room temperature for 1 h then followed by addition of morpholine (4.63 g, 24.8 mmol) dropwise. The mixture was stirred for another 4 h then quenched with water and the organic materials were extracted twice with ethyl acetate. The combined extracts were washed with water, sat. NaHCO₃, brine, and dried over MgSO₄. Volatile materials were removed *in vacuo* to give the white solid (Z)-morpholino(phenyl)methanone oxime which was purified by recrystallization from EtOH (one time) in 56% yield.

(Z)-morpholino(phenyl)methanone oxime (0.9 g, 4.4 mmol) was treated with Ac₂O (0.9 mL, 8.8 mmol) and a catalytic amount of DMAP (5 mg) in pyridine (2 mL) and the reaction mixture was stirred at room temperature for 1 h. After volatile materials were evaporated, the resulting residue was treated with water, and organic materials were extracted twice with ethyl acetate. The combined extracts were washed with 1 M aqueous HCl and brine, and dried over MgSO₄. The solvents were removed under reduced pressure and the crude was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) to provide product 4-1f in 91% yield.

(Z)-Morpholino(phenyl)methanone O-acetyl oxime (4-1f)

Colorless oil; IR (NaCl) 3005, 2970, 2855, 1748, 1566, 1495, 1366, 1263, 1221, 1119 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.86 (3H, s), 3.23 (4H, t, J = 4.8 Hz), 3.70 (4H, t, J = 4.8 Hz), 7.26-7.30 (2H, m), 7.40-7.45 (3H, m); ¹³C NMR (100 MHz, CDCl₃) δ 19.5, 46.9, 66.4, 128.0, 128.6, 129.8, 130.3, 166.3, 169.1; ESI-HRMS: Found: m/z 249.1242. Calcd for C₁₃H₁₇N₂O₃: (M+H)⁺ 249.1239.
6.4.1.3. Preparation of indolyl ketone O-acetyl oximes 4-4a to 4-4e: a typical procedure for synthesis of (E)-tert-butyl 2-(1-(acetoxyimino)ethyl)-1H-indole-1-carboxylate (4-4a).

![Diagram of the reaction](image)

To a solution of 1-(1H-indol-2-yl)ethanone\(^{21}\) (1.75 g, 11.0 mmol) in CH\(_2\)Cl\(_2\) (27 mL), was added 4-(dimethylamino)pyridine (0.13 g, 1.1 mmol) and di-tert-butyl dicarbonate (2.62 g, 12.0 mmol). The reaction mixture was stirred at room temperature for 2.5 h and then quenched with 1 M aqueous HCl, extracted thrice with CH\(_2\)Cl\(_2\). The combined organic extracts were washed with water and brine, as well as dried over anhydrous MgSO\(_4\). Volatile materials were removed \textit{in vacuo} and tert-butyl 2-acetyl-1H-indole-1-carboxylate was used for the next step without purification. To a solution of tert-Butyl 2-acetyl-1H-indole-1-carboxylate in EtOH (5 mL) was added pyridine (2.5 mL, 30.4 mmol) and NH\(_2\)OH-HCl (1.13 g, 16.4 mmol) stirred at room temperature for 1 h. The reaction mixture was then quenched with water and extracted twice with ethyl acetate. The combined organic extracts were washed with 1 M aqueous HCl, brine, and dried over anhydrous MgSO\(_4\). Volatile materials were removed under reduced pressure to give the corresponding oxime, which was used for the next acetylation step without further purification.

To the oxime crude material in pyridine (10 mL), was treated with acetic anhydride (2.0 mL, 21.7 mmol) and 4-(dimethylamino)pyridine (0.13 g, 1.1 mmol) stirred at room temperature for 1 h. The reaction mixture was then quenched with water and

extracted twice with ethyl acetate. The combined organic extracts were washed with 1 M aqueous HCl, brine and dried over anhydrous MgSO₄. Volatile materials were removed \textit{in vacuo} and the crude was purified by flash column chromatography (Silica gel, hexane:ethyl acetate = 90:10) to afford the indole O-acetyl oxime 4-4a (2.72 g, 8.60 mmol) in 78% yield.

\textit{(E)-\textit{tert}-Butyl 2-\textit{(1-(acetoxyimino)ethyl)-1H-indole-1-carboxylate (4-4a)}}

White solid; mp. 62–64 °C; \textit{IR (NaCl)} 1767, 1734, 1618, 1566, 1452, 1327 cm⁻¹; \textit{¹H NMR} (400 MHz, CDCl₃) δ 1.64 (9H, s), 2.26 (3H, s), 2.32 (3H, s), 6.77 (1H, s), 7.23–7.27 (1H, m), 7.36 (1H, ddd, \(J=1.2, 7.2, 8.4\)), 7.56 (1H, d, \(J=7.6\) Hz), 8.09 (1H, dd, \(J=0.8, 8.4\) Hz); \textit{¹³C NMR} (100 MHz, CDCl₃) δ 18.5, 19.7, 28.0, 84.8, 111.8, 115.5, 121.4, 123.3, 124.9, 128.6, 132.9, 136.9, 149.4, 159.5, 168.5; \textit{ESI-HRMS}: Found: m/z 317.1504. Calcd for C₁₇H₂₁N₂O₄: (M+H)⁺ 317.1501.

\textit{(E)-\textit{tert}-Butyl 2-(1-(acetoxyimino)pentyl)-1H-indole-1-carboxylate (4-4b)}

\begin{center}
\includegraphics[width=0.3\textwidth]{chemical_structure.png}
\end{center}

Prepared from 1-(1\textit{H-indol-2-yl)pentan-1-one and purified by recrystallization from hexane-ethyl acetate (one time) in 36% yield; White solid; mp. 81–83 °C; \textit{IR (NaCl)} 2961, 1769, 1732, 1614, 1452, 1329 cm⁻¹; \textit{¹H NMR} (400 MHz, CDCl₃) δ 0.88 (3H, t, \(J=7.2\) Hz), 1.32–1.37 (2H, m), 1.40–1.46 (2H, m), 1.63 (9H, s), 2.25 (3H, s), 2.74–2.78 (2H, m), 6.73 (1H, s), 7.24–7.27 (1H, m), 7.34–7.38 (1H, m), 7.56 (1H, d, \(J=7.6\) Hz), 8.11 (1H, d, \(J=8.4\) Hz); \textit{¹³C NMR} (100 MHz, CDCl₃) δ 13.7, 19.7, 22.6, 27.96, 28.01, 31.5, 84.8, 112.3, 115.5, 121.3, 123.3, 125.4, 128.7, 132.6, 136.8, 150.0, 163.8, 168.6; \textit{ESI-HRMS}: Found: m/z 359.1964. Calcd for C₂₀H₂₇N₂O₄: (M+H)⁺ 359.1971.
Synthesis of 1-(1H-indol-2-yl)pentan-1-one

\[
\begin{array}{c}
\begin{array}{c}
\text{Indole-2-carboxylic acid} \\
\text{(1.2 g, 7.5 mmol)}
\end{array}
\end{array}
\xrightarrow{n-\text{BuLi}}
\begin{array}{c}
\begin{array}{c}
\text{1-(1H-indol-2-yl)pentan-1-one} \\
\text{Yellow solid; mp. 113–115 °C; IR (NaCl) 3321, 3019, 1651, 1524, 1414, 1341, 1167, 1144 cm}^{-1};
\text{H NMR (400 MHz, CDCl}_3) \delta 0.97 (3H, t, J = 7.4 Hz), 1.44 \\
(2H, tq, J = 7.2, 7.6 Hz), 1.78 (2H, tt, J = 7.2, 7.6 Hz), 2.95 (2H, t, J = 7.6 Hz), \\
7.15 (1H, ddd, J = 0.8, 6.8, 8.0 Hz), 7.21 (1H, m), 7.34 (1H, ddd, J = 1.2, 7.2, 8.0 \\
Hz), 7.43 (1H, d, J = 8.4 Hz), 7.71 (1H, dd, J = 0.8, 8.0 Hz), 9.11 (1H, br); \\
C NMR (100 MHz, CDCl}_3) \delta 13.9, 22.5, 27.3, 38.1, 109.1, 112.1, 120.9, 123.0, \\
126.2, 127.6, 135.2, 137.2, 183.7; \\
\text{ESI-HRMS: Found: m/z 202.1241. Calcd for C}_{13}\text{H}_{16}\text{NO: (M+H)}^+ 202.1232.}
\end{array}
\end{array}
\]
(E)-tert-Butyl 2-(1-(acetoxyimino)pent-4-enyl)-1H-indole-1-carboxylate (4-4c)

\[
\begin{align*}
\text{N-OAc} \\
\text{Boc} \\
\end{align*}
\]

Prepared from 1-(1H-indol-2-yl)pent-4-en-1-one and purified by flash column chromatography (hexane : ethyl acetate = 5 : 95) in 55% yield; White solid; mp. 61–63°C; IR (NaCl) 2982, 1763, 1730, 1450, 1369, 1329 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\)

\[\begin{align*}
1.64 & (9H, s), 2.19-2.23 (2H, m), 2.25 (3H, s), 2.87 (2H, m), 4.99 (1H, dd, \(J=1.3, 10.3\) Hz), 5.02 (1H, dd, \(J=1.5, 17.2\) Hz), 5.71-5.81 (1H, m), 6.74 (1H, s), 7.24-7.28 (1H, m), 7.36 (1H, ddd, \(J=1.2, 7.2, 8.4\) Hz), 7.56 (1H, d, \(J=7.6\) Hz), 8.10 (1H, d, \(J=8.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\)
\end{align*}\]

19.7, 28.0, 29.9, 31.1, 84.9, 112.5, 115.6, 115.8, 121.4, 123.3, 125.5, 128.6, 132.3, 136.5, 136.7, 149.5, 162.9, 168.5; ESI-HRMS: Found: m/z 357.1810. Calcd for C\(_{20}\)H\(_{25}\)N\(_2\)O\(_4\): (M+H)\(^+\) 357.1814.

**Synthesis of 1-(1H-indol-2-yl)pent-4-en-1-one**

\[
\begin{align*}
\text{Br} \quad \text{Mg} \\
\text{THF, reflux} & \quad \text{Mg} \\
\text{0 °C to rt} & \quad \text{0 °C to rt} \\
\end{align*}
\]

To a stirred suspension of Mg (0.7 g, 28.8 mmol) in anhydrous THF (30 mL) under N\(_2\) atmosphere was added 4-bromobut-1-ene (0.8 mL, 7.9 mmol) dropwise. Upon initiation, the remaining 4-bromobut-1-ene (1.7 mL, 16.4 mmol) was added dropwise and the reaction mixture was allowed to reflux for 1.5 h. The solution was transferred via cannula to a solution of amide\(^{22}\) (0.8 g, 4.0 mmol) in anhydrous THF (8 mL) at 0 °C and the reaction mixture was stirred for 24 h at room temperature. After completion, the resulting mixture was then quenched with 1 M aqueous HCl, then extracted with diethyl ether, washed with water and

brine, and dried over anhydrous MgSO₄. Volatile materials were removed in vacuo and the resultant crude was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to afford the desired ketone in 52 % yield.

1-(1H-Indol-2-yl)pent-4-en-1-one

Purple solid; mp. 115–117 °C; IR (NaCl) 3310, 3017, 1651, 1524, 1416, 1341, 1142 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.52-2.58 (2H, m), 3.06 (2H, t, J = 7.6 Hz), 5.03 (1H, dd, J = 1.2, 10.0 Hz), 5.11 (1H, dd, J = 1.6, 17.2 Hz), 5.87-5.96 (1H, m), 7.16 (1H, t, J = 7.6 Hz), 7.23 (1H, d, J = 1.2 Hz), 7.33-7.37 (1H, m), 7.43 (1H, d, J = 8.0 Hz), 7.71 (1H, d, J = 8.0Hz), 9.18 (1H, br); ¹³C NMR (100 MHz, CDCl₃) δ 28.8, 37.4, 109.2, 112.2, 115.5, 120.9, 123.0, 126.3, 127.6, 135.1, 137.0, 137.3, 192.5; ESI-HRMS: Found: m/z 200.1078. Calcd for C₁₃H₁₄NO: (M+H)⁺ 200.1075.

(Z)-tert-Butyl 2-(1-(acetoxyimino)-2-ethoxy-2-oxoethyl)-1H-indole-1-carboxylate (4-4d)

Prepared from tert-butyl 2-(2-ethoxy-2-oxoacetyl)-1H-indole-1-carboxylate and purified by flash column chromatography (hexane : ethyl acetate = 5 : 95) in 30% yield; Yellow solid; mp. 134–136 °C; IR (NaCl) 2980, 2936, 1771, 1728, 1717, 1607 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.37 (3H, t, J = 7.2 Hz), 1.63 (9H, s), 2.20 (3H, s), 4.38 (2H, q, J = 7.2 Hz), 6.91 (1H, s), 7.27-7.31 (1H, m), 7.41, (1H, ddd, J = 1.2, 7.6, 8.8 Hz), 7.62 (1H, d, J = 7.6 Hz), 8.11 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 19.5, 27.9, 62.7, 85.6, 114.0, 115.5, 121.8, 123.3, 125.3, 126.1, 128.5, 135.9, 149.6, 150.0, 161.9, 167.7; ESI-HRMS: Found: m/z 375.1571. Calcd for C₁₉H₂₃N₂O₆: (M+H)⁺ 375.1556.
Synthesis of tert-butyl 2-(2-ethoxy-2-oxoacetyl)-1H-indole-1-carboxylate

\[
\text{Boc} \quad \text{LiN(i-Pr)}_2 \quad \text{EtO}_2\text{C-CO}_2\text{Et} \quad \text{THF, -78 °C to rt} \quad \text{Boc}
\]

To a solution of freshly prepared LiN(i-Pr)_2 (LDA) from n-BuLi (4.9 mL, 7.8 mmol) and HN(i-Pr)_2 (1.1 mL, 7.8 mmol) in THF (16 mL) at -78 °C, was added a solution of tert-butyl 1H-indole-1-carboxylate (1.6 g, 7.5 mmol) in THF (2 mL). The reaction was allowed to stir for 1 h at -78 °C before transferred via cannula to a solution of diethyl oxalate (1.5 mL, 11.2 mmol) in THF (12 mL) at -78 °C. The reaction mixture was allowed to slowly warm up to room temperature while stirring for 4 h, then quenched with water and extracted with diethyl ether. The combined organic extracts were washed with water, brine, and dried over anhydrous MgSO_4. Volatile materials were removed in vacuo and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to afford ethyl 2-(1H-indol-2-yl)-2-oxoacetate in 67 % yield.

**tert-Butyl 2-(2-ethoxy-2-oxoacetyl)-1H-indole-1-carboxylate**

Yellow solid; mp. 81–83 °C; IR (NaCl) 1717, 1686, 1541, 1369, 1304, 1225, 1144, 1125 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.39 (3H, t, \(J = 7.2 \text{ Hz}\)), 1.65 (9H, s), 4.37 (2H, q, \(J = 7.1 \text{ Hz}\)), 7.30 (1H, ddd, \(J = 0.8, 6.4, 8.8 \text{ Hz}\)), 7.48 (1H, ddd, \(J = 1.2, 7.2, 8.4 \text{ Hz}\)), 7.67 (1H, d, \(J = 7.6 \text{ Hz}\)), 8.02 (1H, dd, \(J = 0.8, 8.4 \text{ Hz}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.0, 28.0, 62.5, 86.0, 115.4, 117.5, 123.0, 123.7, 127.9, 128.0, 135.2, 137.1, 150.2, 161.3, 178.0; ESI-HRMS: Found: m/z 318.1353. Calcd for C\(_{17}\)H\(_{20}\)NO\(_{5}\): (M+H)\(^+\) 318.1341.
(E)-tert-Butyl 2-((acetoxyimino)methyl)-1H-indole-1-carboxylate (4-4e)

\[
\begin{array}{c}
\text{N} \longrightarrow \text{OAc} \\
\text{H} \\
\text{Boc}
\end{array}
\]

Prepared from 1H-indole-2-carbaldehyde and purified by recrystallization from hexane-ethyl acetate (one time) in 49% yield; White solid; mp. 113–114 °C; IR (NaCl) 2982, 1767, 1734, 1553, 1449, 1329 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 1.71 \text{ (9H, s), 2.23 (3H, s), 7.25-7.29 (1H, m), 7.31 (1H, s), 7.38 (1H, ddd, } J = 1.2, 7.2, 8.4 \text{ Hz), 7.60 (1H, d, } J = 7.6 \text{ Hz), 8.08 (1H, dd, } J = 0.4, 8.4 \text{ Hz), 9.05 (1H, d, } J = 0.4 \text{ Hz); } ^{13}\text{C NMR (100 MHz, CDCl}_3\) \(\delta 19.5, 28.2, 85.4, 112.5, 115.8, 121.9, 123.6, 126.2, 128.5, 129.7, 137.1, 150.1, 150.7, 168.5; \text{ ESI-HRMS: Found: m/z 303.1346. Calcd for } C_{16}H_{19}N_2O_4: (M+H)^+ 303.1345.}

6.4.2 Synthesis of azaheterocycles by Cu–Rh catalytic system: a typical procedure for the reaction of isobutyrophenone O-acetyl oxime (4-1a) and diphenylacetylene (4-2a) (Table 4-1, entry 4).

\[
\text{[Cp*RhCl}_2\text{]_2 (2.5 mol %)} + \text{Cu(OAc)}_2 (10 \text{ mol %}) \\
\text{DMF, 60 °C, 4 h}
\]

To a DMF solution (1.5 mL) of isobutyrophenone O-acetyl oxime (4-1a) (61.6 mg, 0.30 mmol) and diphenylacetylene (4-2a) (64.2 mg, 0.36 mmol) were added [Cp*RhCl\(_2\)\text{] (4.6 mg, 0.0075 mmol) and Cu(OAc)\(_2\) (5.5 mg, 0.03 mmol), and the reaction mixture was stirred at 60 °C under a nitrogen atmosphere for 4 h. After cooled to room temperature, the reaction was quenched with pH 9 buffer and organic materials were...
extracted three times with ethyl acetate. The combined extracts were washed with water (three times) and brine, and dried over MgSO₄. The solvents were removed under reduced pressure and the crude was purified by flash column chromatography (hexane : ethyl acetate = 8 : 92) to afford 1-isopropyl-3,4-diphenylisoquinoline (4-3aa) (92.4 mg, 0.286 mmol) in 95% yield.

1-Isopropyl-3,4-diphenylisoquinoline (4-3aa)²³

White solid; ¹H NMR (400 MHz, CDCl₃) δ 1.53 (6H, d, J = 6.8 Hz), 4.03 (1H, septet, J = 6.8 Hz), 7.17-7.22 (3H, m), 7.23-7.25 (2H, m), 7.34-7.40 (3H, m), 7.43-7.46 (2H, m), 7.53-7.60 (2H, m), 7.66-7.68 (1H, m), 8.29-8.31 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 31.3, 124.5, 124.8, 126.2, 126.5, 126.8, 127.1, 127.4, 128.3, 128.4, 129.3, 130.6, 131.4, 136.5, 138.1, 141.3, 148.6, 165.0.

1-Isopropyl-3,4-bis(4-methoxyphenyl)isoquinoline (4-3ab)

![Diagram of 1-Isopropyl-3,4-bis(4-methoxyphenyl)isoquinoline (4-3ab)](image)

White solid; mp. 127–129 °C; IR (NaCl) 2965, 1609, 1514, 1439, 1389, 1287, 1246, 1177 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.53 (6H, d, J = 6.8 Hz), 3.78 (3H, m), 3.87 (3H, m), 4.01 (1H, septet, J = 6.8 Hz), 6.76 (2H, td, J = 2.8, 9.2 Hz), 6.94 (2H, td, J = 2.8, 8.8 Hz), 7.17 (2H, td, J = 2.8, 8.4 Hz), 7.43 (2H, td, J = 2.8, 9.2 Hz), 7.53 (2H, td, J = 3.6, 9.6 Hz), 7.65-7.69 (1H, m), 8.25-8.28 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 22.3, 31.3, 55.1, 55.2, 112.9, 113.9, 124.5, 124.6, 125.9, 126.4, 127.3, 129.2, 130.4, 131.8, 132.4, 134.0,

²³ Compound 4-3aa is same as compound 2-30a in Chapter 2.
137.0, 148.2, 158.5, 158.6, 164.6; ESI-HRMS: Found: m/z 384.1969. Calcd for 
C_{26}H_{26}NO_{2}: (M+H)^+ 384.1964.

3,4-Bis(4-bromophenyl)-1-isopropylisoquinoline (4-3ac)

Yellow solid; mp. 158–160 °C; IR (NaCl) 2967, 1570, 1504, 1489, 1387, 1265, 1011 cm⁻¹

¹ H NMR (400 MHz, CDCl₃) δ 1.52 (6H, d, J = 6.8 Hz), 4.03 (1H, septet, J = 6.8 Hz), 
7.13 (2H, td, J = 2.4, 8.4 Hz), 7.31 (2H, td, J = 2.0, 8.8 Hz), 7.36 (2H, td, J = 2.0, 8.8 Hz), 
7.54 (2H, td, J = 2.4, 8.4 Hz), 7.56-7.63 (3H, m), 8.29-8.32 (1H, m); ¹³C NMR (100 
MHz, CDCl₃) δ 22.2, 31.3, 121.5, 121.6, 124.7, 124.9, 126.1, 126.7, 127.2, 129.8, 130.8, 
131.8, 132.1, 133.0, 136.2, 136.7, 139.9, 147.4, 165.6; ESI-HRMS: Found: m/z 481.9945. 
Calcd for C_{24}H_{20}N^7Br^81Br: (M+H)^+ 481.9942.

1-Isopropyl-3,4-dipropylisoquinoline (4-3ad)²⁴

Colorless oil; ¹ H NMR (400 MHz, CDCl₃) δ 1.03 (3H, t, J = 7.2 Hz), 1.10 (3H, t, J = 7.2 
Hz), 1.42 (6H, d, J = 6.8 Hz), 1.68 (2H, tt, J = 7.2, 7.6 Hz), 1.86 (2H, tt, J = 7.2, 7.6 Hz), 
2.93 (2H, t, J = 7.6 Hz), 2.98 (2H, t, J = 7.6 Hz), 3.89 (1H, septet, J = 6.8 Hz), 7.47 (1H, 
dd, J = 7.6, 8.4 Hz), 7.62 (1H, dd, J = 7.6, 8.4 Hz), 7.98 (1H, d, J = 8.4 Hz), 8.18 (1H, d,

²⁴ Compound 4-3ad is same as compound 2-6ae in Chapter 2.
$J = 8.4 \text{ Hz}$; $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 14.3, 14.7, 22.3, 23.0, 24.0, 29.8, 30.8, 37.1, 123.8, 124.5, 124.9, 125.0, 125.4, 128.8, 135.7, 151.5, 162.7.

3,4-Bis((tert-butyldimethylsilyloxy)methyl)-1-isopropylisoquinoline (4-3ae)

\begin{center}
\includegraphics[width=0.3\textwidth]{4-3ae.png}
\end{center}

Pale yellow oil; IR (NaCl) 2955, 2928, 2857, 1566, 1472, 1462, 1389, 1360, 1254 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.06 (6H, s), 0.13 (6H, s), 0.89 (9H, t, $J = 2.4$ Hz), 0.92 (9H, t, $J = 2.4$ Hz), 1.41 (6H, d, $J = 6.8$ Hz), 3.91 (1H, septet, $J = 6.8$ Hz), 5.04 (2H, s), 5.25 (2H, s), 7.54 (1H, ddd, $J = 1.2$, 6.8, 8.4 Hz), 7.66 (1H, ddd, $J = 1.2$, 6.8, 8.4 Hz), 8.20 (1H, d, $J = 8.4$ Hz), 8.27 (1H, d, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ -5.2, -5.0, 18.37, 18.41, 22.2, 25.95, 25.96, 31.0, 58.4, 66.6, 124.7, 125.2, 125.76, 125.79, 126.0, 129.0, 136.4, 149.7, 164.9; ESI-HRMS: Found: m/z 460.3086. Calcd for C$_{26}$H$_{46}$NO$_2$Si$_2$: (M+H)$^+$ 460.3067.

1-Isopropyl-4-methyl-3-phenylisoquinoline (4-3af)$^{25}$

\begin{center}
\includegraphics[width=0.3\textwidth]{4-3af.png}
\end{center}

White solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.47 (6H, d, $J = 6.8$ Hz), 2.66 (3H, s), 3.95 (1H, septet, $J = 6.8$ Hz), 7.40 (1H, tt, $J = 1.2$, 7.2 Hz), 7.48 (2H, dd, $J = 7.2$, 7.2 Hz), 7.59 (1H, $J = 8.0$, 8.4 Hz), 7.66-7.74 (3H, m), 8.08 (1H, d, $J = 8.4$ Hz), 8.27 (1H, d, $J = 8.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 15.7, 22.3, 31.1, 121.4, 124.4, 124.8, 125.1, 126.0, 127.3, 127.8, 129.3, 130.3, 136.8, 142.0, 150.2, 163.2.

$^{25}$ Compound 4-3af is same as compound 2-6ab in Chapter 2.
4-((tert-Butyldimethylsilyloxy)methyl)-1-isopropyl-3-phenylisoquinoline (4-3ag)

Isolated as a mixture of 2 regioisomers and the structure of major isomer 4-3ag was characterized.

Yellow solid; mp. 85–88 °C; IR (NaCl) 2959, 2928, 2857, 1614, 1564, 1504, 1470, 1389, 1256 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.15 (6H, s), 0.96 (9H, s), 1.48 (6H, d, J = 6.8 Hz), 3.98 (1H, septet, J = 6.8 Hz), 5.03 (2H, s), 7.44-7.52 (3H, m), 7.60 (1H, ddd, J = 1.2, 6.8, 8.4 Hz), 7.74 (1H, ddd, J = 1.2, 6.8, 8.4 Hz), 7.84-7.87 (2H, m), 8.27 (1H, d, J = 8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ -5.3, 18.4, 22.1, 25.9, 31.3, 60.4, 123.5, 124.9, 125.0, 125.3, 126.1, 127.8 (overlapped), 129.6, 130.3, 136.8, 141.0, 151.0, 165.5; ESI-HRMS: Found: m/z 392.2410. Calcd for C₂₃H₃₄NOSi: (M+H⁺) 392.2410.

Ethyl 1-isopropyl-3-phenylisoquinoline-4-carboxylate (4-3ah)

Regioisomer (4-3ah-minor) was separated by flash column chromatography.

White solid; mp. 93–94 °C; IR (NaCl) 2968, 1717, 1570, 1557, 1504, 1449, 1389, 1265 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.07 (3H, t, J = 7.2 Hz), 1.48 (6H, d, J = 6.4 Hz), 4.00 (1H, septet, J = 6.8 Hz), 4.26 (2H, q, J = 7.2 Hz), 7.39-7.49 (3H, m), 7.62 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.73 (1H, ddd, J = 1.2, 6.8, 8.4 Hz), 7.78-7.81 (2H, m), 8.05 (1H, d, J = 8.4 Hz), 8.28 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.7, 22.1, 31.5,
61.6, 121.3, 124.3, 124.85, 124.88, 127.0, 128.2, 128.3, 129.0, 130.6, 133.9, 140.7, 149.2, 167.3, 169.5; ESI-HRMS: Found: m/z 320.1647. Calcd for C_{21}H_{22}NO_2: (M+H)^{+} 320.1651.

**Ethyl 1-isopropyl-4-phenylisoquinoline-3-carboxylate (4-3ah-minor)**

![Chemical structure of ethyl 1-isopropyl-4-phenylisoquinoline-3-carboxylate](image)

White solid; mp. 92–93 °C; IR (NaCl) 2968, 2934, 1506, 1404, 1389, 1373, 1323, 1234 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.95 (3H, t, \(J = 7.2\) Hz), 1.51 (6H, d, \(J = 6.8\) Hz), 4.00 (1H, septet, \(J = 6.8\) Hz), 4.10 (2H, q, \(J = 7.2\) Hz), 7.35-7.37 (2H, m), 7.42-7.50 (3H, m), 7.58-7.67 (3H, m), 8.31 (1H, dd, \(J = 2.4, 7.2\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 13.6, 22.1, 31.4, 61.0, 124.7, 126.5, 127.0, 127.7, 127.8, 128.1, 129.9, 130.1, 130.8, 135.7, 136.5, 141.9, 165.7, 168.1; ESI-HRMS: Found: m/z 320.1649. Calcd for C_{21}H_{22}NO_2: (M+H)^{+} 320.1651.

**4-Hexyl-1-isopropyl-3-(thiophen-2-yl)isoquinoline (4-3ai)**

![Chemical structure of 4-hexyl-1-isopropyl-3-(thiophen-2-yl)isoquinoline](image)

Yellow oil; IR (NaCl) 2961, 2928, 1560, 1506, 1468, 1447, 1431, 1387 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.95 (3H, t, \(J = 7.2\) Hz), 1.37-1.45 (4H, m), 1.48 (6H, d, \(J = 6.8\) Hz), 1.61 (2H, quintet, \(J = 7.2\) Hz), 1.78-1.86 (2H, m), 3.23-3.27 (2H, m), 3.91 (1H, septet, \(J = 6.8\) Hz), 7.17 (1H, dd, \(J = 3.6, 4.8\) Hz), 7.44 (1H, d, \(J = 5.2\) Hz), 7.46 (1H, d, \(J = 3.6\) Hz),
7.55 (1H, ddd, \( J = 0.8, 6.8, 8.0 \) Hz), 7.70 (1H, ddd, \( J = 1.2, 6.8, 8.4 \) Hz), 8.09 (1H, d, \( J = 8.4 \) Hz), 8.22 (1H, d, \( J = 8.0 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 14.1, 22.2, 22.7, 28.5, 29.8, 30.2, 31.3, 31.7, 124.4, 125.1, 125.2, 125.3, 125.4, 125.9, 127.1, 127.5, 129.5, 136.3, 142.6, 147.1, 163.1; ESI-HRMS: Found: \( m/z \) 338.1944. Calcd for C\(_{22}\)H\(_{28}\)NS: (M+H)+ 338.1942.

\( 1\)-\textit{tert}-Butyl-3,4-diphenylisoquinoline (4-3ba)

\[
\text{White solid; mp. 165–167 °C; IR (NaCl) 2984, 2968, 1547, 1506, 1476, 1396, 1368, 1194 cm}^{-1}; \text{\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 1.76 (9H, s), 7.17-7.22 (3H, m), 7.26-7.29 (2H, m), 7.36-7.42 (3H, m), 7.48-7.56 (4H, m), 7.70-7.73 (1H, m), 8.59-8.62 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 31.3, 40.2, 124.5, 125.1, 126.8, 126.9, 127.0, 127.14, 127.4, 128.4, 128.6, 128.7, 130.6, 131.4, 137.6, 138.2, 141.2, 147.0, 165.8; ESI-HRMS: Found: \( m/z \) 338.1911. Calcd for C\(_{22}\)H\(_{24}\)N: (M+H)+ 338.1909.

\( 1\)-Benzyl-3,4-diphenylisoquinoline (4-3ca)

\[
\text{White solid; mp. 123–124 °C; IR (NaCl) 3063, 1553, 1506, 1495, 1379, 1339, 1265 cm}^{-1}; \text{\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 4.79 (2H, s), 7.18-7.26 (6H, M), 7.30 (2H, dd, \( J = 7.2, 7.6 \) Hz), 7.34-7.40 (3H, m), 7.41-7.44 (4H, m), 7.48-7.56 (2H, m), 7.66 (1H, dd, \( J = 1.6, 7.2 \) Hz), 8.23 (1H, dd, \( J = 1.6, 6.8 \) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 42.4, 125.7 (overlapped), 126.2, 126.4, 126.6, 127.0, 127.2, 127.6, 128.2, 128.5, 128.7, 129.6, 129.8,
130.4, 131.3, 136.7, 137.5, 139.7, 140.9, 149.4, 159.2; ESI-HRMS: Found: m/z 372.1755.

Calcd for C_{28}H_{22}N: (M+H)^+ 372.1752.

1-Diphenylmethyl-3,4-diphenylisoquinoline (4-3da)

White solid; mp. 161-162 °C; IR (NaCl) 3019, 1612, 1601, 1568, 1551, 1495, 1449, 1371 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.51 (1H, s), 7.08-7.14 (3H, m), 7.21-7.33 (10H, m), 7.37-7.44 (7H, m), 7.48-7.55 (2H, m), 7.65-7.69 (1H, m), 8.28-8.32 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 55.1, 124.9, 125.7, 126.3, 126.5, 126.7, 126.9, 127.25, 127.27, 128.1, 128.4, 128.9, 129.5, 129.8, 130.6, 131.3, 136.9, 137.9, 140.7, 143.0, 148.0, 160.0; ESI-HRMS: Found: m/z 448.2066. Calcd for C_{34}H_{28}N: (M+H)^+ 448.2065.

1-Cyclopropyl-3,4-diphenylisoquinoline (4-3ea)

White solid; mp. 149–151 °C; IR (NaCl) 1568, 1549, 1504, 1414, 1321, 1030, 1015 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.12-1.16 (2H, m), 1.38-1.42 (2H, m), 2.80-2.87 (1H, m), 7.15-7.20 (3H, m), 7.21-7.24 (2H, m), 7.33-7.39 (5H, m), 7.57 (1H, ddd, \(J = 1.2, 4.8, 6.0\) Hz), 7.60 (1H, ddd, \(J = 2.0, 7.2, 8.8\) Hz), 7.66 (1H, dd, \(J = 1.6, 6.0\) Hz), 8.50 (1H, dd, \(J = 1.6, 7.2\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 9.4, 13.6, 124.8, 126.2, 126.26, 126.34, 126.8, 127.1, 127.3, 128.0, 128.3, 129.6, 130.4, 131.4, 136.1, 138.0, 141.2, 148.7, 160.6; ESI-HRMS: Found: m/z 322.1600. Calcd for C_{24}H_{20}N: (M+H)^+ 322.1596.
(E)-3,4-Diphenyl-1-(prop-1-enyl)isoquinoline ((E)-4-3ea’)

\[
\begin{align*}
\text{Ph} & \quad \text{N} \\
\text{Ph} & \quad \text{Me} \\
\end{align*}
\]

Regioisomer ((Z)-4-3ea’) was separated by flash column chromatography.

White solid; mp. 147–149 °C; IR (NaCl) 3075, 1653, 1541, 1503, 1445, 1385, 962 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.09 (3H, dd, \(J = 1.6, 6.8\) Hz), 7.18-7.26 (6H, m), 7.33-7.39 (4H, m), 7.39-7.42 (2H, m), 7.55-7.59 (2H, m), 7.65-7.68 (1H, m), 8.34-8.39 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 18.9, 124.6, 124.7, 126.1, 126.37, 126.43, 126.9, 127.1, 127.4, 128.2, 129.3, 129.7, 130.4, 131.4, 134.8, 136.7, 137.8, 141.2, 149.6, 154.2; ESI-HRMS: Found: m/z 322.1595. Calcd for C\(_{24}\)H\(_{20}\)N: (M+H\(^+\)) 322.1596.

(Z)-3,4-Diphenyl-1-(prop-1-enyl)isoquinoline ((Z)-4-3ea’)

\[
\begin{align*}
\text{Ph} & \quad \text{Ph} \\
\text{N} & \quad \text{Me} \\
\end{align*}
\]

White solid; mp. 125–127 °C; IR (NaCl) 1653, 1543, 1504, 1445, 1385, 963 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.07 (3H, dd, \(J = 2.0, 7.2\) Hz), 6.31 (1H, qd, \(J = 7.2, 11.6\) Hz), 7.15-7.24 (4H, m), 7.24-7.28 (2H, m), 7.34-7.42 (6H, m), 7.55-7.60 (2H, m), 7.67-7.70 (1H, m), 8.22-8.24 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 15.7, 125.8, 126.0, 126.1, 126.4, 126.9, 127.2, 127.5, 128.3, 129.8, 130.4, 131.4, 133.5, 136.4, 137.7, 141.1, 149.5, 156.1; ESI-HRMS: Found: m/z 322.1599. Calcd for C\(_{24}\)H\(_{20}\)N: (M+H\(^+\)) 322.1596.
4-(3,4-Diphenylisoquinolin-1-yl)morpholine (4-3fa)

![Chemical structure diagram]

White solid; mp. 145–147 °C; IR (NaCl) 2967, 2855, 1612, 1568, 1551, 1504, 1410, 1115 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.53 (4H, t, J = 4.8 Hz), 4.02 (4H, t, J = 4.8 Hz), 7.17-7.20 (3H, m), 7.21-7.24 (2H, m), 7.33-7.41 (5H, m), 7.49-7.55 (2H, m), 7.59-7.62 (1H, m), 8.17-8.20 (1H, m); ¹³C NMR (100 MHz, CDCl₃) δ 51.9, 67.2, 120.1, 125.0, 125.7, 125.9, 126.3, 126.9, 127.0, 127.4, 128.3, 129.6, 130.3, 131.5, 138.0, 138.5, 140.9, 147.6, 159.8; ESI-HRMS: Found: m/z 367.1810. Calcd for C₂₅H₂₃N₂O: (M+H)⁺ 367.1810.

tert-Butyl 1-methyl-3,4-diphenyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5aa)

![Chemical structure diagram]

White solid; mp. 155–156 °C; IR (NaCl) 1730, 1605, 1570, 1300, 1246, 1096 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.75 (9H, s), 2.89 (3H, s), 6.83 (1H, d, J = 7.5 Hz), 7.01-7.05 (1H, m), 7.17-7.23 (3H, m), 7.29-7.32 (2H, m), 7.38-7.40 (5H, m), 7.46 (1H, ddd, J = 1.2, 7.3, 8.4 Hz), 8.13 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.9, 28.2, 84.7, 115.1, 122.9, 123.3, 124.7, 126.97, 127.00, 127.6, 127.7, 128.6, 128.8, 130.1, 130.5, 132.5, 133.3, 137.6, 140.2, 141.0, 145.2, 150.4, 151.0; ESI-HRMS: Found: m/z 435.2088. Calcd for C₂₉H₂₇N₂O₂: (M+H)⁺ 435.2073.
(E)-tert-Butyl 2-(1-(hydroxyimino)ethyl)-1H-indole-1-carboxylate (4-6a)

![Chemical structure of (E)-tert-Butyl 2-(1-(hydroxyimino)ethyl)-1H-indole-1-carboxylate (4-6a)]

Yellow solid; mp. 148–151 °C; IR (NaCl) 3019, 1730, 1454, 1371, 1331, 1161, 1136 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.64 (9H, s), 2.20 (3H, s), 6.64 (1H, d, J = 0.4 Hz), 7.22-7.24 (1H, m), 7.34 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.55 (1H, d, J = 7.6 Hz), 8.03 (1H, br), 8.13 (1H, dd, J = 0.4, 8.4 Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 16.3, 28.0, 84.4, 110.3, 115.5, 121.1, 123.1, 125.1, 128.8, 136.0, 137.0, 149.7, 152.9; ESI-HRMS: Found: m/z 275.1402. Calcd for C\(_{19}\)H\(_{19}\)N\(_2\)O\(_3\) (M+H)+ 275.1396.

tert-Butyl 3,4-bis(4-methoxyphenyl)-1-methyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5ab)

![Chemical structure of tert-Butyl 3,4-bis(4-methoxyphenyl)-1-methyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5ab)]

White solid; m.p. 176–178 °C; IR (NaCl) 3019, 2980, 1730, 1609, 1514, 1458, 1429, 1369, 1298, 1246, 1152, 1034 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.74 (9H, s), 2.86 (3H, s), 3.77 (3H, s), 3.88 (3H, s), 6.73-6.76 (2H, m), 6.91-6.96 (3H, m), 7.03-7.07 (1H, m), 7.19-7.22 (2H, m), 7.32-7.35 (2H, m), 7.45 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 8.12 (1H, d, J = 8.4 Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.9, 28.2, 55.2, 55.3, 84.6, 113.1, 114.2, 115.2, 122.8, 123.4, 124.9, 126.4, 128.7, 130.1, 131.3, 131.6, 132.9, 133.0, 133.1, 141.1,
144.9, 150.5, 151.0, 158.7, 159.1; ESI-HRMS: Found: m/z 495.2284. Calcd for C_{31}H_{31}N_2O_4: (M+H)^+ 495.2284.

tert-Butyl 3,4-bis(4-bromophenyl)-1-methyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5ac)

White solid; m.p. 188–190 °C; IR (NaCl) 3019, 2982, 1732, 1607, 1576, 1427, 1369, 1337, 1248, 1152, 1094, 1013 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.74 (9H, s), 2.87 (3H, s), 6.89 (1H, d, \(J=8.0\) Hz), 7.09 (1H, t, \(J=7.6\) Hz), 7.18 (2H, d, \(J=8.0\) Hz), 7.24 (2H, d, \(J=8.8\) Hz), 7.36 (2H, d, \(J=8.4\) Hz), 7.47–7.51 (1H, m), 7.56 (2H, d, \(J=8.4\) Hz), 8.13 (1H, d, \(J=8.4\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 24.9, 28.2, 85.0, 115.3, 121.6, 122.2, 123.1, 124.2, 125.6, 129.1, 131.0, 131.7, 132.1, 132.2, 132.3, 133.4, 136.3, 138.8, 141.0, 145.8, 149.6, 150.2; ESI-HRMS: Found: m/z 591.0285. Calcd for C_{29}H_{23}Br_2N_2O_5: (M+H)^+ 591.0283.

tert-Butyl 1-methyl-3,4-dipropyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5ad)

Yellow oil; IR (NaCl) 1732, 1609, 1578, 1246, 1121, 1090 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.06 (3H, t, \(J=7.2\) Hz), 1.15 (3H, t, \(J=7.2\) Hz), 1.69 (9H, s), 1.73–1.81 (4H, m), 2.72 (3H, s), 2.90–2.94 (2H, m), 3.07–3.11 (2H, m), 7.35 (1H, t, \(J=7.4\) Hz), 7.51 (1H, s), 7.81 (1H, t, \(J=7.2\) Hz), 7.88 (1H, t, \(J=7.2\) Hz), 8.06 (1H, d, \(J=8.0\) Hz), 8.08 (1H, d, \(J=8.0\) Hz).
t, J = 7.6 Hz), 8.00 (1H, d, J = 7.6 Hz), 8.15 (1H, d, J = 8.4 Hz); 13C NMR (100 MHz, CDCl₃) δ 14.4, 14.5, 23.0, 24.1, 24.5, 28.2, 30.9, 36.7, 84.4, 115.3, 123.17, 123.24, 124.8, 126.2, 128.2, 131.8, 132.9, 140.8, 143.0, 150.5, 153.4; ESI-HRMS: Found: m/z 367.2391.

Calcd for C₂₉H₃₁N₂O₂: (M+H)⁺ 367.2386.

t-Butyl 1,4-dimethyl-3-phenyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5af)

Regioisomer (4-5af-minor) was separated by flash column chromatography.

Yellow solid; m.p. 140–141 °C; IR (NaCl) 1721, 1609, 1572, 1258, 1244, 1084 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.73 (9H, s), 2.77 (3H, s), 2.80 (3H, s), 7.38-7.44 (2H, m), 7.46-7.49 (2H, m), 7.57-7.61 (3H, m), 8.20 (2H, d, J = 9.2 Hz); 13C NMR (100 MHz, CDCl₃) δ 17.1, 24.7, 28.1, 84.6, 115.2, 121.6, 123.1, 123.6, 125.4, 127.5, 128.1, 128.5, 129.8, 132.7, 133.1, 140.6, 140.9, 143.1, 150.4, 152.6; ESI-HRMS: Found: m/z 373.1923.

Calcd for C₂₄H₂₅N₂O₂: (M+H)⁺ 373.1916.

t-Butyl 1,3-dimethyl-4-phenyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5af-minor)

Yellow oil; IR (NaCl) 2980, 2934, 1726, 1607, 1570, 1440, 1369, 1327, 1304, 1248, 1146, 1113 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.72 (9H, s), 2.32 (3H, s), 2.81 (3H, s), 6.70 (1H, dd, J = 0.4, 8.0 Hz), 6.99-7.03 (1H, m), 7.34-7.37 (2H, m), 7.43 (1H, ddd, J =
1.2, 7.2, 8.4 Hz), 7.52-7.58 (3H, m), 8.08 (1H, d, J = 8.4 Hz); $^{13}\text{C}$ NMR (100 MHz, CDCl$_3$) δ 22.1, 24.6, 28.2, 84.5, 115.1, 122.8, 123.1, 124.5, 127.3, 127.9, 128.7, 129.1, 129.4, 132.1, 132.6, 138.0, 141.0, 144.6, 149.2, 150.5; ESI-HRMS: Found: m/z 373.1910. Calcd for C$_{24}$H$_{23}$N$_2$O$_2$: (M+H)$^+$ 373.1916.

**tert-Butyl 4-((tert-butyldimethylsilyloxy)methyl)-1-methyl-3-phenyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5ag)**

Regioisomer (4-5ag-minor) was separated by flash column chromatography.

Yellow solid; m.p. 54–55 °C; IR (NaCl) 1728, 1609, 1566, 1254, 1240, 1084 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 0.02 (6H, s), 0.86 (9H, s), 1.72 (9H, s), 2.82 (3H, s), 5.06 (2H, s), 7.37-7.48 (4H, m), 7.59 (1H, dd, J = 7.6, 8 Hz), 7.65 (2H, d, J = 6.8 Hz), 8.17 (1H, d, J = 8.4 Hz), 8.36 (1H, d, J = 7.6 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 18.2, 25.0, 25.8, 28.2, 60.3, 84.7, 115.0, 123.1, 123.3, 124.3, 125.0, 127.9, 128.1, 128.9, 129.9, 133.7, 133.8, 140.1, 141.0, 145.4, 150.3, 152.9; ESI-HRMS: Found: m/z 503.2720. Calcd for C$_{36}$H$_{39}$N$_2$O$_2$Si: (M+H)$^+$ 503.2730.
**tert-Butyl 3-((tert-butyl(dimethyl)silyloxy)methyl)-1-methyl-4-phenyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5aj-minor)**

![Chemical Structure]

Yellow solid; m.p. 118–120 °C; IR (NaCl) 1732, 1607, 1578, 1254, 1146, 1072 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ -0.01 (6H, s), 0.82 (9H, s), 1.73 (9H, s), 2.83 (3H, s), 4.70 (2H, s), 6.67 (1H, d, J = 7.6 Hz), 7.01 (1H, t, J = 7.6 Hz), 7.40-7.45 (3H, m), 7.51-7.54 (3H, m), 8.08 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 18.4, 24.7, 26.0, 28.2, 64.9, 84.6, 115.0, 122.9, 123.1, 124.5, 128.0, 128.2, 128.65, 128.69, 129.9, 132.3, 133.5, 136.8, 140.9, 144.8, 150.1, 150.4; ESI-MS: Found: m/z 503.2730. Calcd for C₃₀H₃₉N₂O₃Si: (M+H)⁺ 503.2730.

9-**tert-Butyl 4-methyl 1-methyl-3-phenyl-9H-pyrido[3,4-b]indole-4,9-dicarboxylate (4-5aj)**

![Chemical Structure]

Regioisomer (4-5aj-isomer) was separated by flash column chromatography.

Pale yellow solid; m.p. 115–117 °C; IR (NaCl) 1728, 1609, 1564, 1229, 1209, 1109 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.72 (9H, s), 2.86 (3H, s), 3.79 (3H, s), 7.35-7.43 (4H, m), 7.45-7.49 (1H, m), 7.61 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.69-7.72 (1H, m), 8.02 (1H, d, J = 7.6 Hz), 8.17 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 25.2, 28.1, 52.6, 85.1, 115.3, 118.0, 122.7, 122.9, 123.5, 128.3, 128.4, 128.5, 129.9, 131.1, 133.1, 139.9, 141.2,
147.6, 150.0, 150.3, 169.4; ESI-HRMS: Found: m/z 417.1798. Caled for C_{25}H_{23}N_{2}O_{4}: (M+H)^+ 417.1814.

**9-tert-Butyl 3-methyl 1-methyl-4-phenyl-9H-pyrido[3,4-b]indole-3,9-dicarboxylate (4-5aj-isomer)**

![Chemical structure](attachment:image)

Pale yellow solid; m.p. 154–155 °C; IR (NaCl) 1734, 1607, 1570, 1233, 1217, 1109 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.74 (9H, s), 2.90 (3H, s), 3.75 (3H, s), 6.72 (1H, d, J = 7.6 Hz), 7.06 (1H, ddd, J = 0.9, 7.4, 8.3 Hz), 7.38-7.40 (2H, m), 7.49 (1H, ddd, J = 1.2, 7.4, 8.8 Hz), 7.52-7.56 (3H, m), 8.09 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 24.9, 28.1, 52.4, 85.4, 114.8, 123.2, 123.4, 123.9, 128.2, 128.7, 129.3, 130.3, 132.3, 135.0, 136.7, 140.8, 140.9, 145.5, 149.9, 166.7; ESI-HRMS: Found: m/z 417.1833. Caled for C_{25}H_{23}N_{2}O_{4}: (M+H)^+ 417.1814.

**tert-Butyl 1-butyl-3,4-dipropyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5bd)**

![Chemical structure](attachment:image)

Yellow oil; IR (NaCl) 2959, 2930, 2870, 1732, 1607, 1572, 1464, 1431, 1391, 1369, 1153 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.90 (3H, t, J = 7.4 Hz), 1.04 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.4 Hz), 1.27-1.36 (2H, m), 1.66-1.86 (6H, m), 1.71 (9H, s), 2.89-2.93 (2H, m), 3.08-3.14 (4H, m), 7.35-7.39 (1H, m), 7.50-7.55 (1H, m), 8.02 (1H, d, J = 8.0 Hz), 8.14 (1H, d, J = 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.0, 14.3, 14.5, 22.88, 22.94, 23.7, 28.2, 30.3, 30.9, 36.5, 36.8, 84.2, 115.2, 123.1, 123.2, 125.0, 126.1, 128.1, 131.8, 132.3,
140.9, 147.0, 150.7, 153.3; ESI-HRMS: Found: m/z 409.2849. Calcd for C_{26}H_{37}N_{2}O_{2}: (M+H)^{+} 409.2855.

**tert-Butyl 1-(but-3-enyl)-3,4-dipropyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5cd)**

![Chemical structure](image)

Yellow oil; IR (NaCl) 3019, 2961, 2932, 2872, 1728, 1639, 1607, 1572, 1464, 1431, 1371, 1153, 1121 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.04 (3H, t, \(J = 7.2\) Hz), 1.16 (3H, t, \(J = 7.4\) Hz), 1.70 (9H, s), 1.73-1.84 (4H, m), 2.51-2.57 (2H, m), 2.90-2.94 (2H, m), 3.09-3.13 (2H, m), 3.16-3.20 (2H, m), 3.35-3.39 (2H, m), 3.49-3.53 (2H, m), 3.90-3.94 (2H, m), 4.20-4.22 (1H, dd, \(J = 0.8, 10.0\) Hz), 5.02 (1H, dd, \(J = 1.6, 17.2\) Hz), 5.81-5.91 (IH, m), 7.38 (lH, t, \(J = 7.6\) Hz), 7.53 (1H, t, \(J = 7.8\) Hz), 8.02 (1H, d, \(J = 8\) Hz), 8.14 (1H, d, \(J = 8.4\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.3, 14.5, 22.9, 23.6, 28.2, 30.9, 32.1, 36.1, 36.4, 84.4, 114.3, 115.3, 123.1, 123.2, 125.0, 126.3, 128.1, 131.9, 132.4, 138.7, 140.9, 145.9, 150.8, 153.3; ESI-HRMS: Found: m/z 407.2696. Calcd for C_{26}H_{35}N_{2}O_{2}: (M+H)^{+} 407.2699.

**9-tert-Butyl 1-ethyl 3,4-dipropyl-9H-pyrido[3,4-b]indole-1,9-dicarboxylate (4-5dd)**

![Chemical structure](image)

Yellow solid; m.p. 43–45 °C; IR (NaCl) 3019, 2965, 1736, 1609, 1574, 1464, 1396, 1371, 1344, 1314, 1153, 1125 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.04 (3H, t, \(J = 7.6\) Hz), 1.17 (3H, t, \(J = 7.6\) Hz), 1.43 (3H, t, \(J = 7.2\) Hz), 1.69 (9H, s), 1.73-1.83 (4H, m), 2.97-3.00 (2H, m), 3.15-3.19 (2H, m), 4.48 (2H, q, \(J = 7.2\) Hz), 7.41 (1H, dd, \(J = 0.8, 8\) Hz), 7.58 (1H, dd, \(J = 0.8, 8.4\) Hz), 8.05 (1H, d, \(J = 8.0\) Hz), 8.17 (1H, d, \(J = 8.4\) Hz); \(^{13}\)C NMR
(100 MHz, CDCl₃) δ 14.2, 14.3, 14.5, 22.6, 23.8, 28.1, 31.1, 36.5, 61.5, 84.9, 115.9, 123.3, 123.5, 124.1, 128.8, 131.3, 131.5, 132.5, 136.7, 140.1, 150.6, 153.6, 166.8; ESI-HRMS: Found: m/z 425.2438. Calcd for C₂₅H₃₃N₂O₄: (M+H)⁺ 425.2440.

tert-Butyl 3,4-dipropyl-9H-pyrido[3,4-b]indole-9-carboxylate (4-5ed)

Yellow solid; m.p. 42–43 °C; IR (NaCl) 2961, 2932, 2872, 1730, 1611, 1462, 1433, 1346, 1325, 1157, 1123 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.05 (3H, t, J = 7.2 Hz), 1.16 (3H, t, J = 7.2 Hz), 1.71-1.83 (4H, m), 1.75 (9H, s), 2.93-2.97 (2H, m), 3.11-3.15 (2H, m), 7.38 (1H, t, J = 7.6 Hz), 7.56 (1H, dd, J = 7.6, 8.4 Hz), 8.02 (1H, d, J = 8.0 Hz), 8.49 (1H, d, 8.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 14.4, 22.7, 23.8, 28.3, 31.1, 36.5, 84.5, 116.4, 123.1, 123.3, 124.2, 128.5, 128.9, 130.3, 133.4, 135.0, 139.5, 150.4, 153.3; ESI-HRMS: Found: m/z 353.2232. Calcd for C₂₂H₂₉N₂O₂: (M+H)⁺ 353.2229.

 tert-Butyl 2-cyano-1H-indole-1-carboxylate (4-7)

White solid; m.p. 102–104 °C; IR (NaCl) 3019, 2984, 2230, 1741, 1535, 1445, 1373, 1344, 1325, 1155, 1123, 1092 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.73 (9H, s), 7.31-7.35 (2H, m), 7.50 (1H, ddd, J = 0.8, 7.2, 8.4 Hz), 7.63 (1H, d, J = 8.0 Hz), 8.24 (1H, d, J = 8.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 28.0, 86.7, 108.9, 113.3, 115.9, 121.5, 122.1, 124.1, 127.3, 128.2, 136.6, 148.2; ESI-HRMS: Found: m/z 243.1141. Calcd for C₁₄H₁₃N₂O₂: (M+H)⁺ 243.1134.
**1-Methyl-3,4-dipropylbenzofuro[2,3-c]pyridine (4-5fd)**

![Chemical Structure](image)

White solid; m.p. 60–62 °C; IR (NaCl) 2959, 2930, 2870, 1628, 1599, 1464, 1435, 1109 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.05 (3H, t, J = 7.2 Hz), 1.14 (3H, t, J = 7.2 Hz), 1.71-1.82 (4H, m), 2.88-2.92 (2H, m), 3.06 (2H, m), 7.39 (1H, ddd, J = 0.8, 7.6, 8.4 Hz), 7.55 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.63 (1H, d, J = 8.0 Hz), 7.98 (1H, d, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 14.4, 18.3, 24.0, 24.2, 31.3, 36.5, 112.3, 123.0, 123.28, 123.33, 127.6, 128.6, 129.1, 139.6, 149.8, 152.6, 156.6; ESI-HRMS: Found: m/z 268.1699. Calcd for C₁₉H₂₂NO: (M+H)⁺ 268.1701.

**7-Methyl-4,5-dipropylfuro[2,3-c]pyridine (4-5gd)**

![Chemical Structure](image)

Yellow oil; IR (NaCl) 2961, 2932, 2870, 1614, 1587, 1450, 1377, 1192, 1152 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.98-1.03 (6H, m), 1.60-1.67 (2H, m), 1.69-1.77 (2H, m), 2.70 (3H, s), 2.76-2.84 (4H, m), 6.74 (1H, d, J = 2.4 Hz), 7.65 (1H, d, J = 2.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 18.3, 24.0, 24.2, 31.5, 36.5, 105.2, 125.4, 133.8, 139.2, 146.8, 149.3, 151.6; ESI-HRMS: Found: m/z 218.1547. Calcd for C₁₄H₂₀NO: (M+H)⁺ 218.1545.
7-Methyl-4,5-dipropylthieno[2,3-c]pyridine (4-5hd)

\begin{center}
\includegraphics[width=0.2\textwidth]{7-Methyl-4,5-dipropylthieno[2,3-c]pyridine (4-5hd)}
\end{center}

Yellow oil; IR (NaCl) 2959, 2930, 2870, 1557, 1454, 1425, 1379, 1362, 1165 cm⁻¹; \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 1.03 (3H, t, J = 7.6 Hz), 1.03 (3H, t, J = 7.6 Hz), 1.61-1.70 (2H, m), 1.71-1.80 (2H, m), 2.74 (3H, s), 2.84-2.91 (4H, m), 7.38 (1H, d, J = 5.6 Hz), 7.59 (1H, d, J = 5.6 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 14.3, 14.4, 23.3, 24.1, 24.3, 31.7, 36.6, 122.4, 126.6, 130.2, 133.1, 145.3, 149.4, 153.0; ESI-HRMS: Found: m/z 234.1322. Calcd for C₄₅H₂₅N₅S: (M+H)+ 234.1316.

7-Methyl-4,5-dipropyl-1-tosyl-1H-pyrrolo[2,3-c]pyridine (4-5id)

\begin{center}
\includegraphics[width=0.2\textwidth]{7-Methyl-4,5-dipropyl-1-tosyl-1H-pyrrolo[2,3-c]pyridine (4-5id)}
\end{center}

White solid; mp. 78–80 °C; IR (NaCl) 2961, 2932, 1576, 1454, 1445, 1368, 1173, 1132 cm⁻¹; \textsuperscript{1}H NMR (400 MHz, CDCl₃) δ 0.98 (3H, t, J = 7.2 Hz), 0.99 (3H, t, J = 7.2 Hz), 1.55-1.73 (4H, m), 2.38 (3H, s), 2.71 (3H, s), 2.72-2.78 (4H, m), 6.67 (1H, d, J = 4.0 Hz), 7.25 (1H, d, J = 9.2 Hz), 7.58 (1H, d, J = 8.4 Hz), 7.86 (1H, d, J = 3.6 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl₃) δ 14.28, 14.32, 21.6, 23.7, 24.0, 24.7, 30.8, 36.3, 106.0, 124.6, 126.6, 129.96, 130.01, 132.0, 136.6, 138.9, 141.5, 144.9, 151.9; ESI-HRMS: Found: m/z 371.1783. Calcd for C₂₃H₂₇N₂O₂S: (M+H)+ 371.1793.
6.4.3 **Synthesis of 1,8-diazapyrenes by Cu–Rh catalytic system: a typical procedure for the reaction of (1E,4E)-naphthalene-1,4-dione O,O-diacyl dioxime (4-8) and diphenylacetylene (4-2a) (Table 4-5, entry 1)**

![Chemical Reaction Diagram]

To a DMF solution (2.5 mL) of (1E,4E)-naphthalene-1,4-dione O,O-diacyl dioxime (4-8) (136.1 mg, 0.50 mmol) and diphenylacetylene (4-2a) (178.2 mg, 1.00 mmol) were added [Cp*RhCl₂]₂ (15.5 mg, 0.025 mmol) and Cu(OAc)₂ (18.2 mg, 0.20 mmol), and the reaction mixture was stirred at 60 °C under a nitrogen atmosphere for 18 h. After cooled to room temperature, the reaction was quenched with pH 9 buffer and organic materials were extracted three times with CH₂Cl₂. The combined extracts were washed with water (three times) and brine, and dried over MgSO₄. The solvents were removed under reduced pressure and the crude was purified by flash column chromatography (hexane:ethyl acetate = 80:20) to afford 1,8-diazapyrene 4-9a (92.4 mg, 0.286 mmol) in 72% yield.

**2,3,6,7-Tetraphenylbenzo[lmn][2,9]phenanthroline (4-9a)**

Orange solid; mp. 275–277 °C; IR (NaCl) 1557, 1445, 1381, 1074, 1030 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.34 (10H, m), 7.36–7.41 (6H, m), 7.51–7.54 (4H, m), 8.04 (2H, s), 8.70 (2H, s); ¹³C NMR (100 MHz, CDCl₃) δ 117.2, 127.58, 127.60, 127.8, 128.2, 129.0, 130.5, 130.7, 131.6, 133.0, 134.4, 136.9, 140.9, 147.3, 156.2; ESI-HRMS: Found: m/z 509.2018. Calcd for C₃₈H₂₅N₆: (M+H)⁺ 509.2018.
2,3,6,7-Tetrakis(4-methoxyphenyl)benzo[lmn][2,9]phenanthroline (4-9b)

Yellowish green solid; mp. 242–244 °C; IR (NaCl) 2953, 1607, 1553, 1514, 1377, 1248, 1177, 1034 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.82 (6H, s), 3.87 (6H, s), 6.84 (4H, d, \(J = 8.8\) Hz), 6.95 (4H, d, \(J = 8.8\) Hz), 7.23 (4H, d, \(J = 8.8\) Hz), 7.48 (4H, d, \(J = 8.8\) Hz), 8.01 (2H, s), 8.63 (2H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 55.2, 55.3, 113.4, 113.8, 117.2, 128.8, 129.4, 130.0, 131.9, 132.68, 132.73, 133.8, 134.5, 147.2, 155.9, 159.0, 159.1; ESI-HRMS: Found: m/z 629.2437. Caled for C\(_{42}\)H\(_{33}\)N\(_2\)O\(_4\): (M+H\(^+\) 629.2440.

2,3,6,7-Tetrakis(4-bromophenyl)benzo[lmn][2,9]phenanthroline (4-9c)

Yellowish green solid; mp. 191–193 °C; IR (NaCl) 1587, 1549, 1491, 1377, 1126, 1070, 1011, 833 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.20 (4H, d, \(J = 8.0\) Hz), 7.39 (4H, d, \(J = 8.4\) Hz), 7.47 (4H, d, \(J = 8.4\) Hz), 7.58 (4H, d, \(J = 8.0\) Hz), 8.01 (2H, s), 8.67 (2H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 117.1, 122.4, 122.6, 128.9, 129.3, 131.3, 131.8, 132.1, 133.1, 133.3, 134.2, 135.5, 139.5, 147.7, 154.9; ESI-HRMS: Found: m/z 824.8403. Caled for C\(_{38}\)H\(_{21}\)N\(_2\)\(_{29}\)Br\(_2\)\(_{81}\)Br\(_2\): (M+H\(^+\) 824.8397.
2,3,6,7-Tetrapropylbenzo[lnn][2,9]phenanthroline (4-9d)

Brownish red solid; mp. 77–78 °C; IR (NaCl) 2961, 2932, 2872, 1562, 1477, 1456, 1391, 1263 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.13 (6H, t, J = 7.2 Hz), 1.16 (6H, t, J = 7.2 Hz), 1.76-1.85 (4H, m), 1.92-2.01 (4H, m), 3.23-3.27 (4H, m), 3.28-3.33 (4H, m), 8.39 (4H, s); ¹³C NMR (100 MHz, CDCl₃) δ 14.5, 14.6, 24.0, 25.2, 30.2, 38.3, 117.3, 126.4, 128.8, 131.3, 133.1, 145.7, 158.4; ESI-HRMS: Found: m/z 373.2645. Calcd for C₂₆H₃₃N₂: (M+H)⁺ 373.2644.

3,6-Dimethyl-2,7-diphenylbenzo[lnn][2,9]phenanthroline (4-9f)

Pure 4-9f was obtained by recrystallization from hexane–ethyl acetate.

Yellow solid; mp. 234–236 °C; IR (NaCl) 3057, 2968, 1558, 1474, 1379, 1362, 1016, 833 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.94 (6H, s), 7.48-7.52 (2H, m), 7.56-7.60 (4H, m), 7.71-7.74 (4H, m), 8.52 (2H, s), 8.53 (2H, s); ¹³C NMR (100 MHz, CDCl₃) δ 16.1, 117.2, 124.3, 126.9, 128.0, 128.3, 129.8, 132.1, 134.2, 141.5, 146.0, 157.5; ESI-HRMS: Found: m/z 385.1705. Calcd for C₂₈H₂₁N₂: (M+H)⁺ 385.1705.
Diethyl 2,7-diphenylbenzo[lnn][2,9]phenanthroline-3,6-dicarboxylate (4-9h)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \\
\text{EtO}_2\text{C} & \quad \text{Ph}
\end{align*}
\]

Regioisomer (4-9hv) was separated by flash column chromatography.

Yellow solid; mp. 188–190 °C; IR (NaCl) 2984, 1717, 1558, 1476, 1389, 1246, 1084 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.07 (6H, t, J = 7.2 Hz), 4.31 (4H, q, J = 7.2 Hz), 7.50-7.59 (6H, m), 7.84-7.87 (4H, m), 8.59 (2H, s), 8.69 (2H, s); ¹³C NMR (100 MHz, CDCl₃) δ 13.6, 62.2, 116.3, 122.9, 128.6, 128.88, 128.91, 129.1, 133.3, 134.1, 140.7, 148.4, 155.9, 168.3; ESI-HRMS: Found: m/z 501.1815. Calcd for C₃₂H₂₅N₂O₄: (M+H)⁺ 501.1814.

Diethyl 2,7-diphenylbenzo[lnn][2,9]phenanthroline-3,6-dicarboxylate (4-9hv)

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Ph} \\
\text{N} & \quad \text{N} \quad \text{CO}_2\text{Et} \\
\end{align*}
\]

White solid; mp. 199–201 °C; IR (NaCl) 2982, 1732, 1722, 1557, 1472, 1302, 1244, 1225 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.04 (3H, t, J = 7.2 Hz), 1.08 (3H, t, J = 7.2 Hz), 4.26 (2H, q, J = 7.2 Hz), 4.27 (2H, q, J = 7.2 Hz), 7.49-7.61 (8H, m), 7.84-7.86 (2H, m), 8.20 (1H, d, J = 9.6 Hz), 8.47 (1H, d, J = 9.6 Hz), 8.66 (1H, d, J = 9.6 Hz), 8.73 (1H, d, J = 9.6 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.6, 13.7, 61.9, 62.1, 116.2, 118.3, 122.6, 128.1, 128.4, 128.5, 128.6, 128.9, 129.1, 130.0, 130.5, 131.3, 133.3, 133.8, 134.1
(overlapped), 135.3, 140.6, 146.9, 148.6, 148.9, 156.2, 167.4, 168.2; ESI-HRMS: Found: m/z 501.1818. Calcd for C_{32}H_{25}N_{2}O_{4}: (M+H)^{+} 501.1814.
6.5 Experimental section of Chapter 5:

6.5.1 Synthesis of 2-alkynylbenzaldehyde derivatives

6.5.1.1 Preparation of 2-alkynylbenzaldehydes 5-1a, 5-1b, 5-1k to 5-1s, 5-1u & 5-1v:

A typical procedure for 2-(2-phenylethynyl)benzaldehyde (5-1a).

![Chemical Structure]

To a solution of 2-bromobenzaldehyde (3.70 g, 20.0 mmol), PdCl$_2$(PPh$_3$)$_2$ (0.28 g, 0.40 mmol), and CuI (38 mg, 0.20 mmol) in 80 mL of Et$_3$N was added phenylacetylene (2.08 g, 20.4 mmol). The resulting mixture was heated under nitrogen atmosphere at 50 °C. After the reaction was completed, the reaction mixture was quenched with distilled water and extracted with ethyl acetate (50 mL x 3). The combined extracts were washed with brine and dried over MgSO$_4$. Volatile materials were removed in vacuo and the resulting crude material was purified by flash column chromatography (Si gel, hexane : ethyl acetate = 95 : 5) to give 2-(2-phenylethynyl)benzaldehyde (5-1a) in 94% yield.

2-(2-Phenylethynyl)benzaldehyde (5-1a)$^{26}$

Brown oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36-7.40 (3H, m), 7.45 (1H, tt, $J = 0.8, 7.6$ Hz), 7.55-7.60 (3H, m), 7.64 (1H, dd, $J = 0.8, 7.6$ Hz), 7.95 (1H, dd, $J = 0.8, 7.6$ Hz), 10.65 (d, $J = 0.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 84.8, 96.3, 122.3, 126.8, 127.2, 128.5, 128.6, 129.0, 131.6, 133.2, 133.7, 135.8, 191.7.

$^{26}$ Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* 2011, 13, 2228.
2-[2-(4-Methoxyphenyl)ethynyl]benzaldehyde (5-1b)

Prepared from 2-bromobenzaldehyde and 1-ethynyl-4-methoxybenzene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in quantitative yield; White solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.84 (3H, s), 6.91 (2H, td, $J = 2.4$, 8.8 Hz), 7.42 (1H, dt, $J = 0.4$, 7.2 Hz), 7.50 (2H, td, $J = 2.4$, 8.8 Hz), 7.56 (1H, dt, $J = 1.6$, 7.6 Hz), 7.61 (1H, dd, $J = 0.8$, 7.2 Hz), 7.93 (1H, dd, $J = 0.8$, 8.0 Hz), 10.64 (1H, d, $J = 0.8$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 55.3, 83.7, 96.6, 114.1, 114.3, 127.1, 127.3, 128.2, 133.0, 133.2, 133.7, 135.6, 160.2, 191.8.

2-(Hept-1-ynyl)benzaldehyde (5-1k)

Prepared from 2-bromobenzaldehyde and 1-heptyne and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 89% yield; Yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.93 (3H, t, $J = 7.2$ Hz), 1.32-1.49 (4H, m), 1.65 (2H, tt, $J = 6.8$, 7.6 Hz), 2.48 (2H, t, $J = 7.2$ Hz), 7.35-7.40 (1H, m), 7.48-7.55 (2H, m), 7.89 (1H, d, $J = 8.0$ Hz), 10.54 (1H, d, $J = 0.4$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 13.9, 19.5, 22.1, 28.2, 31.1, 76.3, 98.2, 126.8, 127.8, 127.9, 133.2, 133.6, 135.9, 192.2.

2-(Cyclohexylethynyl)benzaldehyde (5-1)\textsuperscript{29}

\[
\begin{align*}
\text{O} & \\
\text{H} & \end{align*}
\]

Prepared from 2-bromobenzaldehyde and cyclohexylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in quantitative yield; Yellow oil; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 1.32-1.45 (3H, m), 1.46-1.61 (3H, m), 1.71-1.80 (2H, m), 1.87-1.95 (2H, m), 2.68 (1H, m), 7.35-7.40 (1H, m), 7.48-7.54 (2H, m), 7.88 (1H, d, \(J=7.6\) Hz), 10.56 (1H, d, \(J=0.8\) Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 24.8, 25.8, 29.8, 32.4, 76.2, 102.1, 126.8, 127.8, 128.0, 133.2, 133.6, 135.8, 192.2.

2-(2-Cyclopropylethynyl)benzaldehyde (5-1m)\textsuperscript{26}

\[
\begin{align*}
\text{O} & \\
\text{H} & \end{align*}
\]

Prepared from 2-bromobenzaldehyde and cyclopropylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in quantitative yield; Yellow oil; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 0.83-0.90 (2H, m), 0.90-0.98 (2H, m), 1.48-1.56 (1H, m), 7.36 (1H, t, \(J=7.6\) Hz), 7.46-7.53 (2H, m), 7.87 (1H, d, \(J=8.0\) Hz), 10.49 (1H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 0.3, 8.9, 71.4, 101.2, 126.9, 127.7, 127.8, 133.2, 133.6, 136.0, 192.1.

3-Methyl-2-(phenylethynyl)benzaldehyde (5-1n)

\[
\begin{array}{c}
\text{O} \\
\text{Me} \\
\text{H} \\
\text{Ph}
\end{array}
\]

Prepared from 2-bromo-3-methylbenzaldehyde and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 96% yield; Brown solid; mp. 48–50 °C; IR (neat) 691, 756, 1242, 1489, 1682, 1701 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.59 (3H, s), 7.35 (1H, t, \(J = 7.6\) Hz), 7.38-7.42 (3H, m), 7.50 (1H, d, \(J = 7.6\) Hz), 7.56-7.60 (2H, m), 7.80 (1H, dd, \(J = 0.4, 8.0\) Hz), 10.69 (1H, d, \(J = 0.8\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 20.5, 83.6, 100.8, 122.6, 124.6, 126.6, 128.1, 128.5, 129.0, 131.5, 134.8, 136.0, 141.5, 192.3; ESI-HRMS: Found: m/z 221.0964. Calcd for C\(_{16}\)H\(_{13}\)O: (M+H\(^+\)) 221.0966.

4,5-Dimethoxy-2-(2-phenylethynyl)benzaldehyde (5-10)

\[
\begin{array}{c}
\text{O} \\
\text{O} \\
\text{H} \\
\text{Ph}
\end{array}
\]

Prepared from 6-bromo-1,3-benzodioxole-5-carboxaldehyde and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 93% yield; White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.10 (2H, s), 7.03 (1H, s), 7.37 (1H, s), 7.36-7.40 (3H, m), 7.52-7.56 (2H, m), 10.49 (1H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 84.7, 95.1, 102.4, 106.1, 112.0, 122.3, 123.6, 128.5, 129.0, 131.6, 132.1, 148.7, 152.4, 190.0.
5-Methoxy-2-(phenylethynyl)benzaldehyde (5-1p)\textsuperscript{26}

![Image of 5-Methoxy-2-(phenylethynyl)benzaldehyde](image)

Prepared from 2-bromo-5-methoxybenzaldehyde and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 95% yield; Brown solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 3.88 (3H, s), 7.14 (1H, dd, \textit{J} = 2.8, 8.8 Hz), 7.35-7.39 (3H, m), 7.43 (1H, d, \textit{J} = 2.8 Hz), 7.53-7.58 (3H, m), 10.62 (1H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 55.6, 84.8, 94.8, 109.8, 119.6, 121.7, 122.6, 128.5, 128.7, 131.5, 134.5, 137.2, 159.8, 191.6.

5-Fluoro-2-(phenylethynyl)benzaldehyde (5-1q)\textsuperscript{26}

![Image of 5-Fluoro-2-(phenylethynyl)benzaldehyde](image)

Prepared from 2-bromo-5-fluorobenzaldehyde and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 91% yield; Pale yellow solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 7.30 (1H, dt, \textit{J} = 2.8, 8.0 Hz), 7.37-7.41 (3H, m), 7.54-7.57 (2H, m), 7.60-7.67 (2H, m), 10.60 (1H, d, \textit{J} = 3.2 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 83.8, 96.0, 113.7 (d, \textit{J} = 22.9 Hz), 121.3 (d, \textit{J} = 22.5 Hz), 122.1, 123.0 (d, \textit{J} = 3.6 Hz), 128.5, 129.1, 131.6, 135.2 (d, \textit{J} = 7.6 Hz), 137.7 (d, \textit{J} = 6.5 Hz), 162.3 (d, \textit{J} = 251.2 Hz), 190.4.
3-(Phenylethynyl)benzofuran-2-carbaldehyde (5-1r)

![Chemical structure](image)

Prepared from 3-bromobenzofuran-2-carbaldehyde and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 96% yield; Brown solid; mp. 99–101 °C; IR (neat) 685, 748, 881, 1294, 1339, 1667 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.46 (4H, m), 7.58 (1H, dt, J = 1.2, 8.8 Hz), 7.60-7.66 (3H, m), 7.89 (1H, d, J = 8.0 Hz), 10.13 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 77.1, 100.1, 112.8, 115.9, 121.8, 122.5, 124.5, 127.5, 128.6, 129.6, 130.0, 131.9, 152.5, 155.4, 178.0; ESI-HRMS: Found: m/z 247.0761. Calcd for C₁₇H₁₁O₂: (M+H)+ 247.0759.

2-(Phenylethynyl)nicotinaldehyde (5-1s)

![Chemical structure](image)

Prepared from 2-bromonicotinaldehyde and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) in 88% yield; Brown solid; ¹H NMR (400 MHz, CDCl₃) δ 7.37-7.44 (4H, m), 7.64 (2H, d, J = 6.8 Hz), 8.20 (1H, d, J = 7.6 Hz), 8.81 (1H, d, J = 4.4 Hz), 10.66 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 84.6, 95.9, 121.1, 123.1, 128.4, 129.7, 131.6, 132.0, 134.6, 145.8, 154.3, 190.6.

---

2-(2-Trimethylsilylethynyl)benzaldehyde (5-1u)\(^26\)

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{TMS}
\end{array}
\]

Prepared from trimethylsilylacetylene and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 98% yield; Brown solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.29 (9H, s), 7.43 (1H, \(t, J = 7.2\) Hz), 7.54 (1H, \(t, J = 1.2, 7.6\) Hz), 7.57 (1H, \(dd, J = 1.2, 7.6\) Hz), 7.91 (1H, \(d, J = 8.0\) Hz), 10.56 (1H, s); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) -0.3, 100.0, 102.4, 126.7, 126.8, 128.8, 133.5, 133.6, 136.1, 191.8.

**Preparation of 2-ethynylbenzaldehyde**

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{TMS}
\end{array} \xrightarrow[K_2CO_3 (0.3 equiv)]{MeOH, rt} \begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\]

To a solution of 2-((trimethylsilyl)ethynyl)benzaldehyde (5-1u) (3.21 g, 15.9 mmol) in 35 mL of MeOH was treated with K\(_2\)CO\(_3\) (0.66 g, 4.8 mmol). After stirring at room temperature for 1 h, the reaction mixture was quenched with water and extracted with CH\(_2\)Cl\(_2\) (50 mL \(\times\) 3). The combined organic layer was washed with brine and dried over MgSO\(_4\). Volatile materials were removed \textit{in vacuo} and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to give 2-ethynylbenzaldehyde in 71% yield.

**2-Ethynylbenzaldehyde\(^26\)**

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.47 (1H, s), 7.49 (1H, \(t, J = 7.6\) Hz), 7.57 (1H, \(dt, J = 1.2, 7.6\) Hz), 7.62 (1H, \(dd, J = 0.8, 7.6\) Hz), 7.94 (1H, \(dd, J = 1.2, 7.6\) Hz).
7.6 Hz), 10.54 (1H, d, J = 0.4 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 79.2, 84.2, 125.5, 127.2, 129.2, 133.7, 133.9, 136.5, 191.4.

2-(Phenylethynyl)cyclohex-1-enecarbaldehyde (5-1v)$^{31}$

![Chemical structure of 2-(Phenylethynyl)cyclohex-1-enecarbaldehyde](image)

Prepared from 2-bromocyclohex-1-enecarbaldehyde$^{32}$ and phenylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) in 87% yield; Yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.63-1.76 (4H, m), 2.28-2.33 (2H, m), 2.48-2.54 (2H, m), 7.32-7.38 (3H, m), 7.45-7.49 (2H, m), 10.32 (1H, s); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 21.0, 21.8, 22.0, 32.3, 86.2, 98.5, 122.2, 128.4, 129.0, 131.6, 139.9, 142.5, 192.8.

6.5.1.2. Preparation of 2-arylethynylbenzaldehyde 5-1c to 5-1j & 5-1t: a typical procedure for the synthesis of 2-[[2-(4-methylphenyl)ethynyl]benzaldehyde (5-1c).

![Reaction scheme for the preparation of 2-arylethynylbenzaldehyde](image)

To a solution of 2-ethynylbenzaldehyde (195 mg, 1.5 mmol), PdCl$_2$(PPh$_3$)$_2$ (21 mg, 0.03 mmol), and Cul (2.9 mg, 0.015 mmol) in 6 mL of Et$_3$N was added the 1-iodo-4-


methylbenzene (393 mg, 1.8 mmol). The resulting mixture was heated under nitrogen atmosphere at 50 °C. After the reaction was completed, the reaction mixture was quenched with distilled water and extracted with ethyl acetate (50 mL × 3). Volatile materials were removed in vacuo and the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) to give 2-[2-(4-methylphenyl)ethynyl]benzaldehyde (5-1c) in 85% yield.

2-[2-(4-Methylphenyl)ethynyl]benzaldehyde (5-1c)\(^\text{33}\)

Yellow solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 2.39\) (3H, s), 7.19 (2H, d, \(J = 8.0\) Hz), 7.43 (1H, tt, \(J = 0.8, 7.2\) Hz), 7.46 (2H, d, \(J = 8.0\) Hz), 7.57 (1H, dt, \(J = 1.6, 7.6\) Hz), 7.63 (1H, dd, \(J = 0.8, 7.6\) Hz), 7.94 (1H, dd, \(J = 0.8, 7.6\) Hz), 10.65 (1H, d, \(J = 0.8\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 21.6, 84.3, 96.6, 119.2, 127.1, 128.4, 129.3, 131.6\) (overlapped), 133.1, 133.7, 135.7, 139.4, 191.8.

2-[2-(4-Fluorophenyl)ethynyl]benzaldehyde (5-1d)

\[
\begin{align*}
\text{O} & \quad \text{H} \\
\text{C} & \quad \text{F}
\end{align*}
\]

Prepared from 2-ethynylbenzaldehyde and 4-fluoriodobenzene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 82% yield; White solid; mp. 79–81 °C; IR (neat) 758, 829, 1233, 1506, 1591, 1684 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.08\) (2H, tt, \(J = 2.0, 8.8\) Hz), 7.46 (1H, t, \(J = 7.6\) Hz), 7.53–7.61 (3H, m), 7.63 (1H, dd, \(J = 0.8, 7.6\) Hz), 7.95 (1H, dd, \(J = 0.8, 7.6\) Hz), 10.62 (1H, d, \(J = 0.4\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 84.6, 95.2, 155.9\) (d, \(J = 21.9\) Hz), 118.4 (d, \(J = 3.5\) Hz),

126.6, 127.4, 128.7, 133.2, 133.6 (d, J = 8.5 Hz), 133.8, 135.8, 162.9 (d, J = 249.6 Hz), 191.5; ESI-HRMS: Found: m/z 225.0711. Calcd for C_{15}H_{10}FO: (M+H)^+ 225.0716.

**Ethyl 4-((2-formylphenyl)ethynyl)benzoate (5-1e)**

![Ethyl 4-((2-formylphenyl)ethynyl)benzoate](image)

Prepared from 2-ethynylbenzaldehyde and ethyl 4-iodobenzoate, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) in 86% yield; Pale yellow solid; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.42 (3H, t, J = 7.2 Hz), 4.40 (2H, q, J = 7.2 Hz), 7.50 (1H, t, J = 7.6 Hz), 7.59-7.65 (3H, m), 7.67 (1H, dd, J = 0.8, 7.2 Hz), 7.97 (1H, dd, J = 0.8, 7.6 Hz), 8.06 (2H, td, J = 1.6, 8.4 Hz), 10.64 (1H, s); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 14.3, 61.2, 87.6, 95.3, 126.1, 126.8, 127.5, 129.1, 129.6, 130.6, 131.5, 133.4, 133.8, 135.9, 165.9, 191.3.

**2-[2-(4-Trifluoromethylphenyl)ethynyl]benzaldehyde (5-1f)**

![2-[2-(4-Trifluoromethylphenyl)ethynyl]benzaldehyde](image)

Prepared from 2-ethynylbenzaldehyde and 1-iodo-4-(trifluoromethyl)benzene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 74% yield; Pale yellow solid; \(^1^H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.50 (1H, t, J = 7.6 Hz), 7.61 (1H, dt, J = 1.2, 7.6 Hz), 7.63-7.70 (5H, m), 7.97 (1H, dd, J = 1.2, 7.6 Hz), 10.62 (1H, d, J = 0.8 Hz); \(^1^3^C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 87.2, 94.5, 123.8 (q, J = 270.6 Hz), 125.5 (q, J = 249.6 Hz), 126.8 (d, J = 8.5 Hz), 131.5, 133.8, 135.9, 165.9, 191.3.

3.7 Hz), 125.8, 126.1, 127.6, 129.2, 130.7 (q, \( J = 32.7 \) Hz), 131.9, 133.4, 133.8, 136.0, 191.2.

2-[2-(3-Methoxyphenyl)ethynyl]benzaldehyde (5-1g)

![Structure of 2-[2-(3-Methoxyphenyl)ethynyl]benzaldehyde](image)

Prepared from 2-ethynylbenzaldehyde and 1-bromo-3-methoxybenzene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) in 88% yield; Brown oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.84 (3H, s), 6.95 (1H, ddd, \( J = 0.8, 2.4, 8.4 \) Hz), 7.08 (1H, q, \( J = 1.2 \) Hz), 7.16 (1H, d, \( J = 7.6 \) Hz), 7.29 (1H, t, \( J = 7.6 \) Hz), 7.45 (1H, t, \( J = 7.6 \) Hz), 7.58 (1H, dt, \( J = 1.2, 7.6 \) Hz), 7.65 (1H, d, \( J = 7.6 \) Hz), 7.95 (1H, dd, \( J = 0.8, 7.6 \) Hz), 10.65 (1H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 55.3, 84.6, 96.2, 115.7, 116.3, 123.3, 124.2, 126.8, 127.2, 128.6, 129.6, 133.2, 133.8, 135.8, 159.4, 191.7.

2-[2-(2-Methoxyphenyl)ethynyl]benzaldehyde (5-1h)

![Structure of 2-[2-(2-Methoxyphenyl)ethynyl]benzaldehyde](image)

Prepared from 2-ethynylbenzaldehyde and 1-bromo-2-methoxybenzene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) in 87% yield; Pale yellow solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 3.92 (3H, s), 6.92 (1H, d, \( J = 8.0 \) Hz), 6.96 (1H, t, \( J = 7.2 \) Hz), 7.35 (1H, dt, \( J = 1.6, 8.0 \) Hz), 7.42 (1H, t, \( J = 7.6 \) Hz), 7.51 (1H, dd, \( J = 1.2, 7.6 \) Hz).

---

\[ \text{Diamond turning of thin aluminium surfaces with grooved base} \]

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Master of Science (Precision Engineering)
2013

\[ \text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 7.24 (1H, dt, } J = 1.6, 7.6 \text{ Hz), 7.34 (1H, dt, } J = 1.2, 7.6 \text{ Hz), 7.48 (1H, t, } J = 7.6 \text{ Hz), 7.58-7.63 (2H, m), 7.64 (1H, dd, } J = 0.8, 8.0 \text{ Hz), 7.70 (1H, dd, } J = 0.8, 8.0 \text{ Hz), 7.97 (1H, dd, } J = 1.2, 8.0 \text{ Hz), 10.76 (1H, s); } \text{13C NMR (100 MHz, CDCl}_3\text{) } \delta 89.3, 94.6, 124.6, 125.8, 126.4, 127.1, 127.2, 129.0, 130.1, 132.6, 133.4, 133.5, 133.8, 136.1, 191.9. \]

2-[2-(2-Bromophenyl)ethynyl]benzaldehyde (5-li)\(^{37}\)

\[ \text{Prepared from 2-ethynylbenzaldehyde and 2-bromoiodobenzene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 94% yield; White solid; } \]

\[ \text{1H NMR (400 MHz, CDCl}_3\text{) } \delta 7.24 (1H, dt, } J = 1.6, 7.6 \text{ Hz), 7.34 (1H, dt, } J = 1.2, 7.6 \text{ Hz), 7.48 (1H, t, } J = 7.6 \text{ Hz), 7.58-7.63 (2H, m), 7.64 (1H, dd, } J = 0.8, 8.0 \text{ Hz), 7.70 (1H, dd, } J = 0.8, 8.0 \text{ Hz), 7.97 (1H, dd, } J = 1.2, 8.0 \text{ Hz), 10.76 (1H, s); } \text{13C NMR (100 MHz, CDCl}_3\text{) } \delta 89.3, 94.6, 124.6, 125.8, 126.4, 127.1, 127.2, 129.0, 130.1, 132.6, 133.4, 133.5, 133.8, 136.1, 191.9. \]

2-[2-(2-Iodonaphthyl)ethynyl]benzaldehyde (5-iq)

\[ \text{Prepared from 2-ethynylbenzaldehyde and 2-iodonaphthalene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 67% yield; White solid; } \]

\[ \text{mp. 73–75 °C; IR (neat) 743, 758, 1263, 1506, 1591, 1653, 1690 cm}^{-1}; \text{1H NMR (400 } \]

MHz, CDCl₃) δ 7.48 (1H, t, J = 7.6 Hz), 7.51-7.56 (2H, m), 7.58-7.64 (2H, m), 7.70 (1H, dd, J = 0.8, 8.0 Hz), 7.83-7.88 (3H, m), 7.98 (1H, dd, J = 0.8, 8.0 Hz), 8.11 (1H, s), 10.73 (1H, d, J = 0.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 85.2, 96.8, 119.5, 126.8, 126.9, 127.1, 127.3, 127.8, 127.9, 128.0, 128.2, 128.6, 131.9, 132.9, 133.1, 133.2, 133.8, 135.8, 191.7; ESI-HRMS: Found: m/z 257.0964. Calcd for C₁₉H₁₃O: (M+H)⁺ 257.0966.

2-(Pyridin-2-ylethynyl)benzaldehyde (5-1)³⁸

![Image of 2-(Pyridin-2-ylethynyl)benzaldehyde](image)

Prepared from 2-alkynyl benzaldehyde and 2-bromopyridine, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) in 86% yield; Yellow oil; ¹H NMR (400 MHz, CDCl₃) δ 7.31 (1H, ddd, J = 2.0, 4.8, 7.6 Hz), 7.51 (1H, tt, J = 0.8, 8.0 Hz), 7.60 (1H, tt, J = 0.8, 7.6 Hz), 7.62 (1H, dt, J = 1.6, 7.6 Hz), 7.71-7.76 (2H, m), 7.98 (1H, dd, J = 0.8, 7.6 Hz), 8.66 (1H, ddd, J = 1.2, 1.6, 4.8 Hz), 10.67 (1H, d, J = 0.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 84.4, 95.0, 123.4, 125.6, 127.3, 127.4, 129.3, 133.6, 133.8, 136.2, 136.3, 142.6, 150.2, 191.2.

All amines 5-2 were purchased from Sigma-Aldrich Co., Inc. except for 5-2n³⁹ and 5-2o⁴⁰ which were known compounds and synthesized according to the reported literatures.

6.5.2 CuBr-mediated synthesis of 4-bromoisoquinolones: a typical procedure for the reaction of 2-(phenylethynyl)benzaldehyde (5-1a) and benzylamine (5-2a) (Table 5-1, entry 7).

To a stirred solution of 2-alkynylbenzaldehyde (5-1a) (105.0 mg, 0.509 mmol), CuBr-SMe$_2$ (230.2 mg, 1.12 mmol) and SiO$_2$ (0.3 g) in 5 mL of solvent (benzene : pyridine = 5 : 1) at 80 °C under O$_2$ atmosphere were added benzylamine (5-2a) [(55 μL × 3), (0.509 × 3) mmol] three times at every 1 h interval, and the reaction mixture was allowed to stir for another 1 h. After cooled to room temperature, the reaction was quenched with pH 9 buffer and extracted with ethyl acetate (20 mL × 3). The combined extracts were washed with brine and dried over MgSO$_4$. Volatile materials were removed in vacuo, and the resulting crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to give 2-benzyl-4-bromo-3-phenylisoquinolin-1(2H)-one (5-3aa) (158.0 mg, 0.405 mmol) in 80% yield.

2-Benzyl-4-bromo-3-phenylisoquinolin-1(2H)-one (5-3aa)

Sticky yellow oil; IR (neat) 694, 752, 1337, 1582, 1607, 1647 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.16 (2H, brs), 6.80-6.86 (2H, m), 7.06 (2H, d, $J$ = 7.2 Hz), 7.13-7.18 (3H, m), 7.35 (2H, dd, $J$ = 7.2, 7.6 Hz), 7.42 (1H, t, $J$ = 7.2 Hz), 7.58 (1H, dt, $J$ = 0.8, 7.6 Hz), 7.76 (1H, dt, $J$ = 1.2, 7.6 Hz), 8.00 (1H, d, $J$ = 8.0 Hz), 8.55 (1H, dd, $J$ = 0.8, 8.0 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 49.9, 102.8, 125.5, 126.5, 126.7, 127.0, 127.7, 128.2, 128.4, 128.5, 129.2, 129.4, 133.3, 135.5, 135.6, 137.1, 142.2, 162.1; ESI-HRMS: Found: m/z 390.0490. Calcd for C$_{22}$H$_{17}$NO$_7^9$Br: (M+H)$^+$ 390.0494.
4-Bromo-2-(4-methoxybenzyl)-3-phenylisoquinolin-1(2H)-one (5-3ab)

Yellow oil; IR (neat) 748, 1032, 1177, 1246, 1510, 1582, 1607, 1647 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.74 (3H, s), 5.10 (2H, brs), 6.69 (2H, td, \(J = 1.6, 8.8\) Hz), 6.76 (2H, d, \(J = 8.8\) Hz), 7.09 (2H, d, \(J = 7.2\) Hz), 7.39 (2H, t, \(J = 7.6\) Hz), 7.45 (1H, t, \(J = 7.6\) Hz), 7.59 (1H, ddd, \(J = 0.8, 7.2, 8.0\) Hz), 7.78 (1H, ddd, \(J = 1.2, 7.2, 8.0\) Hz), 8.01 (1H, d, \(J = 8.0\) Hz), 8.55 (1H, dd, \(J = 0.8, 8.0\) Hz); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 49.4, 55.2, 102.8, 113.6, 125.6, 126.5, 127.7, 128.35, 128.41, 128.5, 129.2, 129.3, 129.6, 133.3, 135.6, 135.7, 142.2, 158.7, 162.2; ESI-HRMS: Found: m/z 420.0599. Calcd for C\(_{23}\)H\(_{19}\)NO\(_2\)\(^{79}\)Br: (M+H\(^+\))\(^{79}\) 420.0599.

4-Bromo-2-(4-methylbenzyl)-3-phenylisoquinolin-1(2H)-one (5-3ac)

Yellow oil; IR (neat) 692, 907, 1034, 1246, 1510, 1647 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.27 (3H, s), 5.11 (2H, brs), 6.73 (2H, d, \(J = 8.0\) Hz), 6.97 (2H, d, \(J = 8.0\) Hz), 7.09 (2H, d, \(J = 6.8\) Hz), 7.38 (2H, dd, \(J = 6.8, 7.6\) Hz), 7.44 (1H, tt, \(J = 1.2, 7.6\) Hz), 7.60 (1H, ddd, \(J = 1.2, 7.2, 7.6\) Hz), 7.78 (1H, ddd, \(J = 1.2, 7.2, 8.4\) Hz), 8.01 (1H, d, \(J = 8.0\) Hz), 8.55 (1H, dd, \(J = 0.8, 8.0\) Hz); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.0, 49.8, 102.7, 125.6, 126.5, 126.7, 127.7, 128.4, 128.5, 128.9, 129.2, 129.5, 133.2, 134.1, 135.5, 135.7, 136.6, 142.3, 162.1; ESI-HRMS: Found: m/z 404.0650. Calcd for C\(_{23}\)H\(_{19}\)NO\(_2\)\(^{79}\)Br: (M+H\(^+\))\(^{79}\) 404.0650.
4-Bromo-2-(4-fluorobenzyl)-3-phenylisoquinolin-1(2H)-one (5-3ad)

Yellow solid; mp. 149–151 °C; IR (neat) 750, 1219, 1335, 1508, 1582, 1638 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.13 (2H, brs), 6.77-6.88 (4H, m), 7.07 (2H, d, J = 7.2 Hz), 7.39 (2H, dd, J = 7.2, 8.0 Hz), 7.46 (1H, tt, J = 1.2, 7.2 Hz), 7.61 (1H, ddd, J = 0.8, 7.2, 8.0 Hz), 7.79 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.02 (1H, d, J = 8.4 Hz), 8.55 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 49.2, 102.9, 115.0 (d, J = 21.4 Hz), 125.5, 126.6, 127.8, 128.4, 128.5, 128.7 (d, J = 8.0 Hz), 129.3, 129.5, 132.9 (d, J = 3.1 Hz), 133.3, 135.51, 135.53, 141.9, 161.9 (d, J = 244.2 Hz), 162.1; ESI-HRMS: Found: m/z 408.0403. Calcd for C₂₂H₁₈NOF ⁷⁹Br: (M+H)⁺ 408.0399.

4-Bromo-2-phenethyl-3-phenylisoquinolin-1(2H)-one (5-3ae)

White solid; mp. 121–123 °C; IR (neat) 754, 1223, 1337, 1508, 1584, 1609, 1651 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.83-2.90 (2H, m), 3.95-4.03 (2H, m), 6.86 (2H, d, J = 6.4 Hz), 7.13-7.20 (3H, m), 7.27-7.32 (2H, m), 7.53-7.57 (3H, m), 7.60 (1H, dd, J = 7.2, 7.6 Hz), 7.78 (1H, dd, J = 7.6, 8.0 Hz), 8.00 (1H, d, J = 8.4 Hz), 8.54 (1H, d, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 34.7, 49.1, 102.4, 125.6, 126.4, 126.5, 127.7, 128.1, 128.4, 128.7, 128.8, 129.3, 129.4, 133.2, 135.4, 136.0, 138.1, 142.0, 161.7; ESI-HRMS: Found: m/z 404.0649. Calcd for C₂₃H₁₉NO ⁷⁹Br: (M+H)⁺ 404.0650.
4-Bromo-2-(2,2-diphenylethyl)-3-phenylisoquinolin-1(2H)-one (5-3a)

Yellow solid; mp. 159–161 °C; IR (neat) 698, 756, 1508, 1636, 1645, 1653 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 4.52 (2H, brs), 4.60 (1H, t, J = 7.2 Hz), 6.72 (2H, brs), 6.90-6.97 (4H, m), 7.13-7.20 (6H, m), 7.36 (2H, dd, J = 7.2, 8.0 Hz), 7.44 (1H, tt, J = 1.2, 7.6 Hz), 7.57 (1H, ddd, J = 1.2, 6.8, 8.0 Hz), 7.75 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.95 (1H, d, J = 8.0 Hz), 8.50 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 48.0, 52.0, 102.6, 125.6, 126.5, 126.6, 127.6, 128.2, 128.35, 128.43, 128.5, 129.1, 129.8, 133.1, 135.4, 135.6, 141.2, 142.3, 162.2; ESI-HRMS: Found: m/z 480.0963. Calcd for C₈H₂₃NO⁷₉Br: (M+H)⁺ 480.0963.

4-Bromo-2-pentyl-3-phenylisoquinolin-1(2H)-one (5-3a)

Yellow oil; IR (neat) 762, 1092, 1339, 1474, 1582, 1647, 2930, 2955 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.77 (3H, t, J = 6.8 Hz), 1.02-1.17 (4H, m), 1.56 (2H, tt, J = 7.2, 8.0 Hz), 3.79 (2H, t, J = 8.0 Hz), 7.33-7.37 (2H, m), 7.50-7.56 (3H, m), 7.57 (1H, ddd, J = 0.8, 7.2, 8.0 Hz), 7.75 (1H, ddd, J = 1.6, 7.2, 8.4 Hz), 7.98 (1H, d, J = 8.4 Hz), 8.50 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 13.8, 21.9, 28.3, 28.8, 47.4, 102.3, 125.7, 126.4, 127.5, 128.2, 128.7, 129.25, 129.28, 133.0, 135.4, 136.2, 142.2, 161.6; ESI-HRMS: Found: m/z 370.0814. Calcd for C₂₀H₂₃NO⁷₉Br: (M+H)⁺ 370.0807.
4-Bromo-2-(cyclohexylmethyl)-3-phenylisoquinolin-1(2H)-one (5-3ah)

![Chemical structure](attachment:image)

White solid; mp. 140–145 °C; IR (neat) 1335, 1506, 1578, 1645, 1717, 2849, 2926 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.73–0.84 (2H, m), 1.01–1.12 (3H, m), 1.37–1.43 (2H, m), 1.52–1.70 (4H, m), 3.78 (2H, brs), 7.30–7.36 (2H, m), 7.48–7.55 (3H, m), 7.57 (1H, ddd, J = 1.2, 6.8, 8.0 Hz), 7.75 (1H, ddd, J = 1.6, 7.2, 8.4 Hz), 7.99 (1H, d, J = 8.0 Hz), 8.50 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 25.8, 26.1, 30.7, 37.5, 52.6, 102.6, 125.6, 126.4, 127.5, 128.3, 128.5, 129.1, 129.9, 133.0, 135.4, 136.0, 142.4, 162.1; ESI-HRMS: Found: m/z 396.0956. Calcd for C₂₂H₂₃NO ⁷⁹Br: (M+H)⁺ 396.0963.

4-Bromo-2-(cyclopropylmethyl)-3-phenylisoquinolin-1(2H)-one (5-3ai)

![Chemical structure](attachment:image)

Orange solid; mp. 102–104 °C; IR (neat) 694, 764, 1474, 1607, 1645, 2851, 2924 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 0.16–0.22 (2H, m), 0.33–0.38 (2H, m), 0.92–1.03 (1H, m), 3.82 (2H, d, J = 6.8 Hz), 7.33–7.40 (2H, m), 7.48–7.56 (3H, m), 7.55 (1H, t, J = 7.2 Hz), 7.74 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.97 (1H, d, J = 8.0 Hz), 8.50 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 4.2, 10.7, 50.8, 102.4, 125.7, 126.4, 127.5, 128.2, 128.6, 129.2, 129.7, 133.0, 135.4, 136.2, 142.0, 162.1; ESI-HRMS: Found: m/z 354.0498. Calcd for C₁₉H₁₇NO ⁷⁹Br: (M+H)⁺ 354.0494.
4-Bromo-2-(2-(cyclohex-1-en-1-yl)ethyl)-3-phenylisoquinolin-1(2H)-one (5-3aj)

![Chemical structure of 4-Bromo-2-(2-(cyclohex-1-en-1-yl)ethyl)-3-phenylisoquinolin-1(2H)-one (5-3aj)](image)

White solid; mp. 107–109 °C; IR (neat) 752, 1578, 1636, 1647, 2859, 2924 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.40-1.52 (4H, m), 1.66 (2H, brs), 1.85 (2H, brs), 2.15 (2H, t, J = 8.0 Hz), 3.86 (2H, t, J = 8.0 Hz), 5.21 (1H, brs), 7.34-7.38 (2H, m), 7.51-7.58 (4H, m), 7.74 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.97 (1H, d, J = 8.0 Hz), 8.49 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 22.1, 22.7, 25.1, 27.8, 36.9, 46.5, 102.3, 123.4, 125.6, 126.4, 127.5, 128.1, 128.7, 129.27, 129.34, 133.0, 134.1, 135.3, 136.0, 142.0, 161.6; ESI-HRMS: Found: m/z 408.0964. Calcd for C₂₉H₂₃NO79Br: (M+H)⁺ 408.0963.

4-Bromo-2-(2-methoxyethyl)-3-phenylisoquinolin-1(2H)-one (5-3ak)

Yellow oil; IR (neat) 692, 760, 1103, 1115, 1580, 1647, 3003 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.18 (3H, s), 3.54 (2H, t, J = 6.0 Hz), 4.06 (2H, t, J = 6.0 Hz), 7.32-7.37 (2H, m), 7.50-7.55 (3H, m), 7.57 (1H, ddd, J = 1.2, 7.2, 8.0 Hz), 7.77 (1H, ddd, J = 1.2, 7.2, 8.0 Hz), 7.99 (1H, d, J = 8.0 Hz), 8.49 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 46.4, 58.7, 69.4, 102.6, 125.5, 126.5, 127.6, 128.1, 128.7, 129.3, 129.7, 133.2, 135.6, 136.1, 142.4, 161.9; ESI-HRMS: Found: m/z 358.0445. Calcd for C₁₉H₁₇NO₂79Br: (M+H)⁺ 358.0443.
4-Bromo-2-methyl-3-phenylisoquinolin-1(2H)-one (5-3a1)

\[
\begin{align*}
\text{O} & \text{N} \quad \text{Me} \\
\text{Br} & \text{Ph}
\end{align*}
\]

White solid; mp. 132–134 °C; IR (neat) 745, 756, 1117, 1339, 1474, 1636, 1645 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.32 (3H, s), 7.31-7.35 (2H, m), 7.50-7.59 (4H, m), 7.75 (1H, ddd, \(J = 1.2, 7.2, 8.4\) Hz), 7.98 (1H, d, \(J = 8.4\) Hz), 8.50 (1H, dd, \(J = 0.8, 8.0\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 35.1, 101.9, 125.3, 126.4, 127.6, 128.1, 128.98, 129.03, 129.3, 133.0, 135.4, 136.4, 142.2, 162.2; ESI-HRMS: Found: m/z 314.0178. Caled for C\(_{16}\)H\(_{13}\)NO\(_7\)Br: (M+H)+ 314.0181.

2-Methyl-3-phenylisoquinolin-1(2H)-one (5-6a1)

\[
\begin{align*}
\text{O} & \text{N} \quad \text{Me} \\
\text{H} & \text{Ph}
\end{align*}
\]

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.43 (3H, s), 6.46 (IH, s), 7.39-7.43 (2H, m), 7.45-7.51 (6H, m), 7.63 (1H, dd, \(J = 7.2, 7.6\) Hz), 8.46 (1H, d, \(J = 8.0\) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 34.1, 107.5, 124.9, 125.9, 126.6, 127.8, 128.6, 128.7, 128.9, 132.2, 136.2, 136.3, 143.9, 163.3.

2-Benzyl-4-bromo-3-(4-methoxyphenyl)isoquinolin-1(2H)-one (5-3ba)

Sticky yellow oil; IR (neat) 750, 1032, 1173, 1248, 1508, 1609, 1645 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.85 (3H, s), 5.18 (2H, brs), 6.84-6.90 (4H, m), 6.99 (2H, d, \(J = 8.4\) Hz), 7.15-7.20 (3H, m), 7.59 (1H, ddd, \(J = 1.2, 7.2, 8.0\) Hz), 7.78 (1H, ddd, \(J = 1.2, 7.2, 8.0\) Hz), 8.01 (1H, d, \(J = 8.0\) Hz), 8.55 (1H, dd, \(J = 0.8, 8.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 50.0, 55.3, 103.5, 113.8, 125.5, 126.6, 126.7, 127.0, 127.7, 128.1, 128.2, 128.6, 130.8, 133.3, 135.6, 137.3, 142.2, 160.0, 162.3; ESI-HRMS: Found: m/z 420.0605. Calcd for C\(_{23}\)H\(_{19}\)NO\(_2\) \(^{79}\)Br: (M+H\(^+\)) 420.0599.

2-Benzyl-4-bromo-3-(4-methylphenyl)isoquinolin-1(2H)-one (5-3ca)

Sticky yellow oil; IR (neat) 1456, 1474, 1508, 1582, 1607, 1647, 3010 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.40 (3H, s), 5.16 (2H, brs), 6.84-6.89 (2H, m), 6.97 (2H, d, \(J = 8.0\) Hz), 7.14-7.19 (3H, m), 7.56 (1H, ddd, \(J = 1.2, 7.2, 8.0\) Hz), 7.77 (1H, ddd, \(J = 1.2, 7.2, 8.4\) Hz), 8.01 (1H, d, \(J = 8.0\) Hz), 8.54 (1H, dd, \(J = 0.8, 8.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.4, 50.0, 102.9, 125.5, 126.5, 126.7, 127.0, 127.6, 128.2, 128.5, 129.1, 129.3, 132.8, 133.2, 135.6, 137.2, 139.2, 142.4, 162.2; ESI-HRMS: Found: m/z 404.0656. Calcd for C\(_{23}\)H\(_{19}\)NO\(^{79}\)Br: (M+H\(^+\)) 404.0650.
2-Benzyl-4-bromo-3-(4-fluorophenyl)isoquinolin-1(2H)-one (5-3da)

White solid; mp. 131–133 °C; IR (neat) 1223, 1238, 1373, 1506, 1636, 1717, 1734 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.17 (2H, brs), 6.80-6.85 (2H, m), 7.00-7.08 (4H, m), 7.16-7.20 (3H, m), 7.61 (1H, ddd, J = 1.2, 7.2, 8.0 Hz), 7.80 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.01 (1H, d, J = 8.0 Hz), 8.56 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 49.9, 103.3, 115.6 (d, J = 21.7 Hz), 125.6, 126.59, 126.62, 127.2, 127.9, 128.3, 128.6, 131.5 (d, J = 8.4 Hz), 131.6 (d, J = 3.8 Hz), 133.4, 135.4, 137.0, 141.2, 162.1, 162.9 (d, J = 248.6 Hz); ESI-HRMS: Found: m/z 408.0392. Calcd for C₂₂H₁₆NOF ⁷⁹Br: (M+H)⁺ 408.0399.

Ethyl 4-(2-benzyl-4-bromo-1-oxo-1,2-dihydroisoquinolin-3-yl)benzoate (5-3ea)

Yellow oil; IR (neat) 760, 1022, 1099, 1271, 1506, 1653, 1717 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.42 (3H, t, J = 7.2 Hz), 4.42 (2H, q, J = 7.2 Hz), 5.15 (2H, brs), 6.78-6.83 (2H, m), 7.12-7.20 (5H, m), 7.62 (1H, ddd, J = 0.8, 7.2, 8.0 Hz), 7.80 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.01 (1H, d, J = 8.0 Hz), 8.04 (2H, d, J = 8.4 Hz), 8.57 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 14.3, 49.9, 61.3, 102.6, 125.6, 126.6 (overlapped), 127.2, 128.1, 128.4, 128.6, 129.6, 129.7, 131.2, 133.4, 135.4, 136.8, 139.7, 141.2, 162.1, 165.8; ESI-HRMS: Found: m/z 462.0703. Calcd for C₂₅H₂₁NO₃ ⁷⁹Br: (M+H)⁺ 462.0705.
2-Benzyl-4-bromo-3-(4-trifluoromethylphenyl)isoquinolin-1(2H)-one (5-3fa)

![Structural formula of 2-Benzyl-4-bromo-3-(4-trifluoromethylphenyl)isoquinolin-1(2H)-one (5-3fa)](attachment)

Yellow oil; IR (neat) 760, 1067, 1128, 1167, 1321, 1647 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.14 (2H, brs), 6.75-6.81 (2H, m), 7.13-7.20 (5H, m), 7.59-7.66 (3H, m), 7.80 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.01 (1H, d, J = 8.0 Hz), 8.57 (1H, dd, J = 0.8, 8.0 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 49.9, 102.8, 123.7 (q, J = 270.6 Hz), 125.4 (q, J = 3.7 Hz), 125.7, 126.56, 126.63, 127.3, 128.2, 128.4, 128.7, 130.1, 131.3 (q, J = 32.6 Hz), 133.5, 135.3, 136.8, 139.0, 140.6, 162.1; ESI-HRMS: Found: m/z 458.0359. Calcd for C₂₃H₁₆NOF₃ ²⁹Br: (M+H)⁺ 458.0367.

2-Benzyl-4-bromo-3-(3-methoxyphenyl)isoquinolin-1(2H)-one (5-3ga)

![Structural formula of 2-Benzyl-4-bromo-3-(3-methoxyphenyl)isoquinolin-1(2H)-one (5-3ga)](attachment)

Sticky oil; IR (neat) 1040, 1215, 1261, 1456, 1489, 1578, 1651 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.56 (3H, s), 4.94 (1H, brd, J = 14.8 Hz), 5.38 (1H, brd, J = 15.2 Hz), 6.46 (1H, s), 6.73 (1H, d, J = 7.6 Hz), 6.83-6.90 (2H, m), 6.96 (1H, ddd, J = 0.8, 2.4, 8.4 Hz), 7.16-7.21 (3H, m), 7.31 (1H, t, J = 8.0 Hz), 7.60 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 7.79 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.02 (1H, d, J = 8.0 Hz), 8.56 (1H, dd, J = 1.2, 8.0 Hz);

¹³C NMR (100 MHz, CDCl₃) δ 50.0, 55.0, 102.6, 114.3, 115.7, 121.5, 125.5, 126.5, 126.7, 127.0, 127.7, 128.3, 128.5, 129.6, 133.3, 135.6, 136.6, 137.4, 142.0, 159.2, 162.2; ESI-HRMS: Found: m/z 420.0602. Calcd for C₂₃H₁₉NO₂ ²⁹Br: (M+H)⁺ 420.0599.
2-Benzyl-4-bromo-3-(2-methoxyphenyl)isoquinolin-1(2H)-one (5-3ha)

![Chemical Structure](image)

Yellow solid; mp. 108–110 °C; IR (neat) 758, 1256, 1495, 1578, 1599, 1636, 2965 cm⁻¹;

¹H NMR (400 MHz, CDCl₃) δ 3.55 (3H, s), 4.93 (1H, brd, J = 15.2 Hz), 5.33 (1H, brd, J
= 15.2 Hz), 6.82-6.88 (2H, m), 6.88-6.95 (3H, m), 7.11-7.16 (3H, m), 7.40-7.46 (1H, m),
7.58 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 7.77 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.00 (1H, d, J =
8.0 Hz), 8.56 (1H, dd, J = 1.2, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 49.8, 55.2, 103.3,
110.9, 120.4, 124.5, 125.6, 126.4, 126.9, 127.1, 127.5, 128.0, 128.5, 131.1, 131.3, 133.1,
135.7, 137.2, 139.7, 156.5, 162.4; ESI-HRMS: Found: m/z 420.0598. Calcd for
C₂₃H₁₉NO₂Br⁺: (M+H)⁺ 420.0599.

2-Benzyl-4-bromo-3-(2-bromophenyl)isoquinolin-1(2H)-one (5-3ia)

![Chemical Structure](image)

Yellow oil; IR (neat) 792, 1026, 1327, 1472, 1607, 1647 cm⁻¹; ¹H NMR (400 MHz,
CDCl₃) δ 4.49 (1H, d, J = 15.2 Hz), 5.80 (1H, d, J = 15.6 Hz), 6.80-6.87 (3H, m), 7.11-
7.20 (4H, m), 7.30 (1H, dt, J = 1.6, 8.0 Hz), 7.62 (1H, ddd, J = 1.2, 7.6, 8.4 Hz), 7.69
(1H, dd, J = 1.2, 8.0 Hz), 7.79 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.01 (1H, d, J = 8.0 Hz),
8.59 (1H, dd, J = 1.2, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 49.7, 103.4, 123.9, 125.8,
126.6, 127.0, 127.18, 127.22, 128.1, 128.2, 128.6, 130.9, 132.1, 132.7, 133.3, 135.4,
136.4, 136.9, 140.8, 162.2; ESI-HRMS: Found: m/z 469.9583. Calcd for C₂₂H₁₆NO ⁷⁹Br
⁸¹Br: (M+H)⁺ 469.9578.
2-Benzyl-4-bromo-3-(2-naphthyl)isoquinolin-1(2H)-one (5-3ja)

Yellow oil; IR (neat) 748, 1337, 1506, 1582, 1647 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.02 (1H, brd, \(J = 15.2\) Hz), 5.33 (1H, brd, \(J = 15.2\) Hz), 6.77 (2H, d, \(J = 6.8\) Hz), 7.07-7.20 (4H, m), 7.48-7.59 (3H, m), 7.62 (1H, ddd, \(J = 0.8, 7.2, 8.0\) Hz), 7.68 (1H, d, \(J = 8.0\) Hz), 7.80 (1H, ddd, \(J = 1.2, 7.2, 8.4\) Hz), 7.85 (1H, d, \(J = 8.4\) Hz), 7.89 (1H, d, \(J = 8.0\) Hz), 8.03 (1H, d, \(J = 8.4\) Hz), 8.59 (1H, dd, \(J = 0.8, 8.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 50.1, 103.1, 125.6, 126.4, 126.57, 126.62, 126.8, 127.07, 127.13, 127.76, 127.81, 128.22, 128.24, 128.4, 128.6, 129.4, 132.6, 132.8, 133.1, 133.3, 135.6, 137.2, 142.1, 162.2; ESI-HRMS: Found: m/z 440.0654. Calcld for C\(_{26}\)H\(_{19}\)NO\(_7\)Br: (M+H\(^+\))\(^{79}\)Br 440.0650.

2-Benzyl-4-bromo-3-pentylisoquinolin-1(2H)-one (5-3ka)

White solid; mp. 109–111 °C; IR (neat) 764, 1456, 1506, 1558, 1645, 1717 cm\(^{-1}\); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.91 (3H, t, \(J = 6.8\) Hz), 1.30-1.42 (4H, m), 1.56-1.64 (2H, m), 2.90 (2H, t, \(J = 8.0\) Hz), 5.50 (2H, brs), 7.14 (2H, d, \(J = 7.2\) Hz), 7.25 (1H, t, \(J = 7.2\) Hz), 7.31 (2H, dd, \(J = 6.8, 7.6\) Hz), 7.51 (1H, ddd, \(J = 1.2, 7.2, 8.0\) Hz), 7.74 (1H, ddd, \(J = 1.2, 7.2, 8.4\) Hz), 7.98 (1H, d, \(J = 8.4\) Hz), 8.46 (1H, dd, \(J = 1.2, 8.0\) Hz); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 13.9, 22.2, 27.9, 31.7, 33.6, 48.1, 102.3, 124.6, 125.9, 126.1, 127.0, 142.1, 162.2.
127.3, 128.5, 128.8, 133.2, 135.8, 137.0, 142.4, 162.5; ESI-HRMS: Found: m/z 384.0969. Caled for C_{21}H_{23}NO^{79}Br: (M+H)^{+} 384.0963.

2-Benzyl-4-bromo-3-cyclohexylisoquinolin-1(2H)-one (5-31a)

Rotational Isomer X:Y = 1.00:0.22 at room temperature. White solid; mp. 126–128 °C; IR (neat) 1339, 1456, 1506, 1576, 1607, 1636, 1653 cm^{-1}; {^1}H NMR (400 MHz, CDCl3) δ 0.92-1.50 (4H, m), 1.55-1.90 (4H, m), 2.53 (2H, dtd, J = 3.6, 12.4, 12.8 Hz), 3.06 (1H, tt, J = 3.2, 12.0 Hz), 5.57 (2H, brs), 7.19 (2H, d, J = 7.2 Hz), 7.23-7.28 (1H, m), 7.32 (2H, dd, J = 7.2, 7.6 Hz), 7.51 (1H, ddd, J = 1.2, 7.2, 8.0 Hz), 7.72 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.06 (1H, d, J = 8.0 Hz), 8.47 (1H, dd, J = 0.8, 8.0 Hz); {^{13}}C NMR (100 MHz, CDCl3) δ 25.4, 26.8, 27.9, 43.1, 48.6, 101.9, 124.6, 125.8, 126.2, 127.2, 127.3, 128.4, 128.7, 133.0, 136.2, 137.6, 145.2, 163.0; ESI-HRMS: Found: m/z 396.0961. Caled for C_{22}H_{23}NO^{79}Br: (M+H)^{+} 396.0963.

2-Benzyl-4-bromo-3-cyclopropylisoquinolin-1(2H)-one (5-3ma)

White solid; mp. 120–122 °C; IR (neat) 696, 764, 1456, 1506, 1576, 1645, 1717 cm^{-1}; {^1}H NMR (400 MHz, CDCl3) δ 0.95-1.00 (2H, m), 1.23-1.29 (2H, m), 1.65 (1H, tt, J = 6.0, 8.4 Hz), 5.81 (2H, brs), 7.14 (2H, d, J = 7.2 Hz), 7.20-7.30 (3H, m), 7.52 (1H, ddd, J = 0.8, 7.2, 8.0 Hz), 7.73 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 8.02 (1H, d, J = 8.4 Hz), 8.46 (1H, dd, J = 0.8, 8.0 Hz); {^{13}}C NMR (100 MHz, CDCl3) δ 12.1, 15.3, 47.5, 105.5, 125.1, 126.0,
126.3, 127.0, 127.3, 128.3, 128.6, 133.0, 135.8, 137.6, 141.3, 162.5; ESI-HRMS: Found: m/z 354.0497. Calcd for C_{19}H_{17}NO\textsuperscript{79}Br: (M+H\textsuperscript{+}) 354.0494.

2-Benzyl-4-bromo-5-methyl-3-phenylisoquinolin-1(2H)-one (5-3na)

Yellow solid; mp. 141–143 °C; IR (neat) 694, 760, 1327, 1456, 1506, 1578, 1639 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textsuperscript{5} 2.96 (3H, s), 5.11 (2H, brs), 6.78-6.84 (2H, m), 7.04 (2H, d, J = 7.2 Hz), 7.13-7.18 (3H, m), 7.32-7.42 (3H, m), 7.45 (1H, dd, J = 7.6, 8.0 Hz), 7.57 (1H, d, J = 7.2 Hz), 8.54 (1H, d, J = 8.0 Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \textsuperscript{8} 25.6, 50.2, 100.1, 126.8, 127.0, 127.30, 127.33, 127.6, 128.2, 128.5, 128.9, 129.5, 134.2, 135.3, 136.7, 137.1, 137.5, 142.7, 162.3; ESI-HRMS: Found: m/z 404.0647. Calcd for C_{23}H_{19}NO\textsuperscript{79}Br: (M+H\textsuperscript{+}) 404.0650.

6-Benzyl-8-bromo-7-phenyl-[1,3]dioxolo[4,5-g]isoquinolin-5(6H)-one (5-30a)

Sticky yellow oil; IR (neat) 696, 1036, 1231, 1406, 1472, 1568, 1645 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \textsuperscript{5} 5.13 (2H, brs), 6.14 (2H, s), 6.79-6.85 (2H, m), 7.05 (2H, d, J = 6.8 Hz), 7.14-7.19 (3H, m), 7.35 (2H, dd, J = 6.8, 8.0 Hz), 7.42 (1H, s), 7.42 (1H, tt, J = 1.2, 8.0 Hz), 7.90 (1H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \textsuperscript{8} 50.0, 102.1, 102.4, 105.1, 106.3, 121.2, 126.7, 127.0, 128.2, 128.4, 129.1, 129.5, 133.2, 135.8, 137.2, 141.0, 148.4, 152.8, 161.3; ESI-HRMS: Found: m/z 434.0389. Calcd for C_{23}H_{17}NO\textsuperscript{79}Br: (M+H\textsuperscript{+}) 434.0392.
2-Benzyl-4-bromo-7-methoxy-3-phenylisoquinolin-1(2H)-one (5-3pa)

![Chemical structure](attachment:image.png)

Yellow solid; mp. 161–163 °C; IR (neat) 698, 939, 1038, 1406, 1474, 1645 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.97 (3H, s), 5.16 (2H, brs), 6.80-6.87 (2H, m), 7.07 (2H, d, J = 7.2 Hz), 7.14-7.19 (3H, m), 7.32-7.39 (3H, m), 7.42 (1H, t, J = 7.2 Hz), 7.94 (1H, d, J = 9.2 Hz), 7.96 (1H, d, J = 2.4 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 50.1, 55.8, 102.7, 108.4, 123.6, 126.7, 127.0, 128.2, 128.37, 128.40 (overlapped), 129.1, 129.6, 129.8, 135.7, 137.2, 139.7, 159.4, 161.9; ESI-HRMS: Found: m/z 420.0599. Calcd for C₂₃H₁₉NO₂Br: (M+H)⁺ 420.0599.

2-Benzyl-4-bromo-7-fluoro-3-phenylisoquinolin-1(2H)-one (5-3qa)

![Chemical structure](attachment:image.png)

Yellow solid; mp. 104–106 °C; IR (neat) 696, 752, 941, 1341, 1489, 1585, 1647 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.15 (2H, brs), 6.79-6.85 (2H, m), 7.06 (2H, d, J = 6.8 Hz), 7.14-7.20 (3H, m), 7.37 (2H, dd, J = 7.2, 8.0 Hz), 7.44 (1H, tt, J = 1.2, 7.2 Hz), 7.51 (1H, ddd, J = 2.8, 8.0, 8.8 Hz), 8.04 (1H, dd, J = 4.8, 8.8 Hz), 8.21 (1H, d, J = 1.2, 9.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 50.2, 102.1, 113.7 (d, J = 23.2 Hz), 121.8 (d, J = 23.4 Hz), 126.8, 127.1 (d, J = 7.8 Hz), 127.2, 128.3, 128.5, 129.3, 129.4 (d, J = 8.2 Hz), 129.5, 132.2 (d, J = 2.2 Hz), 135.4, 136.9, 141.5 (d, J = 2.8 Hz), 161.4 (d, J = 4.2 Hz), 162.0 (d, J = 247.9 Hz); ESI-HRMS: Found: m/z 408.0405. Calcd for C₂₂H₁₆NOF₂Br: (M+H)⁺ 408.0399.
2-benzyl-4-bromo-3-phenylbenzofuro[2,3-c]pyridin-1(2H)-one (5-3ra)

White solid; mp. 182–184 °C; IR (neat) 743, 1038, 1456, 1474, 1647, 1668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.28 (2H, brs), 6.79-6.85 (2H, m), 7.05 (2H, d, J = 7.2 Hz), 7.13-7.19 (3H, m), 7.39 (2H, t, J = 7.6 Hz), 7.42-7.49 (2H, m), 7.62 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.75 (1H, d, J = 8.8 Hz), 8.45 (1H, d, J = 0.4, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 50.0, 95.5, 112.8, 123.4, 123.5, 123.6, 127.0, 127.3, 128.29, 128.32, 128.6, 129.3, 129.5, 129.8, 134.4, 136.7, 142.7, 143.3, 154.1, 156.9; ESI-HRMS: Found: m/z 430.0437. Calcd for C₂₄H₁₇N₂O₂⁷⁵Br: (M+H)+ 430.0443.

6-Benzyl-8-bromo-7-phenyl-1,6-naphthyridin-5(6H)-one (5-3sa)

Yellow solid; mp. 138–140 °C; IR (neat) 698, 1435, 1456, 1541, 1558, 1638 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.17 (2H, brs), 6.80-6.87 (2H, m), 7.10 (2H, d, J = 7.2 Hz), 7.15-7.21 (3H, m), 7.39 (2H, dd, J = 6.8, 7.6 Hz), 7.46 (1H, tt, J = 1.2, 7.2 Hz), 7.54 (1H, dd, J = 4.8, 8.0 Hz), 8.81 (1H, dd, J = 1.6, 8.0 Hz), 9.09 (1H, dd, J = 1.6, 4.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 50.0, 104.7, 121.4, 122.6, 126.7, 127.2, 128.3, 128.5, 129.0, 129.4, 135.0, 136.6, 137.1, 146.2, 150.2, 155.1, 162.1; ESI-HRMS: Found: m/z 391.0443. Calcd for C₂₁H₁₆N₂O⁷⁵Br: (M+H)+ 391.0446.
6-Benzyl-7-phenyl-1,6-naphthyridin-5(6H)-one (5-6sa)

![Chemical Structure of 6-Benzyl-7-phenyl-1,6-naphthyridin-5(6H)-one (5-6sa)]

Yellow solid; mp. 113-115 °C; IR (neat) 704, 839, 1358, 1437, 1506, 1558, 1653 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.24 (2H, brs), 6.72 (1H, s), 6.87-6.93 (2H, m), 7.15-7.20 (3H, m), 7.23 (2H, d, J = 7.2 Hz), 7.36 (2H, dd, J = 7.2, 8.0 Hz), 7.41-7.46 (2H, m), 8.74 (1H, dd, J = 1.2, 8.0 Hz), 8.93 (1H, dd, J = 1.6, 4.8 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 48.6, 109.8, 120.9, 121.7, 126.8, 127.1, 128.3 (overlapped), 128.8, 129.2, 135.2, 136.6, 137.1, 147.8, 152.9, 154.8, 163.1; ESI-HRMS: Found: m/z 313.1335. Calcd for C₂₁H₁₇N₂O: (M+H)⁺ 313.1341.

4-Bromo-3-phenylisoquinoline (5-4t)

![Chemical Structure of 4-Bromo-3-phenylisoquinoline (5-4t)]

White solid; ¹H NMR (400 MHz, CDCl₃) δ 7.41-7.53 (3H, m), 7.66 (1H, ddd, J = 0.8, 7.2, 8.0 Hz), 7.71-7.76 (2H, m), 7.82 (1H, ddd, J = 1.2, 6.8, 8.4 Hz), 7.98 (1H, d, J = 8.0 Hz), 8.31 (1H, dd, J = 0.8, 8.8 Hz), 9.22 (1H, s); ¹³C NMR (100 MHz, CDCl₃) δ 118.2, 126.9, 127.7, 127.8, 127.9, 128.3, 128.5, 129.8, 131.8, 135.9, 140.7, 151.0, 152.3.

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3-Phenylisoquinoline (5-5)\textsuperscript{43}

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\text{Ph} \\
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\text{N} \\
\text{Ph}
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White solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.41 (1H, tt, \( J = 1.2, 7.6 \) Hz), 7.48-7.53 (2H, m), 7.57 (1H, ddd, \( J = 1.2, 6.8, 8.0 \) Hz), 7.68 (1H, ddd, \( J = 1.2, 6.8, 8.0 \) Hz), 7.86 (1H, d, \( J = 8.0 \) Hz), 7.97 (1H, d, \( J = 8.0 \) Hz), 8.06 (1H, s), 8.10-8.15 (2H, m), 9.33 (1H, s); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 116.5, 126.8, 126.9, 127.0, 127.7, 128.4, 128.7, 130.4, 136.5, 139.5, 151.2, 152.3.

2-(Phenylethynyl)benzonitrile (5-7)\textsuperscript{44}

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\text{Ph} \\
\begin{array}{c}
\text{CN} \\
\text{Ph}
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\]

Yellow solid; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.35-7.40 (3H, m), 7.40 (1H, dt, \( J = 1.2, 7.6 \) Hz), 7.56 (1H, dt, \( J = 1.2, 7.6 \) Hz), 7.59-7.64 (3H, m), 7.67 (1H, ddd, \( J = 0.8, 7.6 \) Hz); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \( \delta \) 85.5, 95.9, 115.2, 117.5, 122.0, 127.2, 128.2, 128.4, 129.2, 131.95, 132.04, 132.3, 132.6.


\textsuperscript{44} Pu, X.; Li, H.; Colacot, T. \textit{J. J. Org. Chem.} \textbf{2013}, \textit{78}, 568.
6.5.3 The reactions with CuCl and CuI (Scheme 5-24)

2-Benzyl-4-chloro-3-phenylisoquinolin-1(2H)-one (5-3aa′)

![Chemical structure](image)

Synthesized from 2.2 equiv of CuCl; Yellow oil; IR (neat) 696, 752, 1477, 1495, 1585, 1611, 1647 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.15 (2H, brs), 6.80-6.86 (2H, m), 7.09 (2H, d, J = 6.8 Hz), 7.14-7.18 (3H, m), 7.36 (2H, dd, J = 6.8, 7.6 Hz), 7.43 (1H, t, J = 7.6 Hz), 7.61 (1H, dt, J = 0.8, 7.6 Hz), 7.79 (1H, dt, J = 1.2, 7.6 Hz), 8.00 (1H, d, J = 8.0 Hz), 8.57 (1H, dd, J = 0.8, 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 49.5, 111.8, 123.8, 125.5, 126.8, 127.1, 127.8, 128.3, 128.5, 128.6, 129.2, 129.6, 133.1, 133.6, 134.7, 137.2, 140.5, 162.0; ESI-HRMS: Found: m/z 346.1003. Calcd for C₂₂H₁₇NOCl: (M+H)⁺ 346.0999.

2-Benzyl-4-iodo-3-phenylisoquinolin-1(2H)-one (5-3aa'’)

![Chemical structure](image)

Synthesized from 2.2 equiv of CuI in pyridine (0.1 M); White solid; mp. 86–88 °C; IR (neat) 696, 762, 1030, 1339, 1587, 1603, 1647 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.20 (2H, brs), 6.80-6.86 (2H, m), 7.02 (2H, d, J = 7.6 Hz), 7.14-7.18 (3H, m), 7.35 (2H, dd, J = 7.2, 7.6 Hz), 7.42 (1H, t, J = 7.2 Hz), 7.57 (1H, t, J = 7.6 Hz), 7.75 (1H, t, J = 7.6 Hz), 7.96 (1H, d, J = 8.0 Hz), 8.51 (1H, d, J = 8.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 50.8, 79.9, 125.2, 126.7, 127.0, 127.8, 128.2, 128.4, 128.6, 129.3, 129.5, 131.7, 133.6, 137.2, 137.4, 139.3, 145.7, 162.5; ESI-HRMS: Found: m/z 438.0354. Calcd for C₂₂H₁₇NOI: (M+H)⁺ 438.0355.
6.5.4 Control experiments to elucidate the reaction mechanism (Scheme 2-25 & 2-26)

6.5.4.1. Preparation of \(N\)-benzylaldimines 5-8

\[
\begin{align*}
\text{5-1a} & \quad + \quad \text{H}_2\text{N} \quad \text{Ph} \\
\text{5-2a} & \quad \text{MS 4Å} \\
\text{CH}_2\text{Cl}_2, \text{rt} & \quad 24 \text{ h} \\
\text{5-8} & 
\end{align*}
\]

To a solution of 2-(2-phenylethynyl)benzaldehyde (5-1a) (206 mg, 1.0 mmol) in 1 mL of \(\text{CH}_2\text{Cl}_2\) were added benzylamine (5-2a) (107 mg, 1.0 mmol) and MS 4Å (20 mg). The reaction mixture was allowed to stir at room temperature for 24 h. After the completion of reaction, the mixture was filtered and volatile materials were removed \textit{in vacuo} and the crude material of 5-8 was used for next reaction without further purification.

\(N\)-Benzyl-2-(2-phenylethynyl)benzaldimine (5-8\)\textsuperscript{27}

Brown oil; \(^1\text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 4.90 (2\text{H, s}), 7.36-7.40 (10\text{H, m}), 7.50-7.57 (3\text{H, m}), 8.14 (1\text{H, d, } J = 6.8 \text{ Hz}), 8.99 (1\text{H, s}); ^{13}\text{C NMR} (100 \text{ MHz, CDCl}_3) \delta 65.1, 86.4, 94.9, 122.9, 124.1, 126.4, 127.0, 128.1, 128.4, 128.5, 128.58, 128.63, 130.3, 131.5, 132.5, 136.7, 139.1, 160.5.
6.5.4.2. Preparation of 2-alkynylbenzamide 5-9

*N*-Benzyl-2-(phenylethynyl)benzamide (5-9)\textsuperscript{45}

\[
\begin{align*}
\text{N} & \text{H} \\
\text{Ph} & \text{Ph}
\end{align*}
\]

Prepared from *N*-benzyl-2-iodobenzamide and phenylacetylene by the same procedure with the Chapter 6.5.1.1., and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) in 95% yield; White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.70 (2H, d, \(J = 5.6\) Hz), 7.13 (2H, d, \(J = 7.2\) Hz), 7.22-7.29 (5H, m), 7.30-7.40 (3H, m), 7.42-7.48 (2H, m), 7.56-7.61 (1H, m), 7.80 (1H, brs), 8.12-8.17 (1H, m); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 44.5, 87.5, 95.8, 119.6, 121.8, 127.5, 128.2, 128.4, 128.75, 128.86, 128.92, 130.2, 130.6, 131.4, 133.6, 135.0, 137.8, 166.1.

NMR data of imine 5-11 in Scheme 5-25 (c)

*N*-Benzyl-benzaldimine (5-11)\textsuperscript{46}

\[
\begin{align*}
\text{N} & \text{H} \\
\text{Ph} & \text{Ph}
\end{align*}
\]

Prepared from benzaldehyde and benzylamine; Brown oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.83 (2H, s), 7.33-7.50 (8H, m), 7.75-7.82 (2H, m), 8.39 (1H, s); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 65.0, 126.9, 127.9, 128.18, 128.22, 128.4, 128.5, 129.0, 130.7, 161.9.


\textsuperscript{46} Marinescu, L. G.; Pedersen, C. M.; Bols, M. \textit{Tetrahedron} \textbf{2004}, \textit{61}, 123.
6.5.4.3. Preparation of 2-benzyl-3-phenylisoquinolin-1(2H)-one (5-6aa)

To a 2-neck flask with Pd (10 wt. % loading) (53 mg, 0.05 mmol) under nitrogen atmosphere, was added a solution of 5-3aa (195 mg, 0.5 mmol) in EtOH (50 mL). The reaction mixture was allowed to stir for 6 h and then the filtered through a pad of celite. After solvent was removed in vacuo, the crude material was subjected to flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to afford 5-6aa (109 mg, 0.35 mmol) in 70% yield.

2-Benzyl-3-phenylisoquinolin-1(2H)-one (5-6aa)47

White solid; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 5.25 (2H, s), 6.44 (1H, s), 6.88-6.92 (2H, m), 7.14-7.22 (5H, m), 7.32 (2H, t, \(J = 7.2 \) Hz), 7.39 (1H, t, \(J = 7.2 \) Hz), 7.47-7.53 (2H, m), 7.66 (1H, dt, \(J = 0.8, 7.2 \) Hz), 8.49 (1H, d, \(J = 8.4 \) Hz); \(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 48.5, 108.1, 125.2, 125.8, 126.7, 126.8, 126.9, 128.18, 128.25, 128.27, 128.8, 129.1, 132.5, 135.8, 136.4, 137.6, 143.8, 163.1.