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

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A thesis submitted to the Nanyang Technological University

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Doctor of Philosophy

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With deepest gratitude,

Pei Chui

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List of Abbreviations

δ	chemical shift
Δ	heating
°C	degree centigrade
Ac	acetyl
acac	acetylacetonate
AcOH	acetic acid
APC	allylpalladium(II) chloride dimer
atm	standard atmosphere
brs	broad singlet
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Bu	butyl
Calcd	calculated
CAS	camphorsulfonic acid
$CDCl_3$	deuterated chloroform
Cp*	1,2,3,4,5-pentamethylcyclopentadiene
cod	1,5-cyclooctadiene
Cy	cyclohexyl
d	doublet
D	deuterium
dba	dibenzylideneacetone

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DBPO	dibenzoylperoxide
DBU	1,8-diazabicycloundec-7-ene
DCC	*N*,*N*'-dicyclohexylcarbodiimide
dd	doublets of doublet
ddd	doublets of doublets of doublet
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DMA	*N*,*N*-dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMI	1,3-dimethyl-2-imidazolindinone
DMSO	dimethyl sulfoxide
dppm	1,1-bis(diphenylphosphino)methane
dppe	1,1-bis(diphenylphosphino)ethane
dppf	1,1-bis(diphenylphosphino)ferrocene
dt	doublets of triplet
DTBMP	2,6-di-*tert*-butyl-4-methylpyridine
equiv	equivalent
ESI	electronspray ionization
Et	ethyl
Et_3N	triethylamine
EtOH	ethanol
FT-IR	Fourier transform infrared spectroscopy

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g	gram
h	hour
HRMS	high resolution mass spectroscopy
Hz	Hertz
hv	photoirradiation
i-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	megahertzs
min	minutes
mL	milliliters
mmol	millimoles
mol	moles
MS 4 Å	molecular sieves 4 angstroms

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NCS	*N*-chlorosuccinimide
NMR	nuclear magnetic resonance
NOESY	nuclear overhauser enhancement spectroscopy
OTf	trifluoromethanesulfonate
Pd(TFA)	palladium(II) trifluoroacetate
Ph	phenyl
Piv	pivalyl
PivOH	pivalic acid
ppm	parts per million
Pr	propyl
q	quartet
qd	quartet of doublet
rt	room temperature
s	singlet
sat.	saturated
t	triplet
TBS	*tert*-butyldimethylsilyl
t-Bu	*tert*-butyl
t-AmOH	2-methyl-2-butanol
TFA	trifluoroacetic acid
TfOH	trifluoromethanesulfonic acid
THF	tetrahydrofuran

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TLC	thin layer chromatography
TMS	trimethylsilyl
Tol	tolyl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
tt	triplet of triplet
tq	triplet of quartet

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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 $[Cp^*RhCl_2]_2$ 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).

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First Approach

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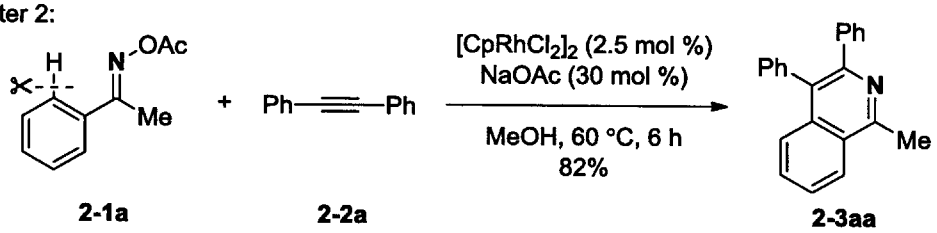
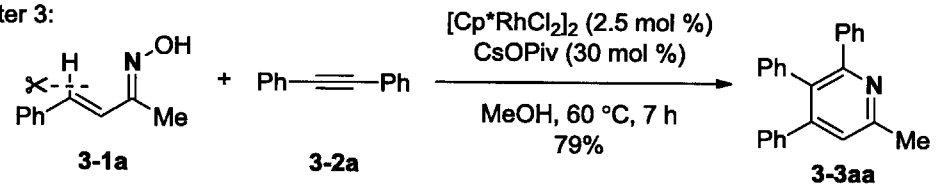


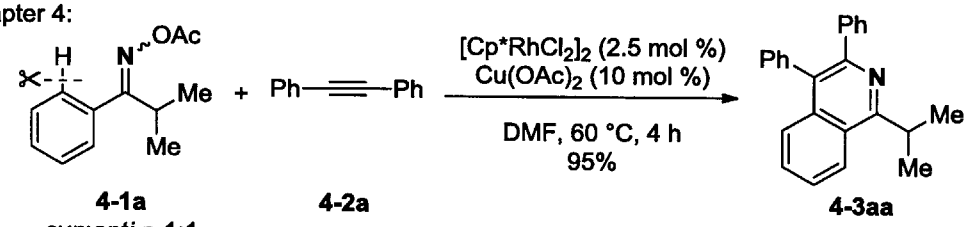
2-1a **2-2a** **2-3aa**

Chapter 3:



3-1a **3-2a** **3-3aa**

Chapter 4:

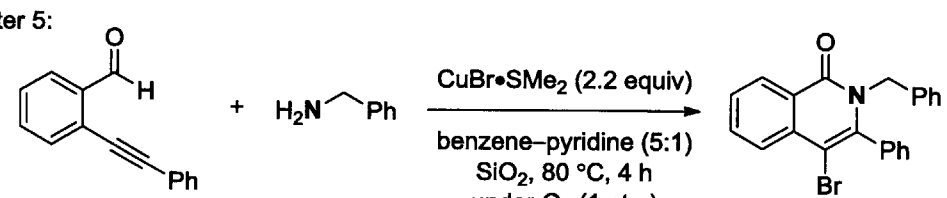


4-1a **4-2a** **4-3aa**

syn:*anti* = 1:1

Second approach

Chapter 5:



5-1a **5-2a** **5-3aa**

Scheme 1. Representative reaction schemes for two different approaches

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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)).

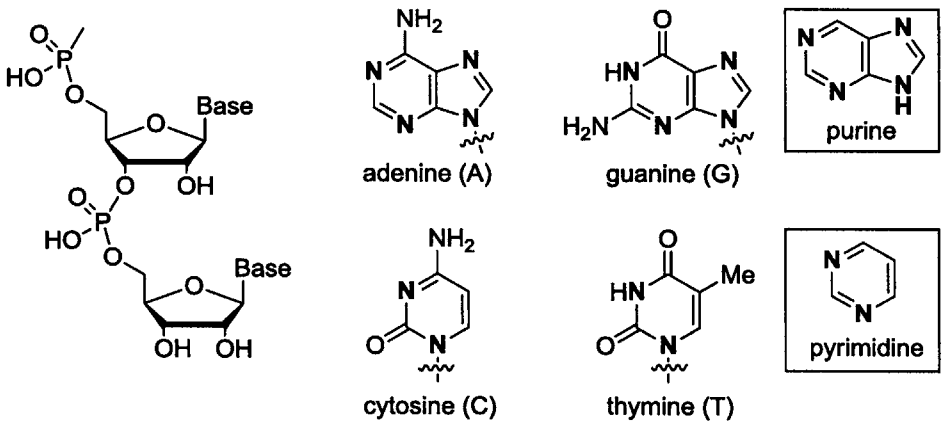

Figure 1-1. Nucleobases are important azaheterocycles in DNA

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

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involved in local immune responses to foreign pathogens as well as acting as a neurotransmitter.[1]

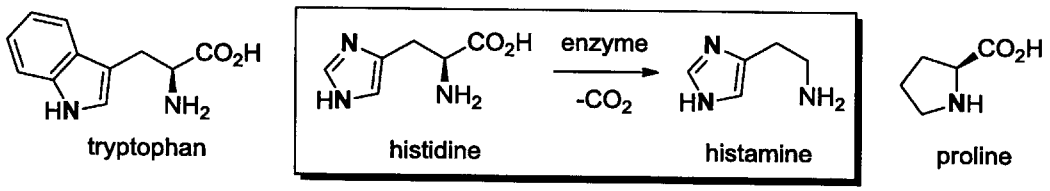

Figure 1-2. Three amino acids bearing azaheterocycles and one hormone

In addition to azaheterocycles involved in protein synthesis and gene expression, water-soluble vitamins are essential azaheterocycles in human metabolism. Vitamin B_3 (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 B_6 (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]

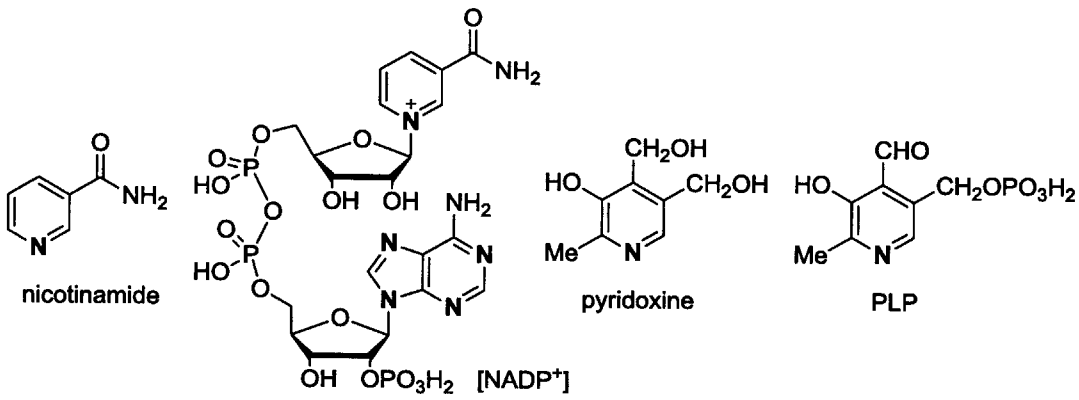

Figure 1-3. Nicotinamide and pyridoxine and their co-enzymes

Besides azaheterocycle-containing DNAs and amino acids, there are many plant-produced alkaloids bearing molecular structure based on isoquinolines (azaheterocycles).

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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.[4] Papaverine is also an alkaloid based on isoquinoline. It was first been discovered by Georg Merck in 1848[5] and known for treatment of heart attack, chest pain and blood clot.[6]

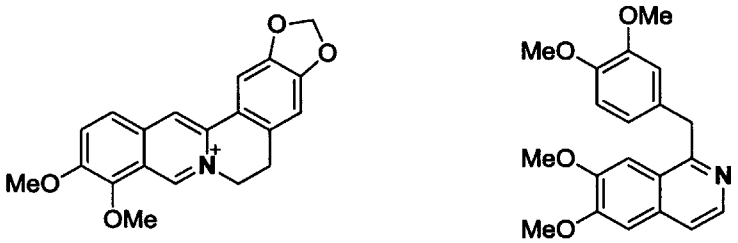

Figure 1-4. Berberine and papaverine

The kibdelones A–C are aromatic polyketide natural products that feature the isoquinolone and tetrahydroxanthone ring systems.[7] They display significant antibiotic activity as well as potent cytotoxicity toward a range of human cancer cell lines.[8] Fredericamycin A is one of the active antitumor antibiotics, which can be isolated from bacteria, *Stretomyces griseus*.[9] It possesses both quinone and isoquinolone moieties and acts as inhibitor in RNA expression and protein synthesis.[10]

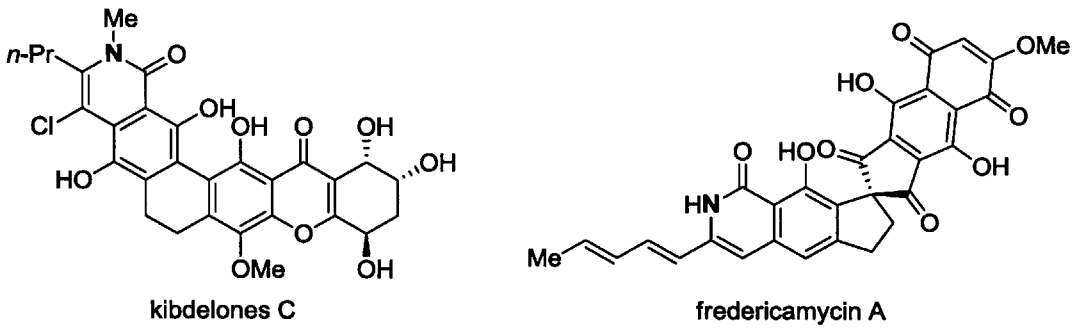

Figure 1-5. Kibdelones C and fredericamycin A

In addition to biologically active natural compounds, isoquinolone-derived structures can also be found in pharmaceutical drugs. For example, indenoisoquinoline

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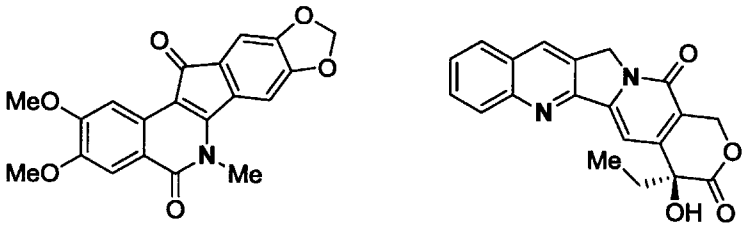
NSC314622 which was first synthesized in 1978,[11] and its derivatives both possess significant anti-cancer activity. Cytotoxicity analysis revealed that the indenoisoquinoline NSC314622 is potential topoisomerase I poison and its DNA strand breaking-site is different from camptothecin (CPT).[12]



indenoisoquinoline NSC314622 camphothecin

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.[13] Of the top 3 best-selling drugs (by total dollars) in 2012,[14] 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.[15]

The second top-selling drug is Abilify (aripiprazole), which is belongs to a class of medications called atypical antipsychotics and primarily used to treat the symptoms of mental disorders such as schizophrenia, [16] bipolar disorder, [17] major depressive disorder, [18] and irritability associated with autism. [19]

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.

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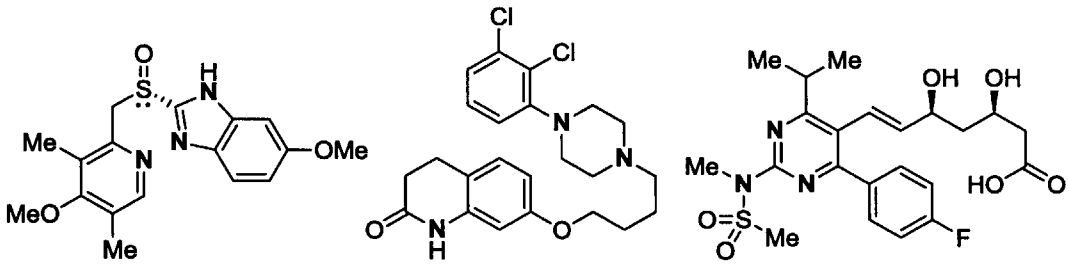

Figure 1-7. Top-selling drugs in 2012

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[20] and the Bischler-Napieralski[21] isoquinoline synthesis, as well as the Guareschi-Thorpe[22] and the Hantzsch[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.[24]

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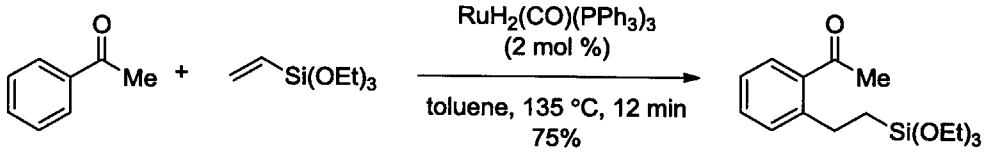
Despite many advantages, the significant challenge of the approach is the high bond dissociation energy of C–H bonds in alkanes and arenes (e.g. CH_3–H, 105 kcal mol^{-1}; Ar–H, 113 kcal mol^{-1}) compared to that of C–X (X = halides) bonds in traditional metal catalysis (e.g. Ar–I, 67 kcal mol^{-1}).[25] 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 sp^2 C–H bond activation was achieved by Murai and co-workers to solve the drawback of low efficiency and poor regioselectivity.[26] 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 sp^2 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

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).[27] 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.

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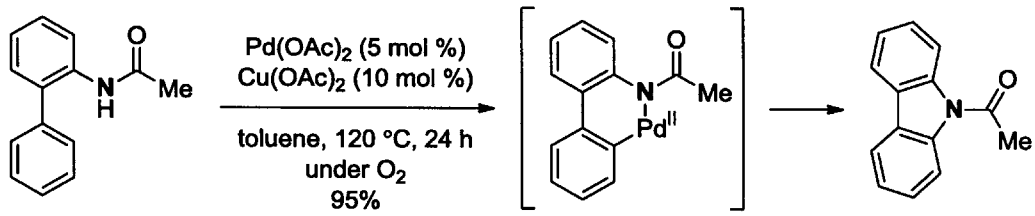
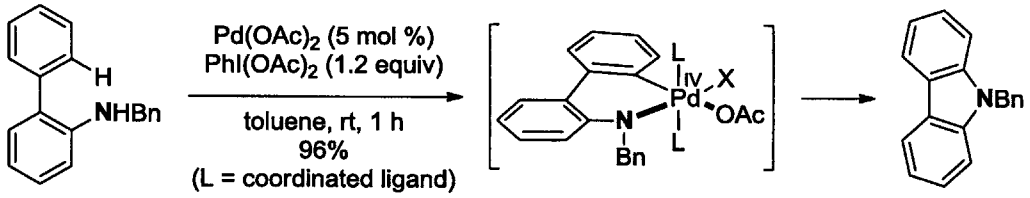
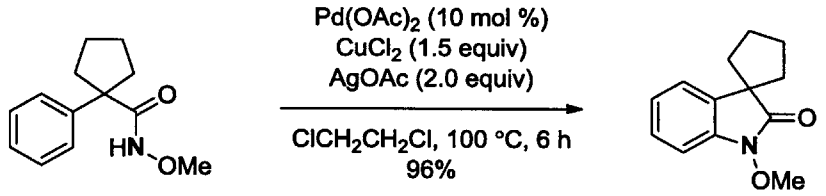


Scheme 1-2. An example of Pd(II)-catalyzed intramolecular C–H aminations of 2-phenylacetanilide derivatives

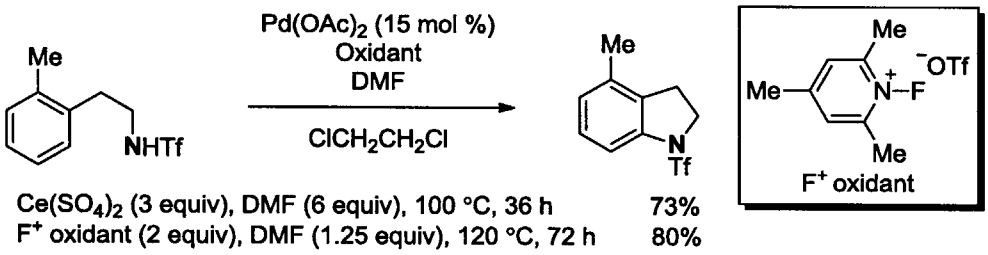


Scheme 1-3. An example of Pd(II)/Pd(IV)-catalyzed C-H aminations using $PhI(OAc)_2$ as an oxidant

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 $PhI(OAc)_2$ 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]



Scheme 1-4. An example of Pd(II)/Pd(IV)-catalyzed C-H aminations using $CuCl_2$ as an oxidant



Scheme 1-5. An example of Pd(II)/Pd(IV)-catalyzed C-H aminations using $Ce(SO_4)_2$ or F^+ source as an oxidant

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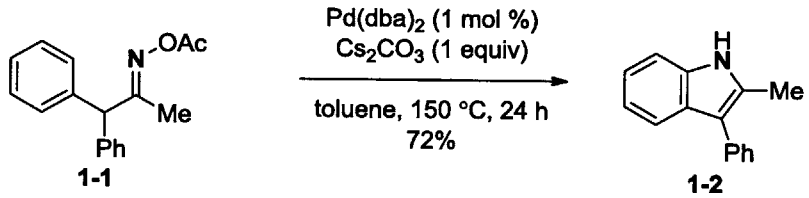
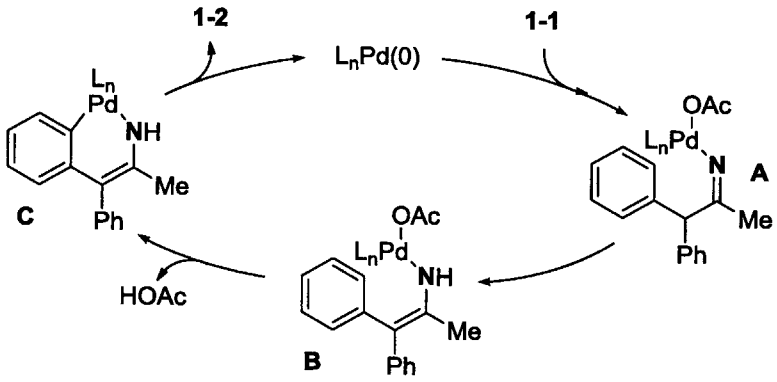
In addition, by utilizing $CuCl_2$ as an oxidant, Yu and co-workers reported Pd(II)/Pd(IV)-catalyzed C–H aminations of *N*-methoxy-2-phenylacetamide derivatives for the synthesis of *N*-methoxy 2-indolinones (Scheme 1-4).[29] They proposed that the reaction may involve a chloronium ion which is generated from $CuCl_2$ to oxidize Pd(II) to Pd(IV) *via* the Shilov mechanism. Similarly, by using $Ce(SO_4)_2$ 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:



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 Cs_2CO_3 (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

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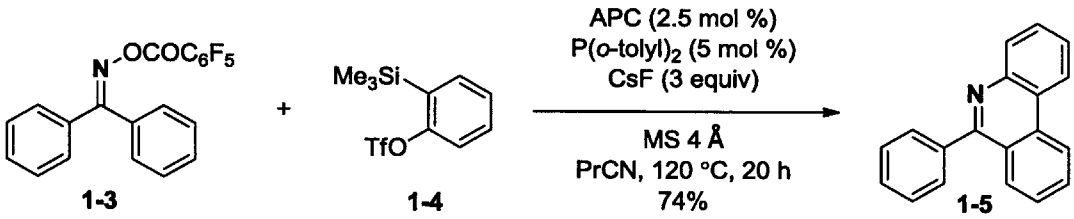
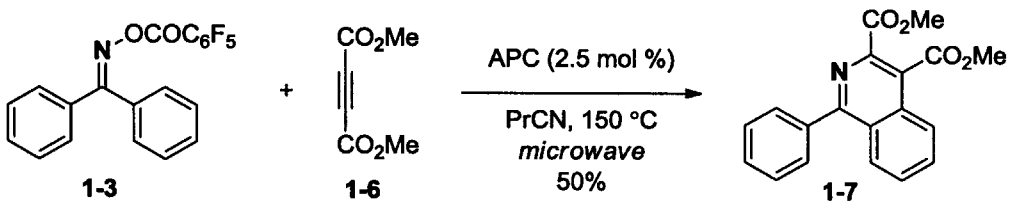
activation to form palladacycle **C**. Final C–N bond reductive elimination provides indole **1-2** and regenerates Pd(0) for the next catalytic cycle.

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



Scheme 1-8. An example of Pd(II)-catalyzed annulations of *O*-acyloximes with activated alkynes

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 azaheterocycle synthesis

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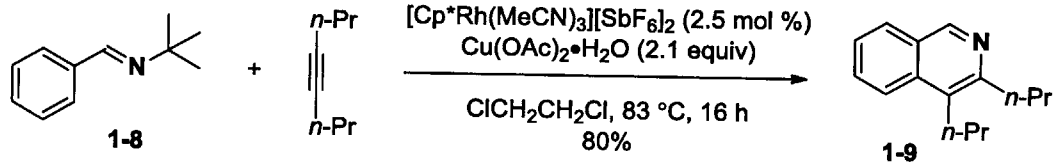
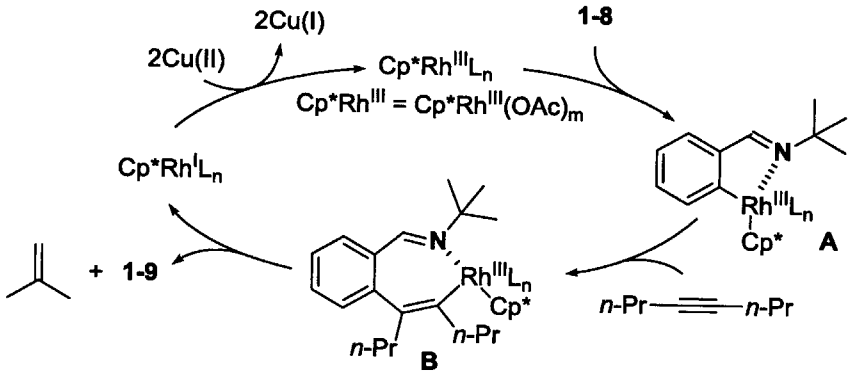
was reported by Fagnou and Guimond. They presented oxidative cross-couplings/cyclizations of aryl aldimines and alkynes using $[Cp^*Rh(MeCN)_3][SbF_6]_2$ as the catalyst (Scheme 1-9).[33] As shown in the proposed catalytic cycle, the first step is commenced by C–H bond activation of imine **1-8** using 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:



Scheme 1-9. An example of Rh(III)-catalyzed oxidative cross-couplings of aryl aldimines and alkynes and its proposed catalytic cycle

During the past few years, extensive investigations showed that Cp*Rh(III) complexes especially $[Cp^*RhCl_2]_2$, 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 $[Cp^*RhCl_2]_2$ as a catalyst. The detail synthetic utilities of $[Cp^*RhCl_2]_2$ will be discussed in Chapter 2.1.4.

Inspired by the successful application of $[Cp^*RhCl_2]_2$ as the catalyst for the synthesis of diverse azaheterocycles, researchers started to investigate the possibility of

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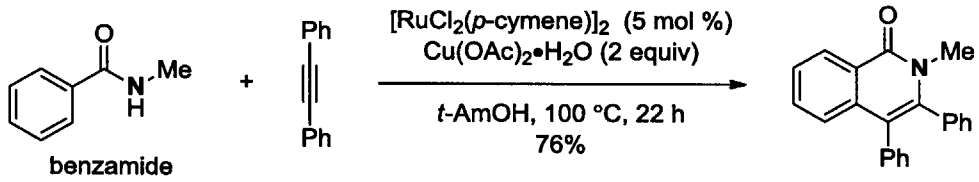
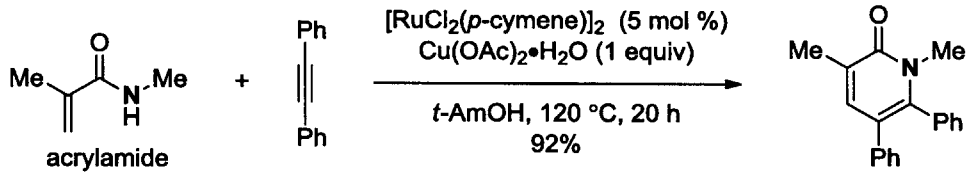
using ruthenium for C–H bond activation. As compared to Rh (Group 9), Ru (Group 8) is also a late transition metal in Period 5 of the periodic table, so they may share similar chemical reactivities. In fact, the oxidative annulations of benzamides and internal alkynes have been achieved using $[RuCl_2(p\text{-cymene})]_2$ 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) counter parts. However, in terms of cost, $[RuCl_2(p\text{-cymene})]_2$ is economically more favorable than $[Cp^*RhCl_2]_2$.



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

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 examample of Ru(II)-catalyzed oxidative annulations of acrylamides and internal alkynes

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

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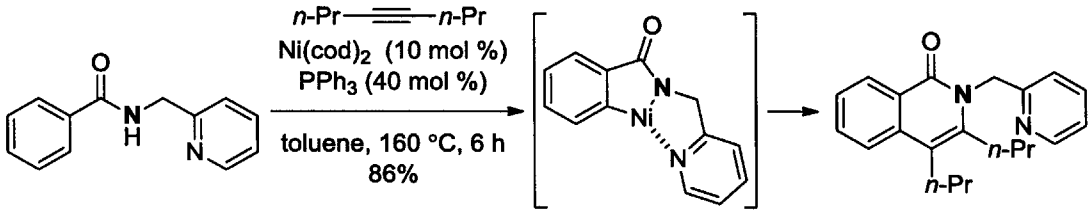
directing groups with strong chelation properties worked well under the $Ni(cod)_2$–PPh_3 catalytic system. Among all the directing groups examined, 2-pyridinylmethylamine provided the best results. By utilizing similar bidentate system, Ni(II)-catalyzed direct alkylation of C–H bonds of benzamides and acrylamides with functionalized halides could be achieved.[37] 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.[38]



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

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 nuclephile, 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.

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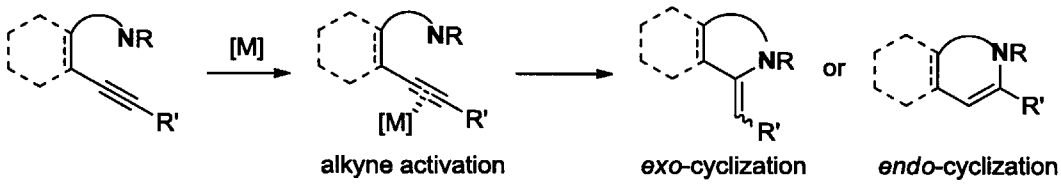
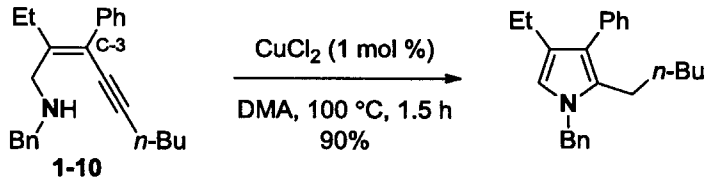
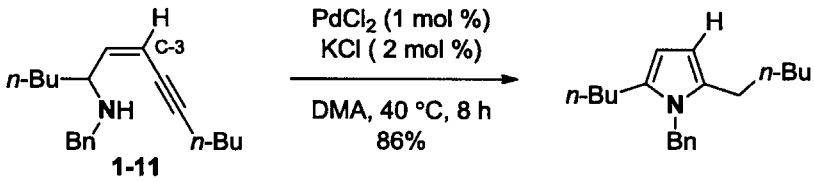


Scheme 1-13. General Lewis acid-catalyzed intramolecular alkyne annulation

In the effort to synthesis pyrroles, Gabriele and co-workers disclosed Cu(II)- and Pd(II)-catalyzed annulation of (*Z*)-(2-en-4-ynyl)amines *via* 5-*exo*-cyclization.[39] In these studies, $CuCl_2$ 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 $PdCl_2$–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).



Scheme 1-14. An example of Cu(II)-catalyzed intramolecular cyclizations of enynamines



Scheme 1-15. An example of Pd(II)-catalyzed intramolecular cyclizations of enynamines

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).[40] The method is quite general for the synthesis of various indole derivatives bearing electron-donating and

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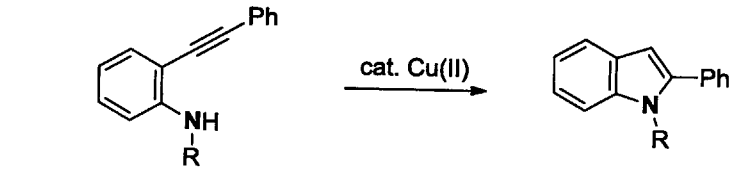
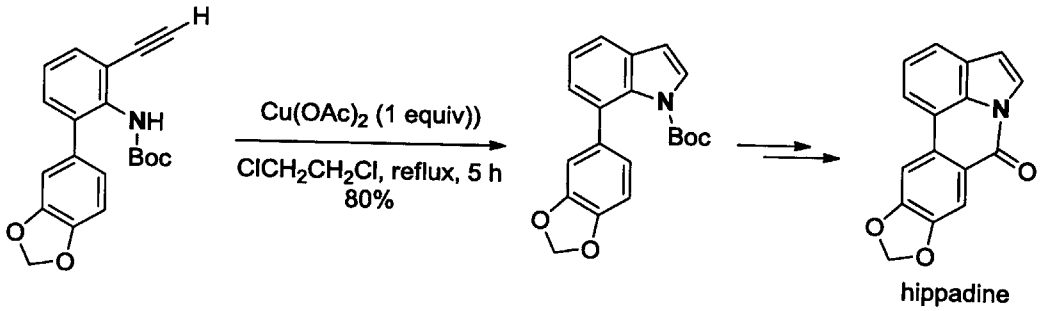
electron-withdrawing substituents on the aromatic ring. By using 1 equiv of $Cu(OAc)_2$ under similar reaction conditions, the indole moiety of hippadine, a natural alkaloid, was constructed in 80% yield (Scheme 1-17).



$Cu(OAc)_2$ (20 mol %), $ClCH_2CH_2Cl$, reflux, 27 h — 98% (R = SO_2Me)

$Cu(OTf)_2$ (10 mol %), $ClCH_2CH_2Cl$, reflux, 28 h — 88% (R = CO_2Et)

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



Scheme 1-17. Total synthesis of hippadine *via* intramolecular cyclization of 2-ethynylaniline derivative

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.[41] Various β- and γ-carbolines have been synthesized using similar reaction conditions (Scheme 1-18).[42] More examples on the reactivity of 2-alkynyl benzaldimines will be explored in Chapter 5.1.4.

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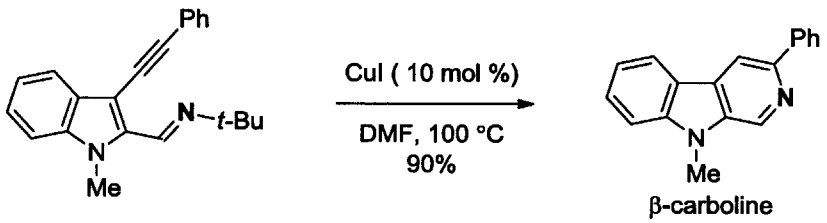
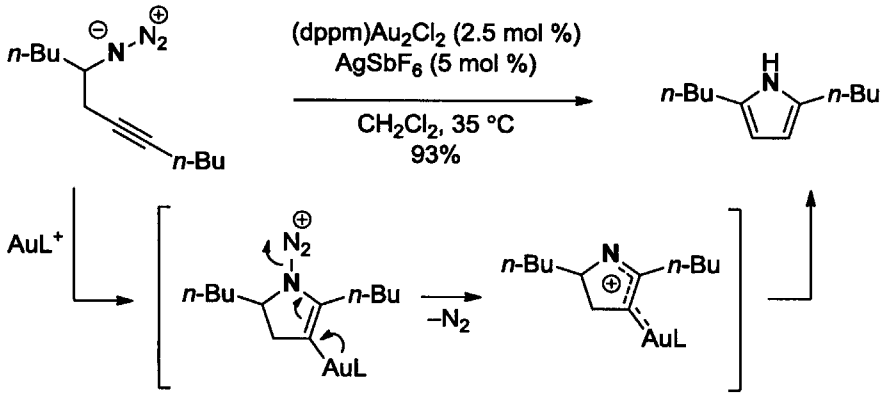


Scheme 1-18. An example of Cu(I)-catalyzed cyclizations of 2-alkynyl benzaldimines to β-carbolines *via* 6-*endo*-cyclization

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).[43] 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.



Scheme 1-19. An example of Au(I)-catalyzed intramolecular acetylenic Schmidt reactions of homopropargyl azides

By slight modification of the substrate, intramolecular hydroaminations of *O*-propargyl-*N*-Boc-hydroxylamines can also be achieved by employing $Au(PPh_3)OTf$ as a catalyst to construct 2,5-dihydroisoxazoles (Scheme 1-20 (a)).[44] In addition, similar methodology has been successfully applied for the synthesis of communesin B as shown in Scheme 1-20 (b).[45]

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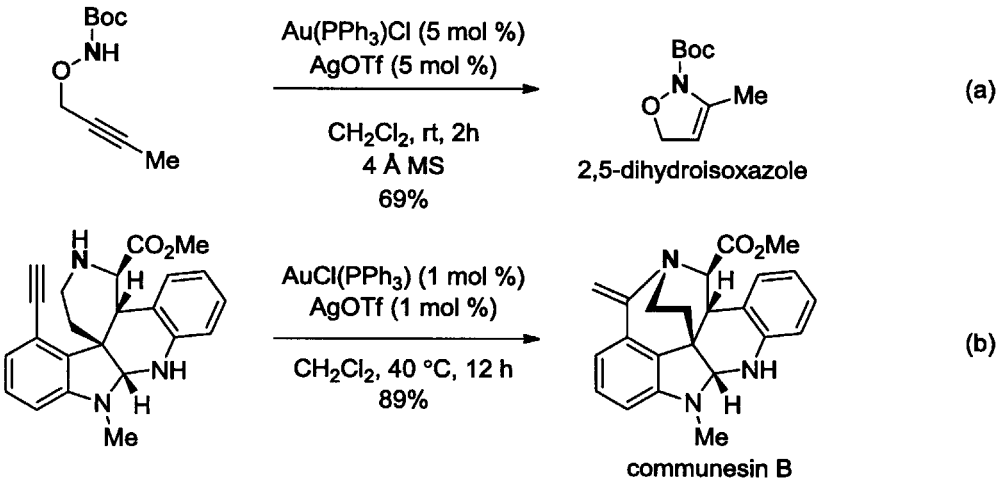

Scheme 1-20. An example of Au(I)-catalyzed intramolecular hydroaminations of alkynes and its application for the synthesis of communesin B

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 $[Cp^*RhCl_2]_2$-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[46] and Chapter 3,[47] respectively). The advantage of the approach is that the N–O bonds of *anti*-isomers of

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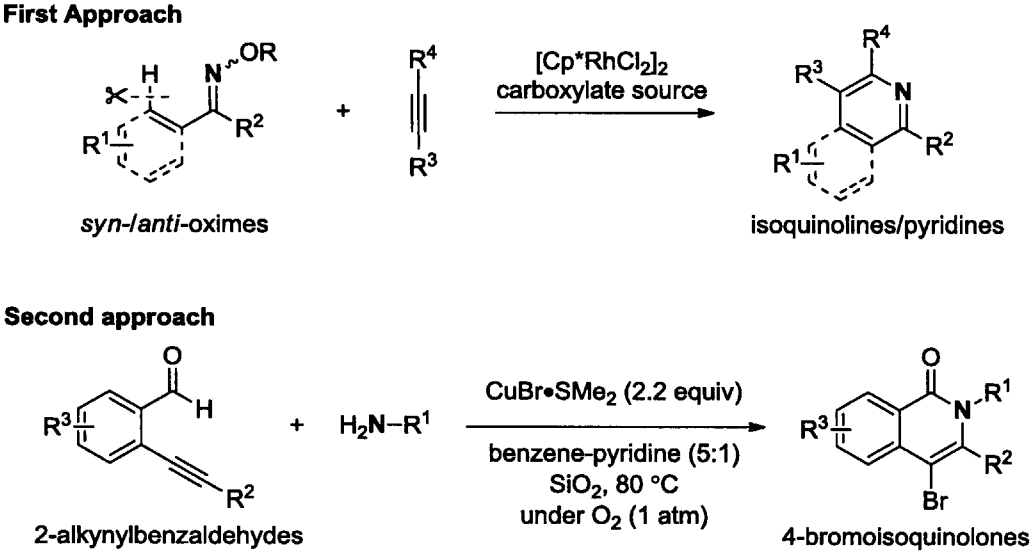
oximes could work as internal oxidants to maintain Rh^{III}–Rh^{I} catalytic cycle in a redox-neutral process.

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]



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

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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 azaheterocyles 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]

2-7 **2-8**

Figure 2-1. Benzopyridines: isoquinoline and quinoline

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-*a*]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]

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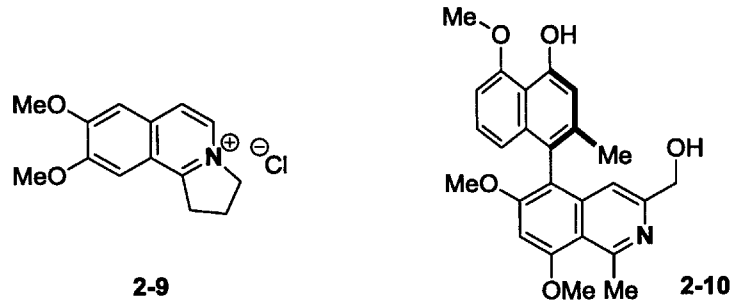
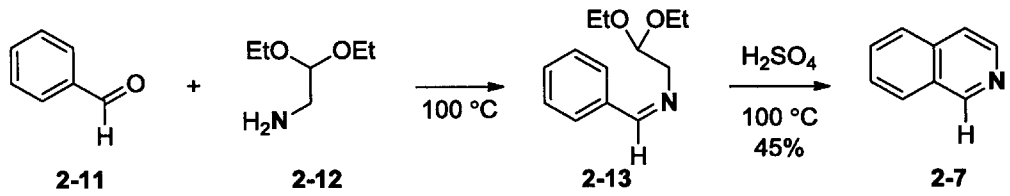


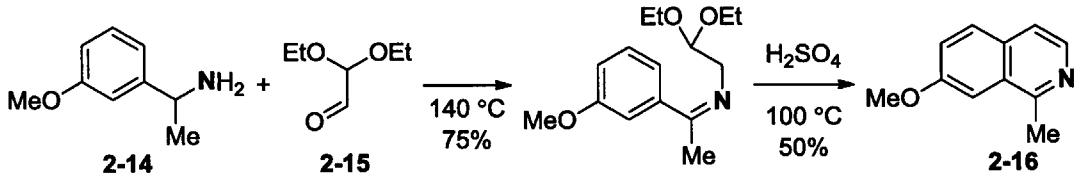
Figure 2-2. Alkaloids with isoquinoline derivatives as structural backbone

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–Fristsch** synthesis[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 C1-substituent, benzylamine **2-14** and glyoxal acetal **2-15** are used for the same transformation (Scheme 2-2).[8]



Scheme 2-1. An example of The Pomeranz-Fristsch synthesis of aryl aldehydes and 2-aminoaldehyde acetals



Scheme 2-2. An example of The Pomeranz-Fristsch synthesis of benzylamines and glyoxal diethyl acetals

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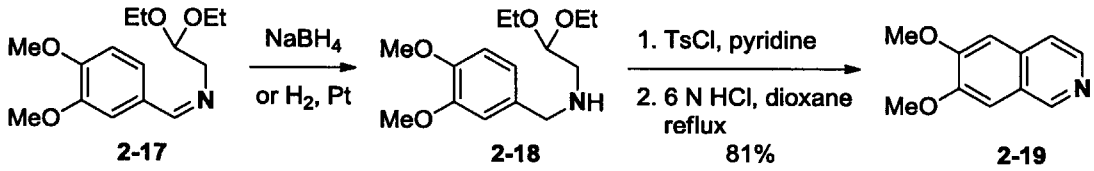
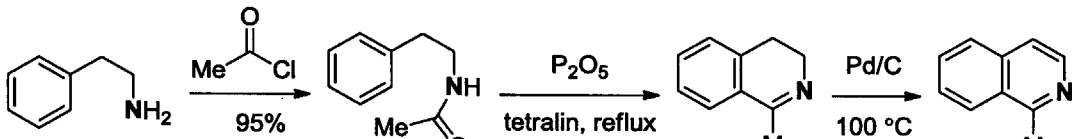
However, decomposition of imines *via* hydrolysis during cyclization step is the major drawback of the **Pomeranz–Fristsch** synthesis and leads to low yields. In order to solve the limitation, imine **2-17** is first converted to amine **2-18** by $NaBH_4$ reduction or hydrogenation, and then protected with a tosyl group on the nitrogen atom. By treatment with acidic conditions, electrophilic cyclization and elimination of toluenesulfinic acid proceed to afford isoquinoline **2-19** in high yield (Scheme 2-3).[9]



2-17 **2-18** **2-19**

Scheme 2-3. An example of the modified Pomeranz-Fristsch synthesis

The **Bischler–Napieralski** isoquinoline synthesis[10] 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 (P_2O_5). By treatment with dehydrogenative conditions, **2-22** is converted to isoquinoline **2-23**.



2-20 **2-21** **2-22** **2-23**

Scheme 2-4. An example of the Bischler-Napieralski isoquinoline synthesis

The **Pictet–Gams** synthesis[11] 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 P_2O_5 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.

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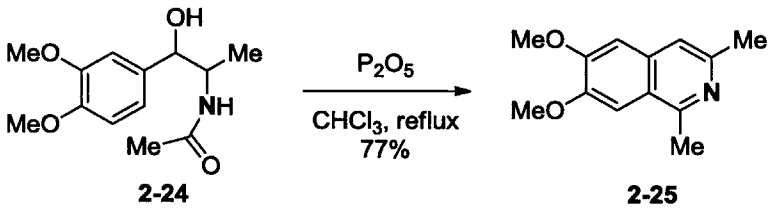
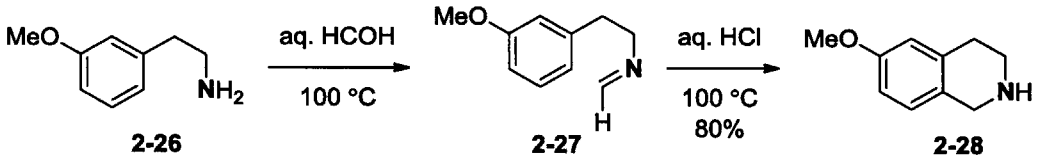


2-24 **2-25**

Scheme 2-5. An example of the Pictet-Gams synthesis

The **Pictet–Spengler** synthesis[12] involves the condensation between 2-phenylethylamine **2-26** and formaldehyde to form imine **2-27** which will then undergo a Mannich-type cyclization by treatment with acid to provide tetrahydroisoquinoline **2-28** (Scheme 2-6). The electrophilic cyclization of imine **2-27** normally required a strong donating substituent on the benzene ring for an efficient ring closure.



2-26 **2-27** **2-28**

Scheme 2-6. An example of the Pictet-Spengler synthesis

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).[13] As shown in the proposed catalytic cycle, the transformation involves initial oxidative addition of the C–I bond of *o*-iodobenzaldimine **2-29** to Pd(0) to produce aryl-Pd(II) intermediate **A**, then followed by alkyne insertion to generate vinyl-Pd(II)

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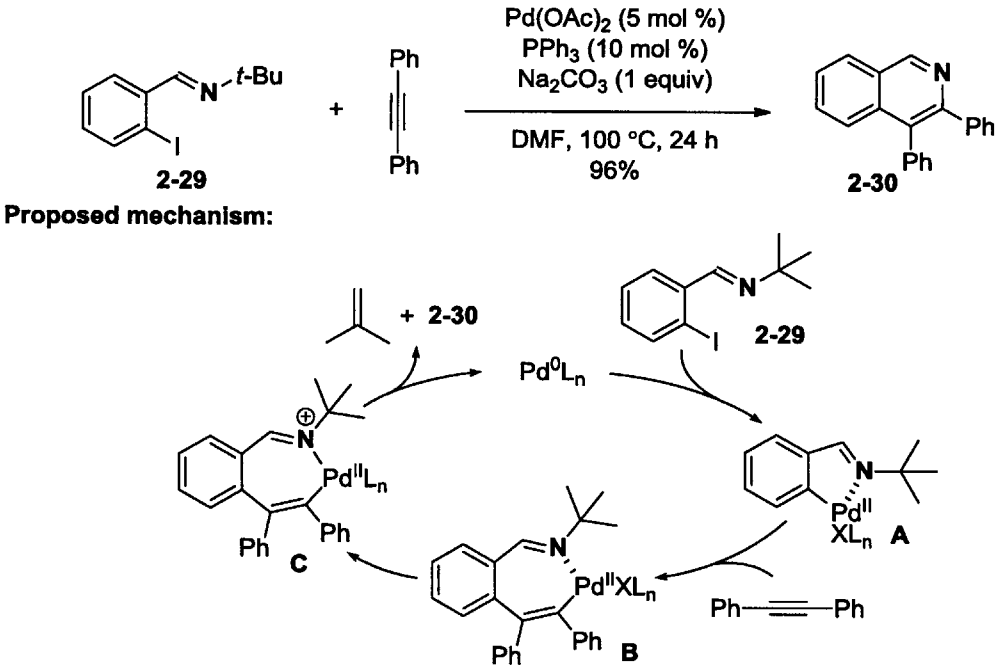
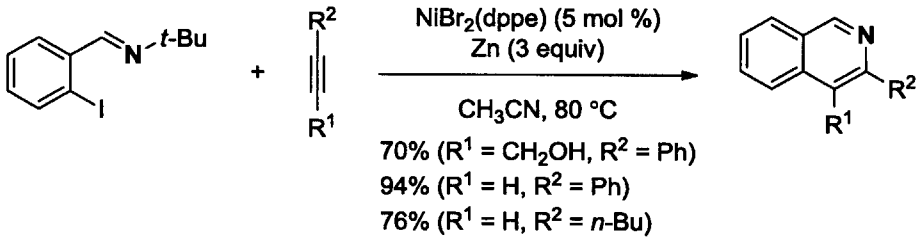
intermediate **B**. Further intramolecular transformation of the intermediate **B** leads to 7-membered palladacyclic ammonium salt **C**. The subsequent C–N bond reductive elimination completes the catalytic cycle to provide isoquinoline **2-30** along with regeneration of Pd(0).



Scheme 2-7. An example of Pd(II)-catalyzed annulation 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).[14] 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.



Scheme 2-8. Ni(II)-catalyzed annulation reactions for the synthesis of isoquinolines

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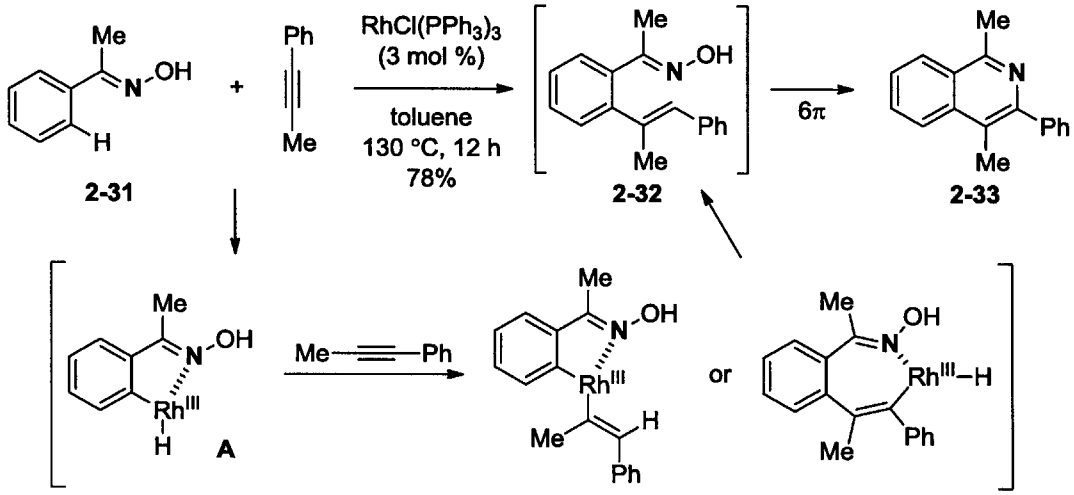
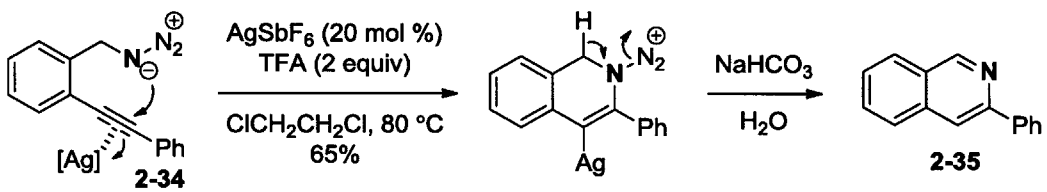
On the other hand, Cheng and co-workers also reported Rh(I)-catalyzed synthesis of isoquinolines from ketoximes and alkynes *via ortho* C–H bond activation (Scheme 2-9).[15] The proposed mechanism involves *ortho* C–H oxidative addition to Rh(I) assisted by chelation of the nitrogen atom of ketoxime **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**.



Scheme 2-9. An example of Rh(I)-catalyzed synthesis of isoquinolines from ketoximes and alkynes

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).[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.



Scheme 2-10. An example of Ag(I)-catalyzed cyclizations of 2-alkynyl benzyl azides

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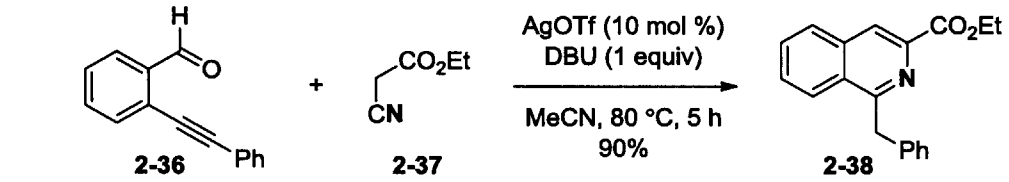
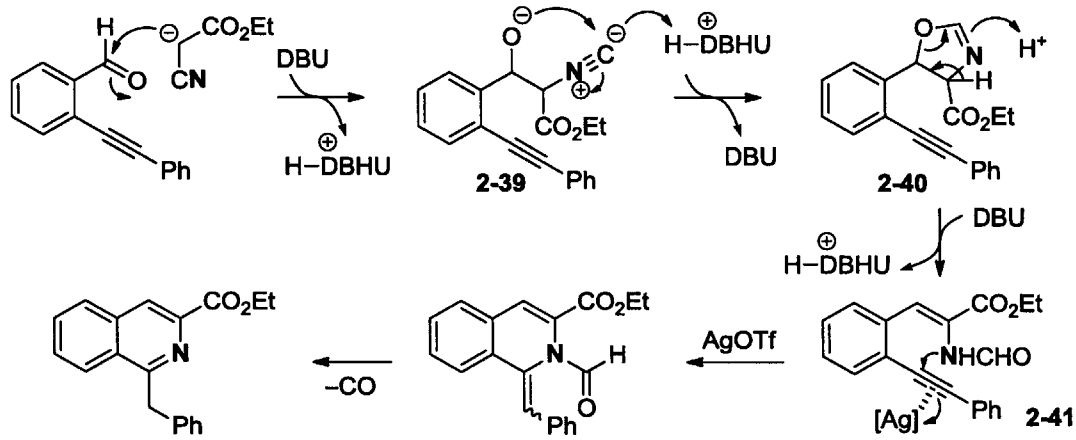
Recently, Wu and co-workers reported an unprecedented reaction between 2-alkynylbenzaldehyde **2-36** with isocyanoacetates **2-37** to give isoquinolines **2-38** using AgOTf as a catalyst and DBU as a base.[17] They proposed the mechanism as follow: (1) isocyanoacetate **2-37** undergoes nucleophilic 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**;[18] (3) **2-41** undergoes 6-*exo*-cyclization and decarbonylation to furnish isoquinoline **2-38** (Scheme 2-11).[19]



Proposed Mechanism:



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 $[Cp^*RhCl_2]_2$ 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.[20]

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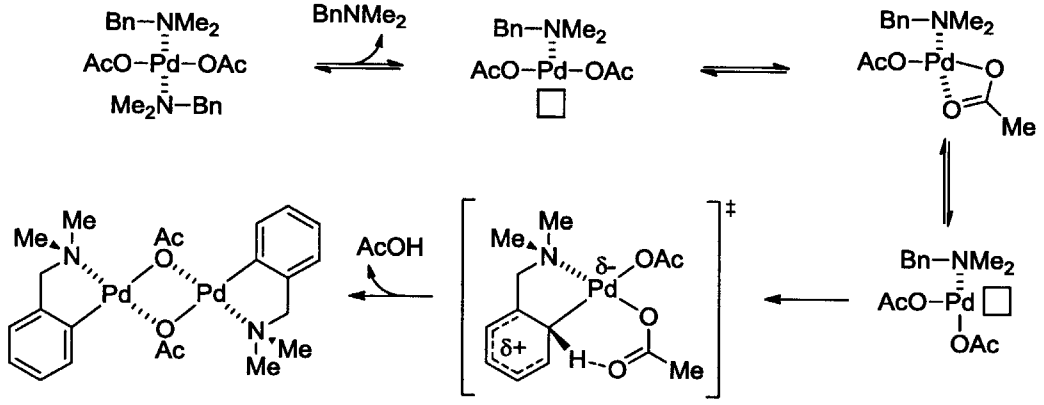
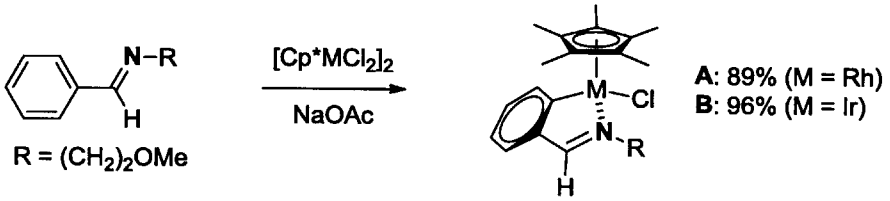
Many mechanisms for the C–H bond cleavage have been proposed and studied based on palladium cyclometallation.[21] In one of the early detailed mechanistic studies on the *ortho*-palladation of *N,N*-dimethylbenzylamine (DMBA-H) using $Pd(OAc)_2$ reported by Ryabov and co-workers (the proposed mechanism 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.[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.*"[23]



Scheme 2-12. Mechanism of cyclometallation of DMBA-H with $Pd(OAc)_2$

In general, these studies showed that $Pd(OAc)_2$ 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.[24] In fact, the addition of an acetate source can induce cyclometalation in several palladium catalytic systems.[25]



Scheme 2-13. Cyclometallation of $[Cp^*MCl_2]_2$ and imine *via ortho* C–H activation

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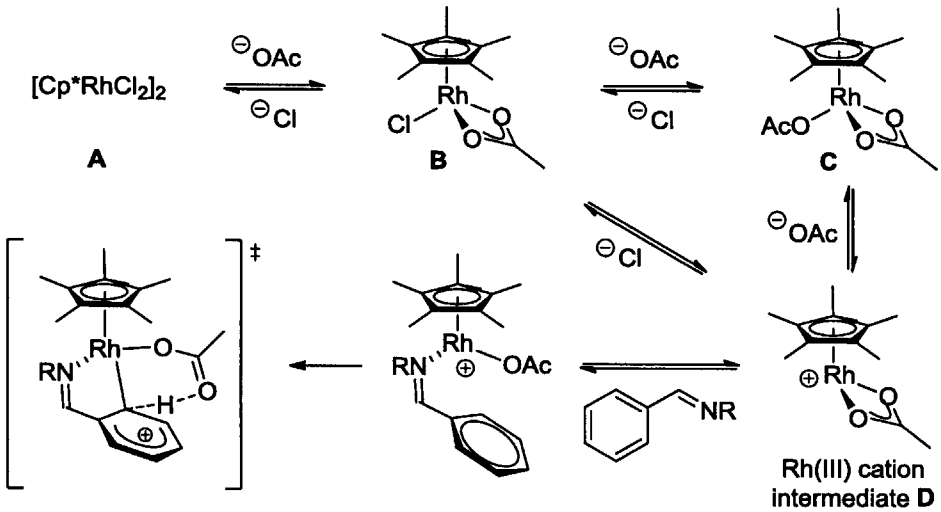
In addition to acetate-promoted cyclopalladation, the cyclometallations of phenyl oxazolones can also be achieved using $[Cp^*IrCl_2]_2$ and NaOAc (the acetate source) *via* a similar mechanism.[26] In that context, Davies and co-workers began to investigate the use of NaOAc to promote cyclometallations of nitrogen-containing ligands in the preparation of Cp*Rh(III) and Cp*Ir(III) complexes *via* C–H bond activation. Indeed, the reaction of $[Cp^*RhCl_2]_2$ or $[Cp^*IrCl_2]_2$ 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).[27]



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).[28] 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

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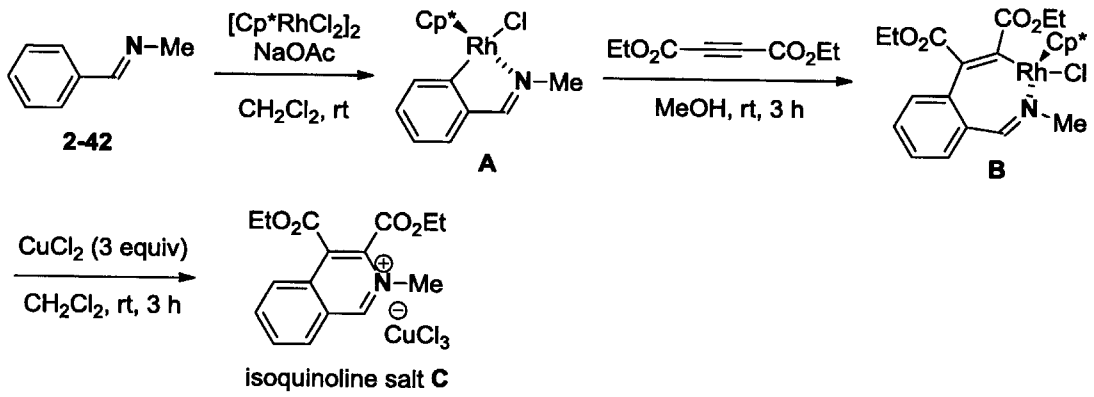
activation. These findings are in agreement with Ryabov's proposal on the mechanism of cyclometallation of DMBA-H with $Pd(OAc)_2$ as shown in Scheme 2-12.

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).[29] The studies showed that *ortho* C–H bond activation, alkyne insertion, and subsequent C–N bond formation can be realized by utilizing $[Cp^*RhCl_2]_2$, NaOAc and a suitable nitrogen-containing directing group.



Scheme 2-15. Three steps formation of isoquinoline salt

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).[30] The reaction is initiated by the coordination of carboxyl oxygen of benzoic acid (**2-43**) to the Cp*Rh(III)

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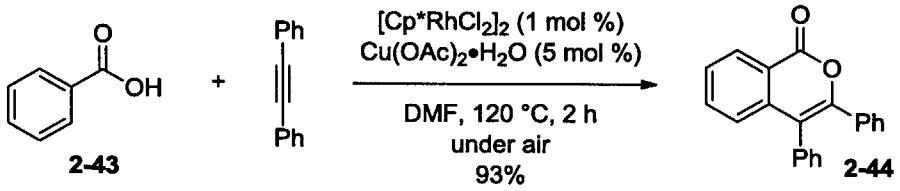
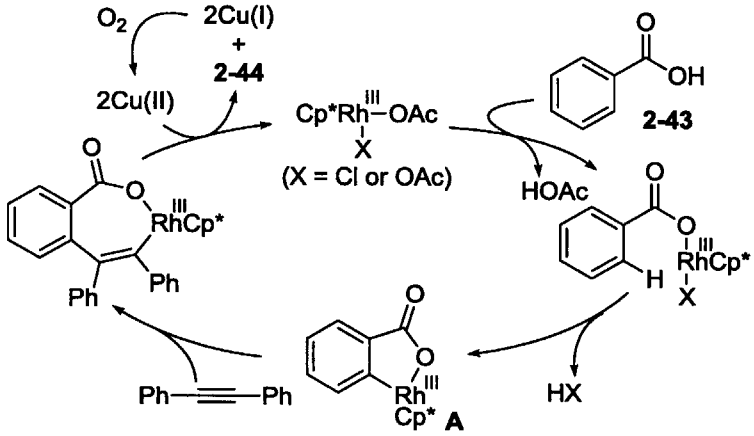
catalyst, and followed by *ortho* C–H bond activation to generate 5-membered rhodacycle **A**. The subsequent alkyne insertion and reductive elimination release isocoumarin **2-44**. The resulting Cp*Rh(I) species is oxidized by Cu(II) to regenerate active Cp*Rh(III) species and Cu(I). In this case, 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.

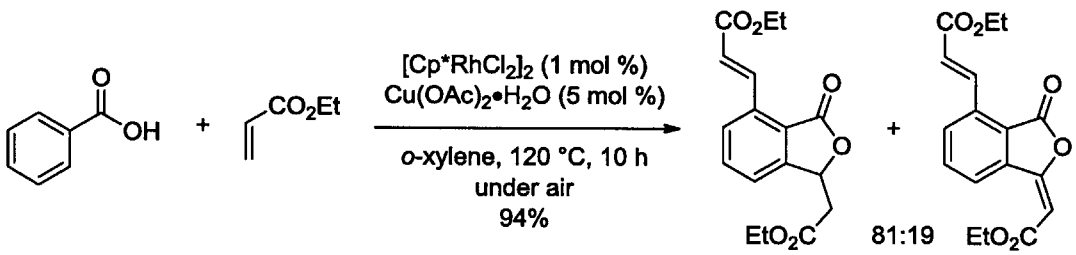


Proposed Mechanism:



Scheme 2-16. An example of Rh(III)-catalyzed synthesis of isocoumarins from benzoic acids and alkynes

Under similar conditions, couplings of benzoic acids with acrylates takes place to provide 7-vinylphthalides *via* sequential divinylation and cyclization (Scheme 2-17).[31]



Scheme 2-17. An example of Rh(III)-catalyzed synthesis of isocoumarins from benzoic acids and acrylates

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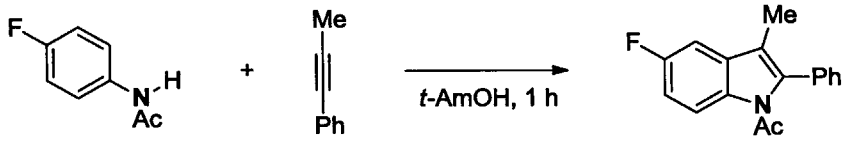
In 2008, Fagnou and co-workers reported the oxidative couplings of *N*-acetyl anilines and internal alkynes for the synthesis of highly functionalized indoles by using $[Cp^*RhCl_2]_2$ as the catalyst (Condition A, Scheme 2-18).[32] The reaction is more efficient by the addition of AgOTf, which sequesters Cl ligands on $[Cp^*RhCl_2]_2$; 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 $[Cp^*Rh(MeCN)_3][SbF_6]_2$ under milder reaction conditions with molecular oxygen as the terminal oxidant (Condition B, Scheme 2-18).[33]



Condition A: $[Cp^*RhCl_2]_2$ (2.5 mol %), $AgSbF_6$ (10 mol %) 47%
$Cu(OAc)_2 \cdot H_2O$ (2.1 eq), 120 °C.

Condition B: $[Cp^*Rh(MeCN)_3][SbF_6]_2$ (5 mol %) 74%
$Cu(OAc)_2 \cdot H_2O$ (20 mol %), 60 °C, O_2 (1 atm).

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 $[Cp^*RhCl_2]_2$ 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 Cp*Rh(I) and hydrolysis.

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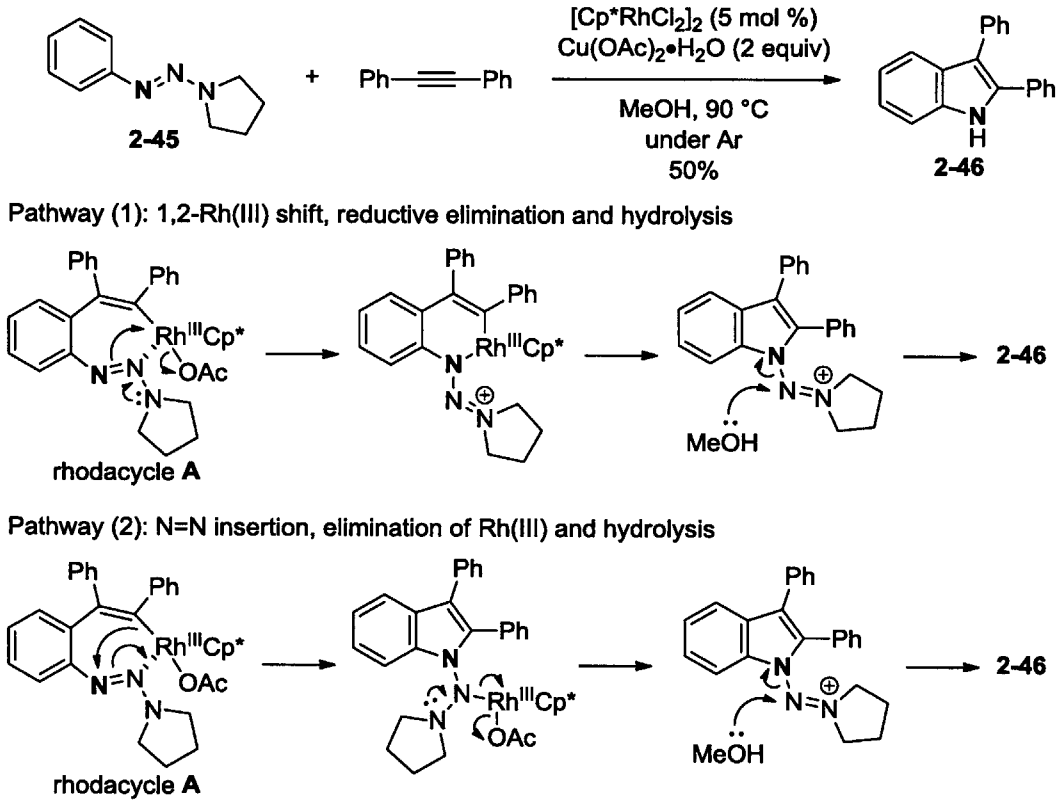

Scheme 2-19. An example of Rh(III)-catalyzed synthesis of indoles from triazenes and alkynes and its possible mechanism

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 $[Cp^*RhCl_2]_2$ as the catalyst.[35] In the case of benzylidene 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 $[Cp^*RhCl_2]_2$-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).[36] A typical reaction proceeds through an initial N–H metalation of the amide, and followed by

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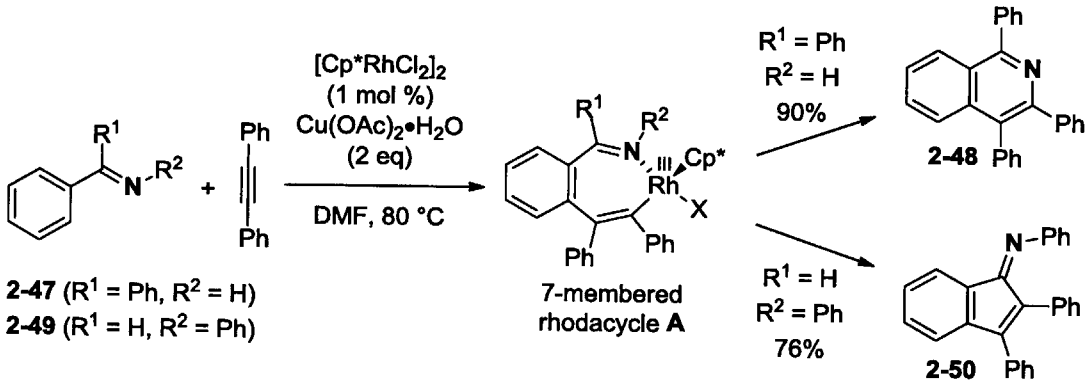
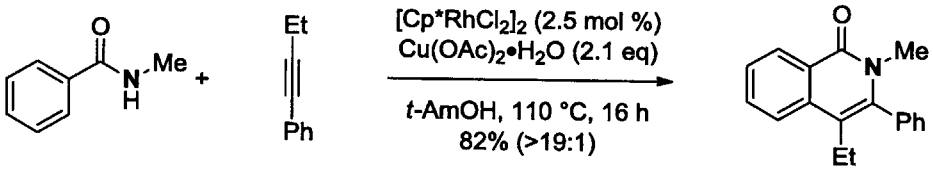
ortho C–H bond activation, which is the turnover-limiting step. High regioselectivity is observed for unsymmetrical alkynes.

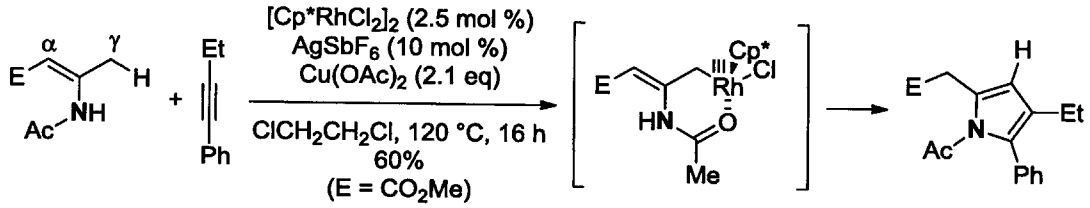


Scheme 2-20. Rh(III)-catalyzed diverse synthesis of isoquinoline and indenone imine



Scheme 2-21. An example of Rh(III)-catalyzed oxidative cycloadditions of benzamides and alkynes

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.



Scheme 2-22. An example of Rh(III)-catalyzed allylic sp^3 C–H functionalizations of enamines

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,

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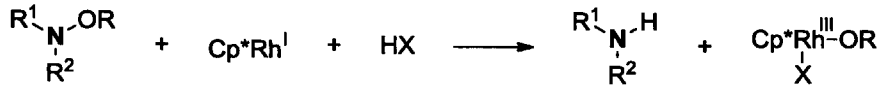
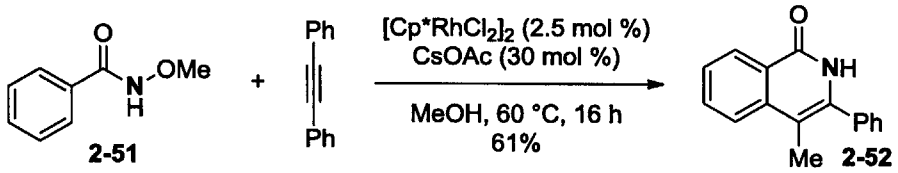
such strategies normally require an external oxidant to encounter the change in oxidation state from Cp*Rh(III) to Cp*Rh(I) due to C–N or C–O bond reductive elimination.

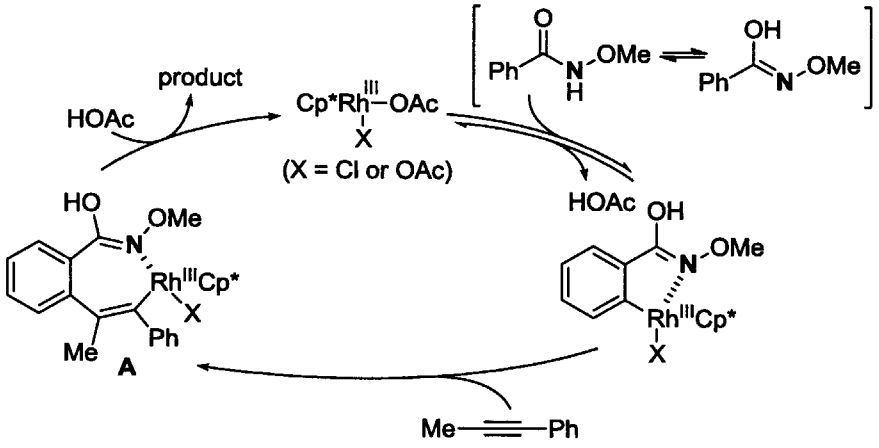


Scheme 2-23. Redox neutral process between N–O bond and Rh(I)

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.[38] 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).



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 $[Cp^*RhCl_2]_2$ and CsOAc, the cycloaddition of benzhydroxamic acid **2-51** and diphenylacetylene is achieved to furnish isoquinolone **2-52** in high yield (Scheme 2-24).[39] The N–OMe bond is utilized as an internal oxidant for regeneration of Cp*Rh(III) to

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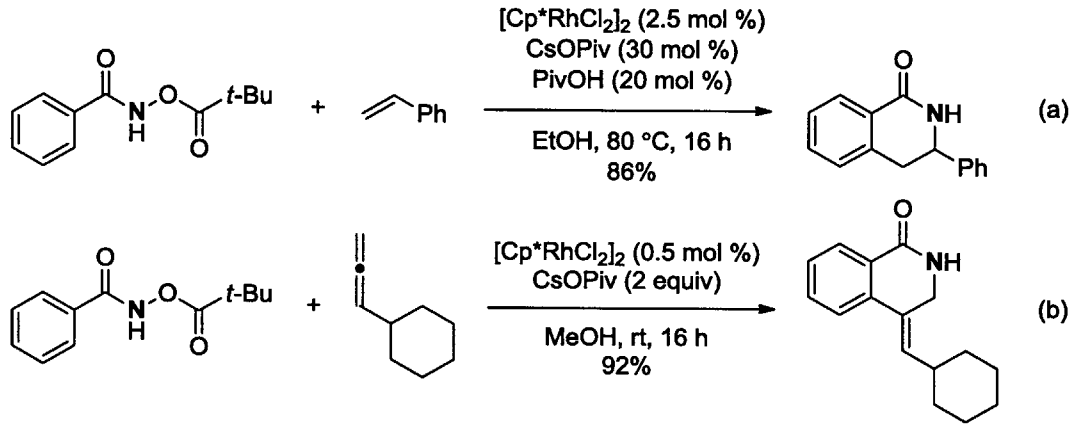
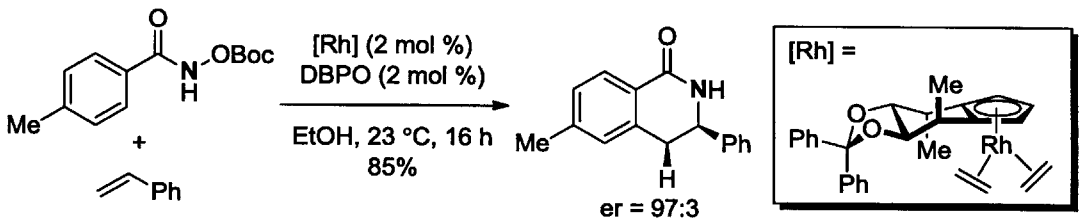
avoid the use of external oxidant. The first step of the mechanism involves a reversible *ortho* C–H bond activation, which is followed by alkyne insertion to generate 7-membered rhodacycle **A**. At this point, C–N bond formation and N–OMe bond cleavage occur to provide isoquinolone **2-52** and regenerate 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 % $[Cp^*RhCl_2]_2$.[40] Similar approach can be applied for the coupling reactions of benzhydroxamic acid derivatives bearing an N–OPiv bond and alkenes[41] or allenes[42] 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 tetrahydroisoquinolinones 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



Scheme 2-26. An example of Rh(III)-catalyzed enantioselective synthesis of tetrahydroisoquinolinones

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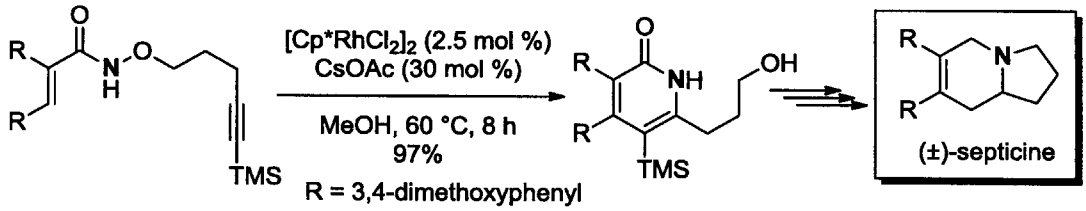
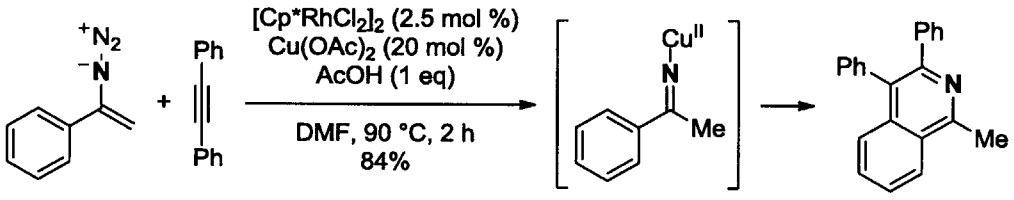
By applying Rh(III)-catalyzed N–O bond cleavage redox-neutral process in an intramolecular manner, Park and co-workers developed Rh(III)-catalyzed intramolecular reaction of alkyne-tethered hydroxamic esters for the synthesis of isoquinolines with C-3 substituent bearing alcohol moiety. [44] In this 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

In the effort to achieve an overall redox-neutral process, our group developed a redox $[Cp^*RhCl_2]_2$–$Cu(OAc)_2$ bimetallic catalytic system such that the coupling of α-aryl vinyl azides and internal alkynes proceeded to form highly substituted isoquinolines (Scheme 2-28).[45] 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 $[Cp^*RhCl_2]_2$-$Cu(OAc)_2$ bimetallic catalytic system

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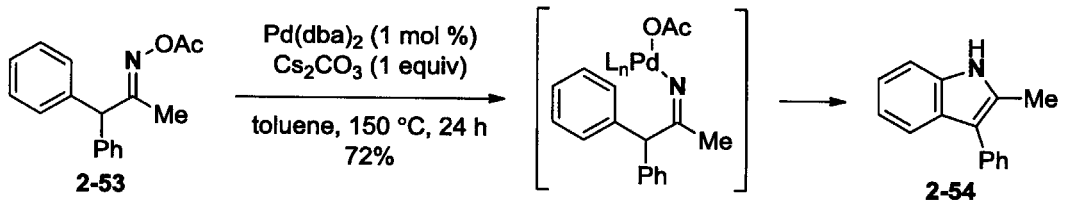
2.1.5 New redox-neutral approach with oximes

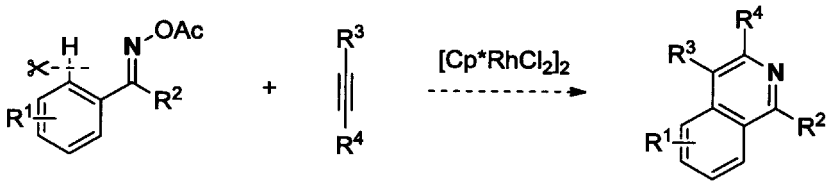
As discussed previously, the use of benzyhydroxamic acid derivatives (the attachment of an alkoxy or ester groups on the nitrogen of benzamides) as the precursor for the synthesis of isoquinolones has been successfully achieved under redox-neutral conditions where the N–O bond of benzyhydroxamic acid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



Scheme 2-29. An example of Pd(0)-catalyzed C–H amination of *O*-acetyl oximes

Inspired by Hartwig's work, we proposed a redox-neutral process which involves the synthesis of isoquinolines from *O*-acetyl oximes and alkynes using $[Cp^*RhCl_2]_2$ 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.



Scheme 2-30. Proposed reaction of *O*-acetyl oximes and alkynes

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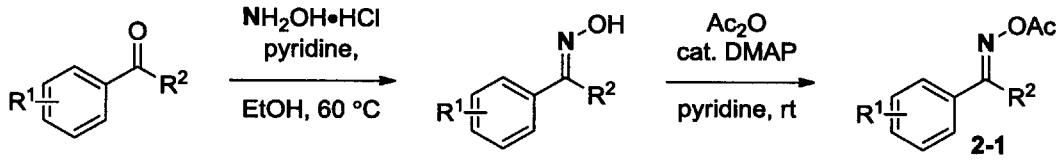
2.2 Results and discussion

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

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 $[Cp^*RhCl_2]_2$ 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 $[Cp^*RhCl_2]_2$ 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).

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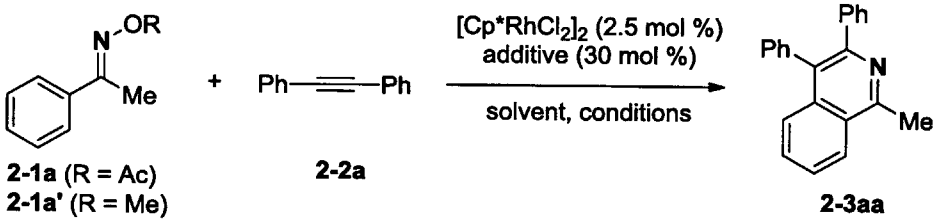
By changing R-substituent from acetyl to methyl protecting group, reaction became sluggish and affording isoquinoline **2-3aa** in 13% yield with 64% recovery of *O*-methyl oxime **2-1a'** even after 19 h (Table 2-1, entry 6). This indicates that the leaving group reactivity (as –OR group) is essential for isoquinoline formation. It is worth to note that Rh(I) catalysts such as Wilkinson's catalyst, $RhCl(PPh_3)_3$ did not provide any product for the present process.

Table 2-1. Optimization of reaction conditions[a]



2-1a (R = Ac)
2-1a' (R = Me)

2-2a

2-3aa

entry	oxime	additive	solvent	conditions	yield of **2-3aa** / %[b]
1	**2-1a**	none	MeOH	60 °C, 7 h	0[c]
2	**2-1a**	NaOAc	MeOH	60 °C, 6 h	82
3	**2-1a**	CsOAc	MeOH	60 °C, 4 h	80
4	**2-1a**	CsOAc	*t*-BuOH	80 °C, 7 h	14[c]
5	**2-1a**	CsOAc	DMF	80 °C, 23 h	4[c]
6	**2-1a'**	NaOAc	MeOH	60 °C, 19 h	13[d]

[a] Reactions were carried out on the scale of 0.3 mmol of **2-1a** and **2-2a** in MeOH (0.2 M) under N_2 atmosphere. [b] Isolated yield. [c] ^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 $[Cp^*RhCl_2]_2$–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).

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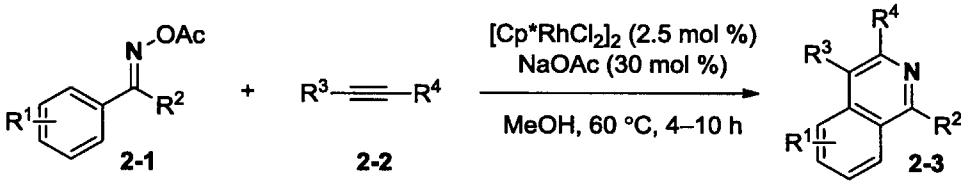
Table 2-2. Synthesis of Isoquinolines from aryl ketone *O*-acetyl oximes and alkynes[a]



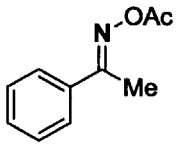
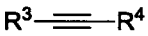
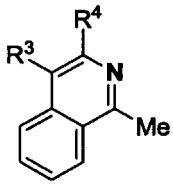
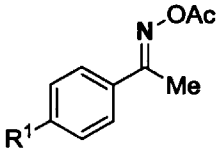
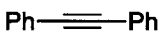
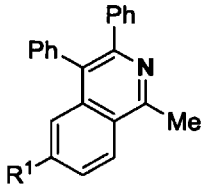
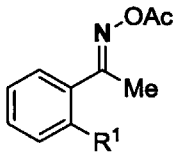
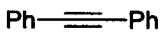
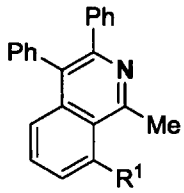
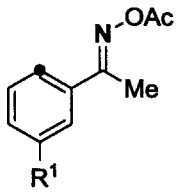
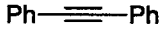
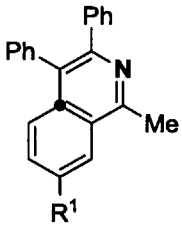
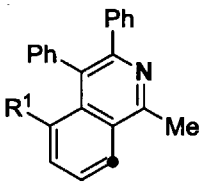
entry	oxime **2-1**	alkyne **2-2**	isoquinoline **2-3** / yield[b]	
				
1	**2-1a**	**2-2b** (R^3 = Me, R^4 = Ph)	**2-3ab**: 72%	
2	**2-1a**	**2-2c** (R^3 = CH_2OH, R^4 = Ph)	**2-3ac**: 42% (9:1)[c,d]	
3	**2-1a**	**2-2d** (R^3 = CH_2OTBS, R^4 = Ph)	**2-3ad**: 65% (14:1)[d]	
4	**2-1a**	**2-2e** (R^3 = *n*-Pr, R^4 = *n*-Pr)	**2-3ae**: 87%	
5	**2-1a**	**2-2f** (R^3 = R^4 = CH_2OTBS)	**2-3af**: 73%	
				
6	**2-1b** (R^1 = OMe)	**2-2a**	**2-3ba**: 87%	
7	**2-1c** (R^1 = Ph)	**2-2a**	**2-3ca**: 92%	
8	**2-1d** (R^1 = Br)	**2-2a**	**2-3da**: 94%	
9	**2-1e** (R^1 = CF_3)	**2-2a**	**2-3ea**: 89%	
				
10	**2-1f** (R^1 = OMe)	**2-2a**	**2-3fa**: 89%	
11	**2-1g** (R^1 = Br)	**2-2a**	**2-3ga**: 82%	
				
12	**2-1h** (R^1 = OMe)	**2-2a**	**2-3ha**: 58%	**2-3ha'**: 31%
13	**2-1i** (R^1 = Br)	**2-2a**	**2-3ia**: 67%	**2-3ia'**: 25%

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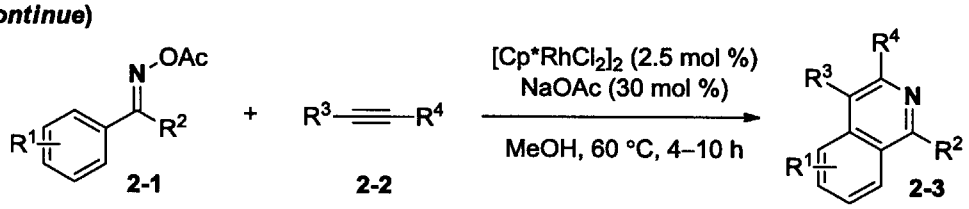
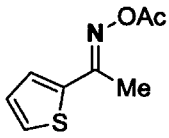
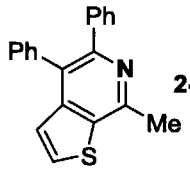
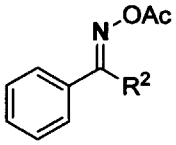
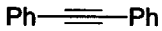
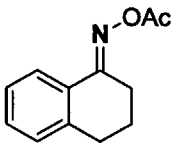
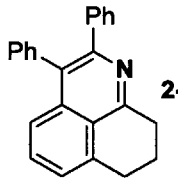
Table 2-2. Synthesis of isoquinolines from aryl ketone *O*-acetyl oximes and alkynes[a] (*continue*)



entry	oxime **2-1**	alkyne **2-2**	isoquinoline **2-3** / yield[b]
14	 **2-1j**	**2-2a**	 **2-3ja**: 69%
			
15	**2-1k** (R^2 = Ph)	**2-2a**	**2-3ka**: 98%
16	**2-1l** (R^2 = *trans*-CH=CHPh)	**2-2a**	**2-3la**: 95%
17	**2-1m** (R^2 = CO_2Me)	**2-2a**	**2-3ma**: 91%
18	 **2-1n**	**2-2a**	 **2-3na**: 76%

[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 ^1H 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).

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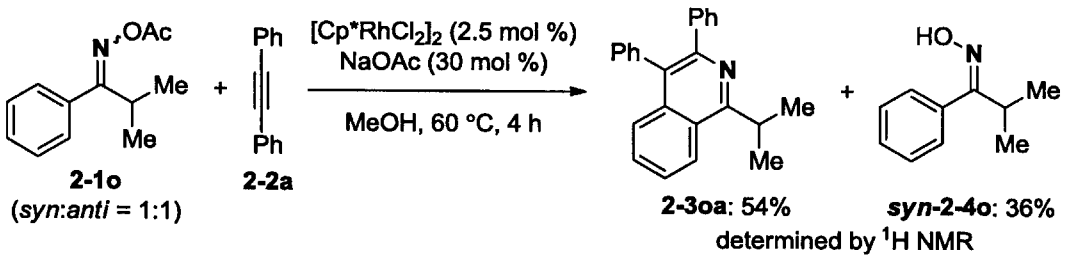
Generally, both electron-donating and electron-withdrawing groups could be introduced as R^1-substituent on the benzene ring of acetophenone *O*-acetyl oximes **2-1**. It is worth to note that even a C–Br bond or a C–CF_3 bond on benzene could be tolerated under the reaction conditions (Table 2-2, entries 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 **2-1o** (*syn*:*anti* = 1:1) which possesses a bulky R^2-substituent (isopropyl group) under the standard conditions, the desired isoquinoline **2-3oa** was formed in 54% along with recovery of *syn*-isobutyrophenone oxime (***syn*-2-4o**) in 36% yield *via* deacetylation (Scheme 2-32). The result might suggest that only the *anti*-isomer is reacted.



2-1o (*syn*:*anti* = 1:1) + **2-2a** → **2-3oa**: 54% + ***syn*-2-4o**: 36% determined by ^{1}H NMR

Scheme 2-32. Limitation of Rh(III)-catalyzed synthesis of isoquinoline from mixture of *syn*- and *anti*-ketoxime

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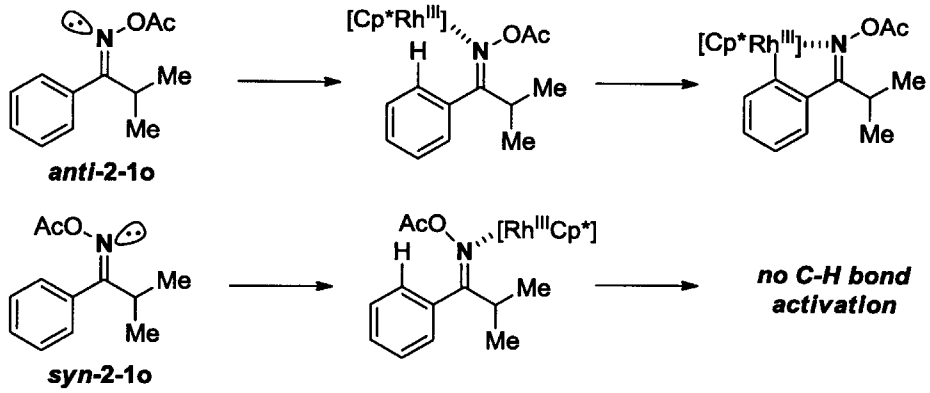
The phenomenon could be attributed to the stereochemical requirement of oxime where only the *anti*-isomer of **2-1o** provides the correct geometry to direct the Cp*Rh(III) center in close proximity with *ortho* aryl C–H bond for C–H rhodation prior to the next transformation (Scheme 2-33). In contrast, 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]

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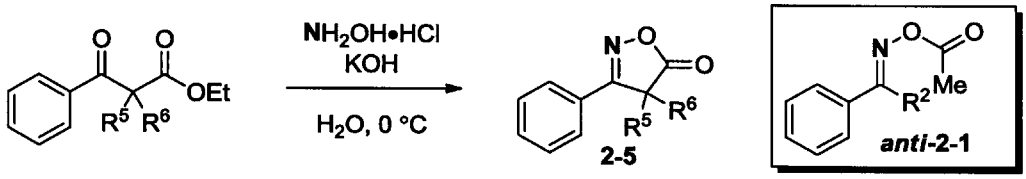
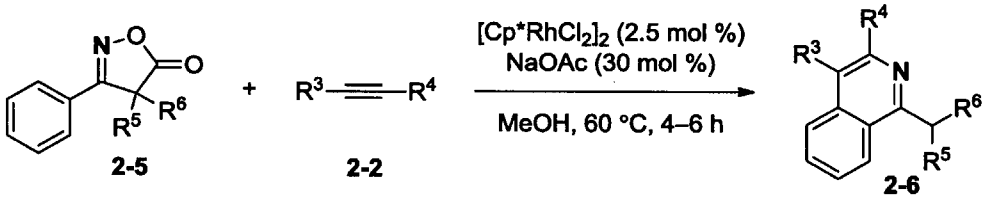
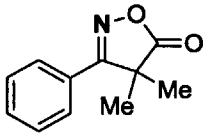
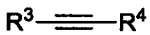
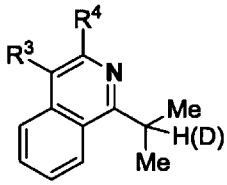
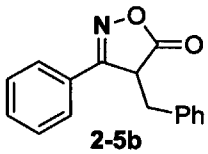
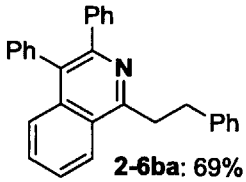
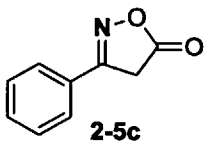
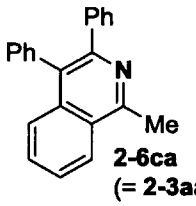


Scheme 2-34. *anti*-*O*-acetyl oximes 2-1 and isoxazol-5-ones 2-5

Fortunately, when 3-phenylisoxazol-5-one **2-5a** and diphenylacetylene (**2-2a**) was subjected to the present reaction conditions (2.5 mol % $[Cp^*RhCl_2]_2$, 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[a]



entry	isoxazolone **2-5**	alkyne **2-2**	isoquinoline **2-6** / yield[b]
			
1	**2-5a**	**2-2a** (R^3 = R^4 = Ph)	**2-6aa** (= **2-3oa**): 91%
2	**2-5a**	**2-2a** (R^3 = R^4 = Ph)	**2-6aa-*d***: 94% (93% D)[c]
3	**2-5a**	**2-2b** (R^3 = Me, R^4 = Ph)	**2-6ab**: 56%[d]
4	**2-5a**	**2-2e** (R^3 = *n*-Pr, R^4 = *n*-Pr)	**2-6ae**: 82%
5	 **2-5b**	**2-2a**	 **2-6ba**: 69%
6	 **2-5c**	**2-2a**	 **2-6ca** (= **2-3aa**): 72%

[a] 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 N_2 atmosphere. [b] Isolated yield. [c] The reaction was performed in MeOD. [d] The reaction was conducted for 28 h and **2-5a** was recovered in 38% yield.

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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 **2-6ca** (=**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

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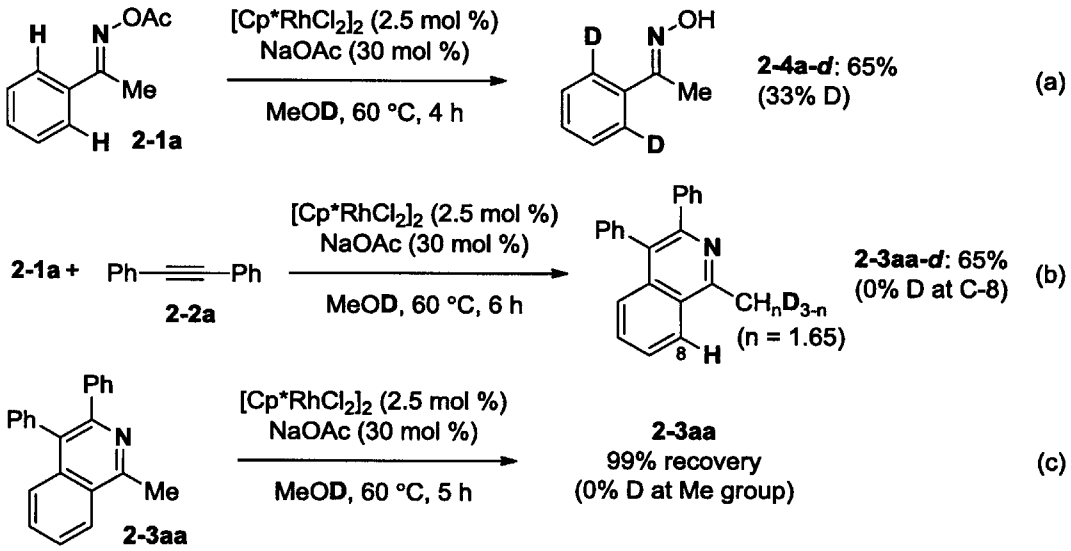
isoquinoline **2-3aa** with no deuteration on methyl group (Scheme 2-35 (c)). These observations indicated that deuterium incorporation into methyl group of isoquinoline **2-3aa** may occur during the catalytic ring formation process.



Scheme 2-35. Investigation of reaction mechanism–1

Subsequently, *ortho*-alkenyloxime **2-1p** was synthesized from the corresponding *ortho*-alkenylketone, which was synthesized according to the reported procedure,[48] by treatment with NH_2OH•HCl and pyridine in EtOH at 60 °C. **2-1p** was employed to investigate the possibility of 6π-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*-alkenyloxime **2-1p** was treated with alkyne **2-2e**; only isoquinoline **2-3pe** was formed as the only cyclized product (Scheme 2-36 (b)). Accordingly, 6π-electrocyclization is most likely ruled out from the possible reaction pathways.

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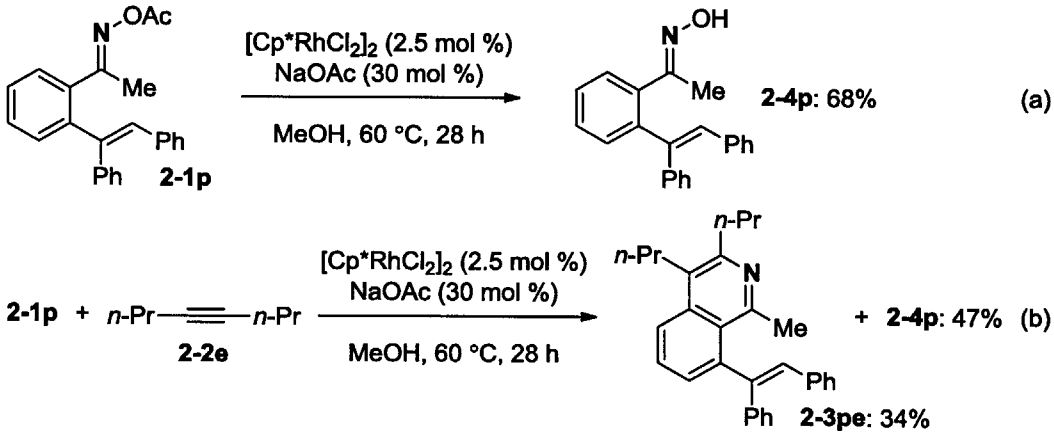

Scheme 2-36. Investigation of reaction mechanism–2

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**[28] 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 α-protons with enough acidity for deuterium/hydrogen exchange in the reaction course.[51] Furthermore, the deuterium/hydrogen exchange is possible only if the extrusion of Cp*Rh(III) species from intermediate **B** is the rate-determining step.

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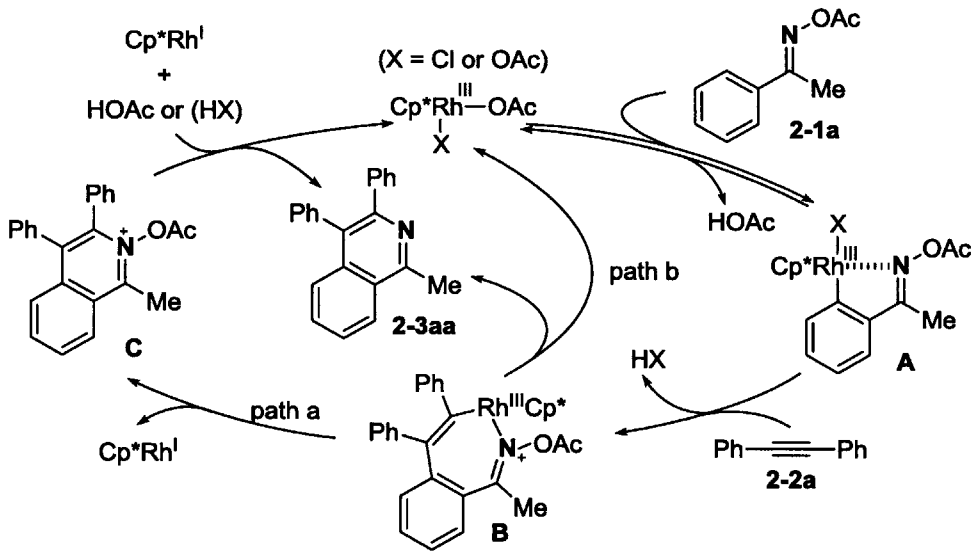
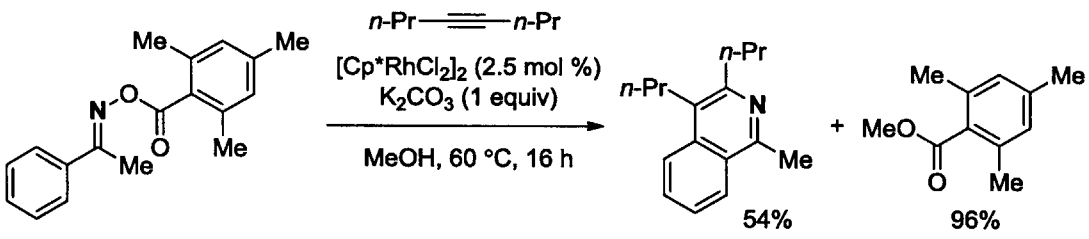


Scheme 2-37. Proposed catalytic cycle

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.[40] 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.



Scheme 2-38. Observation of a methyl mesitoate as side-product

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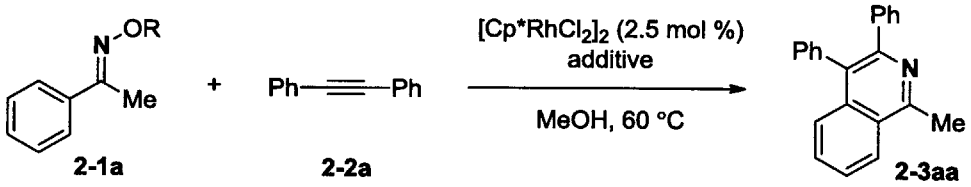
However, we believed that the basic methanolysis of *O*-acetyl oximes under our mild basic conditions (with NaOAc) is unfavorable compared to the strongly basic conditions (with K_2CO_3) developed by Fagnou and Guimond. In addition, shorter reaction time of 6 h observed in the case of NaOAc revealed 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]



R	additive	time	yield
Ac	NaOAc (30 mol %)	6 h	82% (Isolated yield)
H	K_2CO_3 (1 equiv)	16 h	80% (^{1}H NMR yield)

Scheme 2-39. Comparison of the effect of additive

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**.

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2.3 Conclusion

A method of isoquinoline synthesis from aryl ketone *O*-acyloxime derivatives and internal alkynes has been developed using $[Cp^*RhCl_2]_2$–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 rhodacyclic 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 $[Cp^*RhCl_2]_2$–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).

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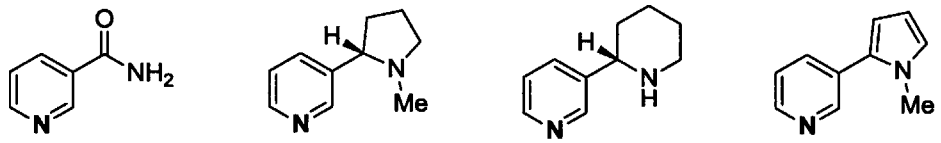
Chapter 3 Rhodium(III)-Catalyzed Synthesis of Pyridines from α,β-Unsaturated Ketoximes and Internal Alkynes

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.



3-5 **3-6** **3-7** **3-8**

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

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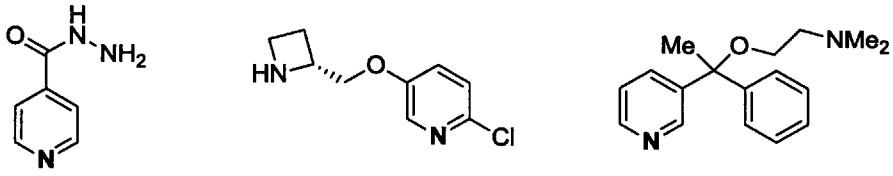
used for short-term treatment of insomnia and also symptom of soft allergy and common cold.[4]



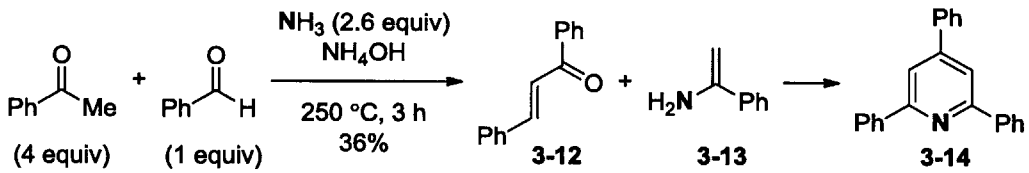
3-9 3-10 3-11

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 α,β-unsaturated ketone **3-12**. Michael addition of enamine **3-13** to α,β-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.



(4 equiv) (1 equiv) 250 °C, 3 h 36% 3-12 3-13 3-14

Scheme 3-1. An example of the Chichibabin pyridine synthesis

The first synthetically useful pyridine synthesis was discovered by Arthur Rudolf Hantzsch in 1881.[7] The **Hantzsch** pyridine synthesis is a multi-component organic

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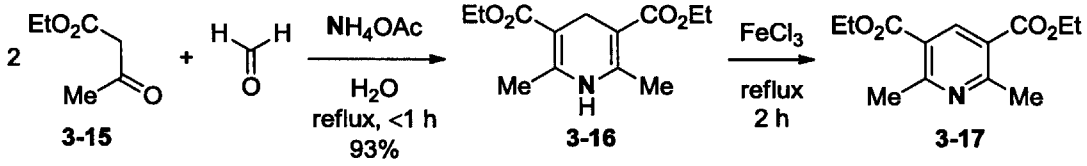
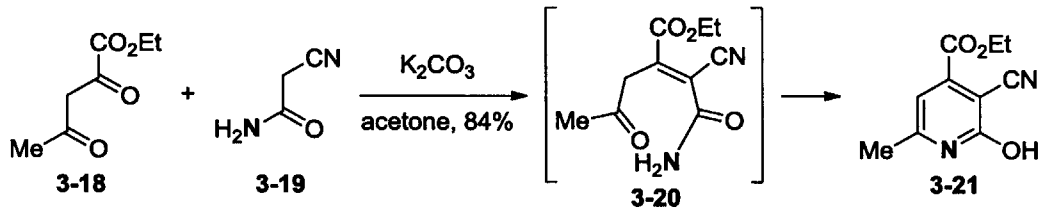
reaction, typically, which utilizes acetoacetate **3-15**, formaldehyde, and ammonium salt in a 2:1:1 ratio to construct 1,4-dihydropyridine **3-16** (Scheme 3-2). Further oxidation of 1,4-dihydropyridine by $FeCl_2$ or $KMnO_4$ provides pyridine **3-17** in an one-pot manner.



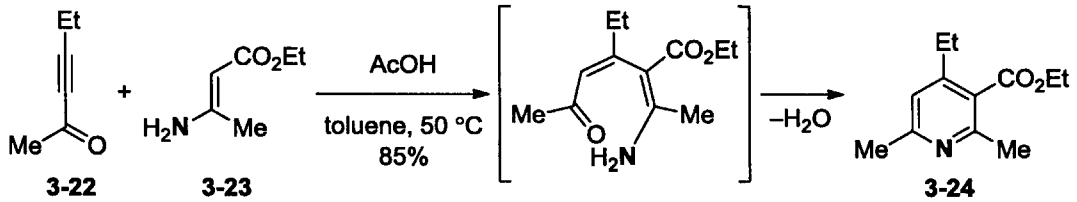
Scheme 3-2. An example of the Hantzsch pyridine synthesis

The **Guareschi–Thorpe** pyridine synthesis is closely related to the **Hantzsch** synthesis but it utilizes cyanoacetamide **3-19** as a coupling partner.[8] 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).



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).[9] 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.



Scheme 3-4. An example of the Bohlmann-Rahtz reaction

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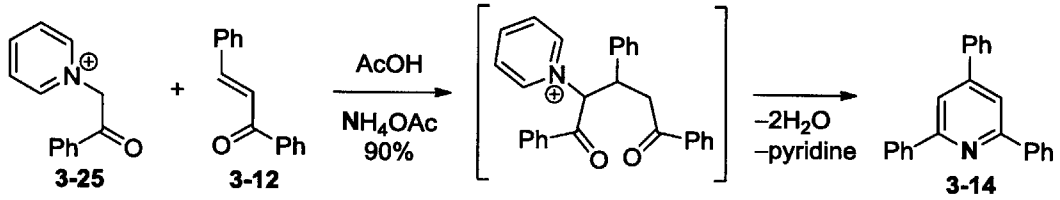
When Kröhnke compared the structure and reactivity of phenylacylpyridinium betains to 1,3-dicarbonyl compounds, he noticed that both of them have similar nucleophilic reactivity towards the Michael addition. As such, the reaction of phenylacylpyridinium betain **3-25** and α,β-unsaturated ketone **3-12** proceeds smoothly in the presence of AcOH and NH_4OAc 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

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**.

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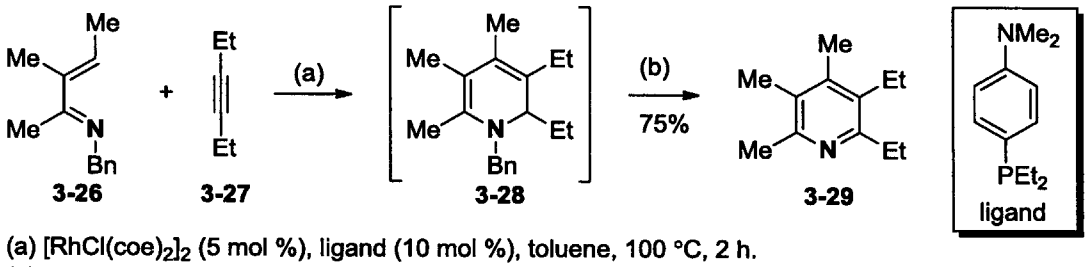
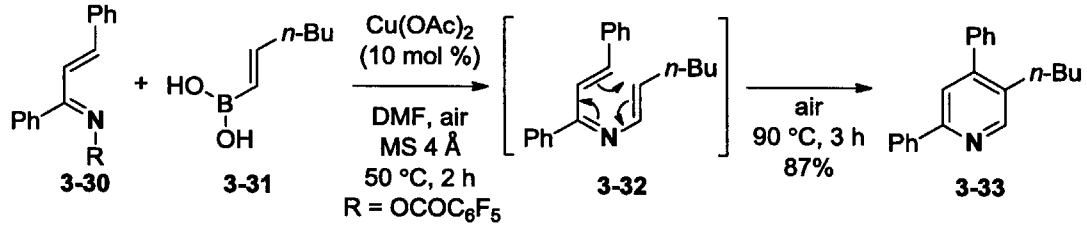


(a) $[RhCl(coe)_2]_2$ (5 mol %), ligand (10 mol %), toluene, 100 °C, 2 h.
(b) Pd/C (20 mol %), toluene:TFA = 3:1, H_2 (1 atm), 75 °C, 16 h

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).[12] 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.[13] 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.[14] 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.

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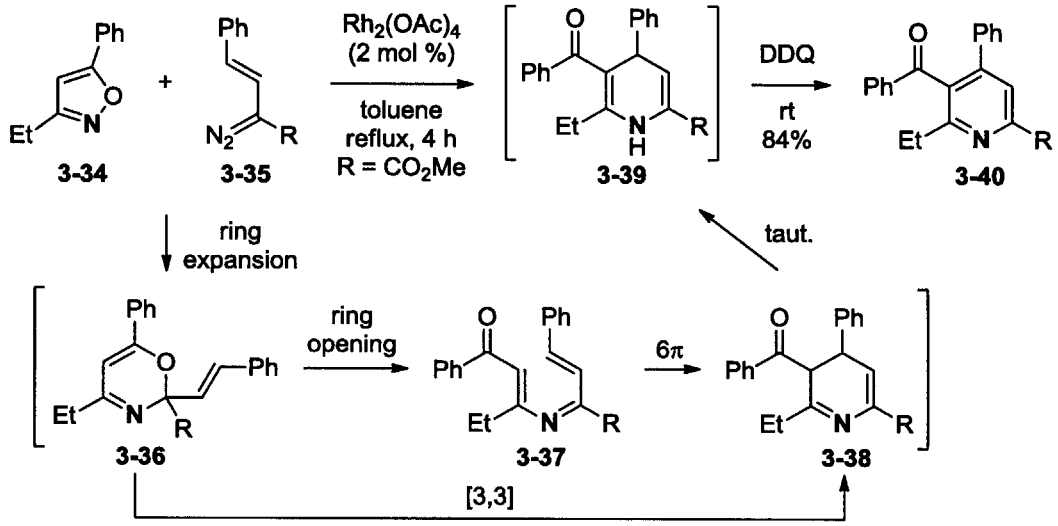
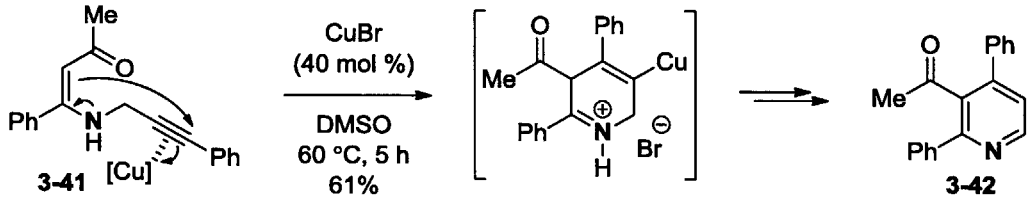


Scheme 3-8. An example of Rh(II)-catalyzed one-pot synthesis of multi-substituted pyridines and the intermediates involved

Besides, Filisti and co-workers showed that construction of pyridines can also be achieved by intermolecular cyclizations of *N*-propargylic β-enaminones using a catalytic amount of CuBr.[15] The process is initiated by the coordination of CuBr to the alkynyl moiety of **3-41** to facilitate the intramolecular nucleophilic addition of enamine to alkyne (Scheme 3-9). Further protonation and oxidation provides pyridine **3-42**.



Scheme 3-9. An example of Cu(I)-catalyzed synthesis of pyridines from *N*-propargylic β-enaminones

Another strategy for pyridine synthesis is one example reported by our group utilizing Pd(II)-catalyzed ring-expansion reactions of cyclic 2-azidoalcohols.[16] In a typical reaction, they envisioned that alkoxy–Pd(II) species **A**, which is generated from 2-azidoalcohol **3-43**, undergoes β-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 **3-44** (Scheme 3-10).

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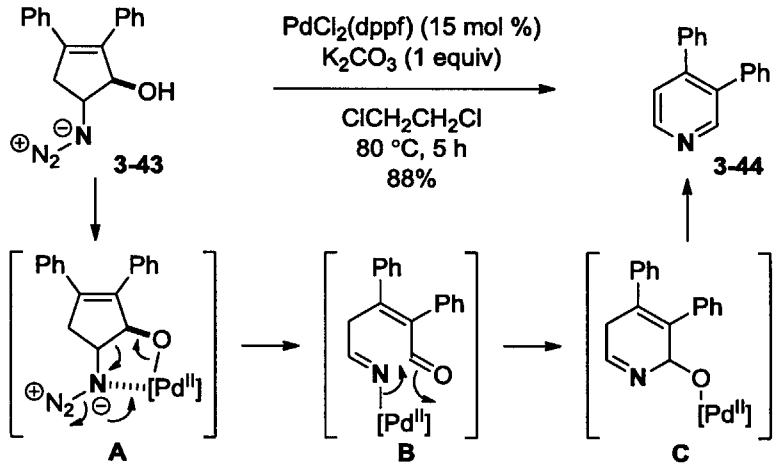
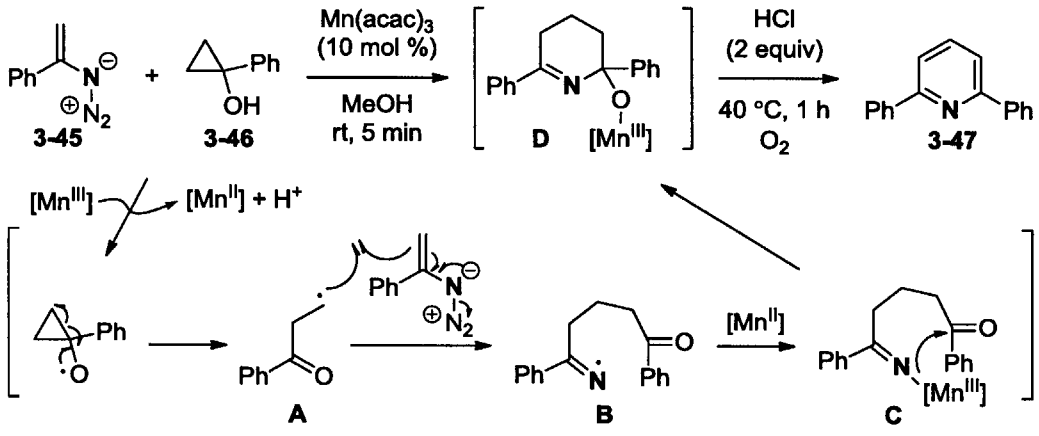


Scheme 3-10. An example of Pd(II)-catalyzed ring-expansion reactions of cyclic 2-azidoalcohols

In addition, our group has also revealed a versatile synthetic method of pyridine by Mn(III)-catalyzed reactiosn of cyclopropanols and vinyl azides.[17] 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**.



Scheme 3-11. An example of Mn(III)-catalyzed reactions of cyclopropanols with vinyl azides

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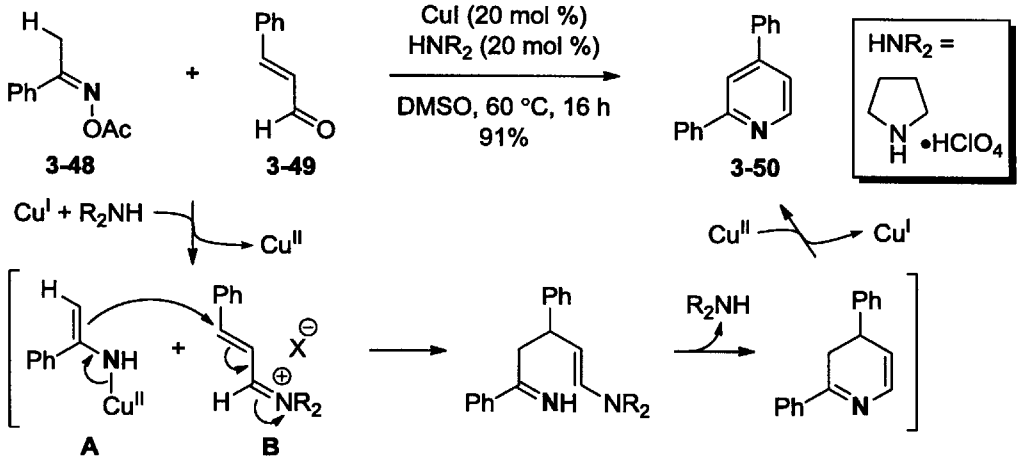
Recently, Yoshikai and co-workers developed a modular pyridine synthesis from oximes and α,β-unsaturated aldehydes through synergistic copper/iminium catalysis (Scheme 3-12).[18] They strategically utilize CuI as the catalyst where Cu(I) is used to reduce N–O bond of oxime **3-48** to form enaminyl-Cu(II) species **A** at the first step and 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 α,β-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 α,β-unsaturated aldehydes

3.1.4 Synthetic plan for pyridines using $[Cp^*RhCl_2]_2$ 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 $[Cp^*RhCl_2]_2$-catalyzed *aryl* C–H bond activation, alkyne insertion and C–N bond formation. Based on

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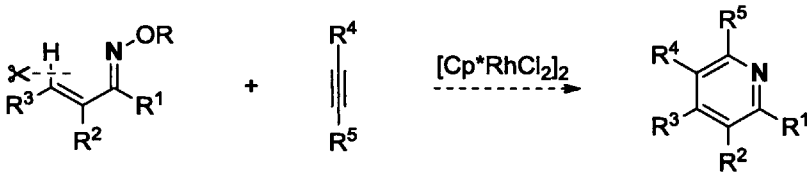
the finding, our attention has been drawn to use $[Cp^*RhCl_2]_2$ as the catalyst for *vinylic* C–H bond activation using α,β-unsaturated oximes as a substrate for the pyridine synthesis (Scheme 3-13).

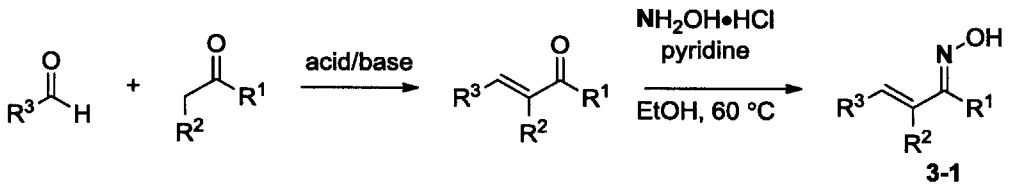


Scheme 3-13. Proposed reaction of Rh(III)-catalyzed synthesis of pyridines from α,β-unsaturated oximes and alkynes

3.2 Results and discussion

3.2.1 Synthesis of α,β-unsaturated oximes

As shown in Scheme 3-14, the synthesis of α,β-unsaturated oximes begins with aldol condensation between aldehydes and ketones to afford the corresponding α,β-unsaturated ketones. Subsequent treatment of α,β-unsaturated ketones with hydroxylamine provides α,β-unsaturated oximes **3-1**.



Scheme 3-14. Synthesis of α,β-unsaturated oximes–1

Commercially available (*E*)-4-phenylbut-3-en-2-one and (1*E*,4*E*)-1,5-diphenyl-1,4-pentadien-3-one were used directly for the synthesis of α,β-unsaturated oximes **3-1a** and **3-1i**. Generally, α,β-unsaturated ketones with R^2 = H were prepared by treating arylaldehydes and ketones with NaOH in ethanol (Scheme 3-15 (a)). The corresponding α,β-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

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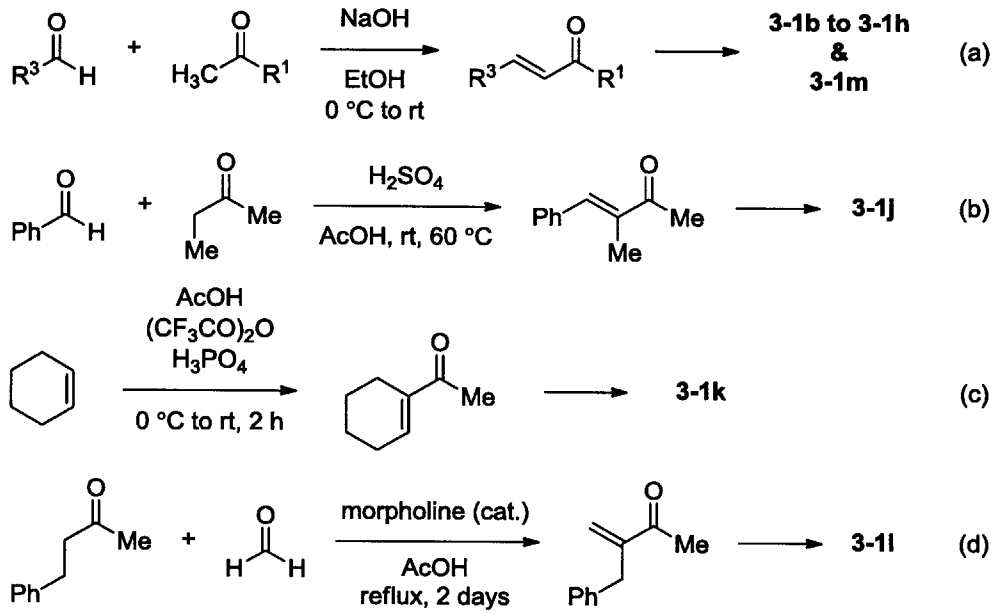
substituted α,β-unsaturated ketones ($R^2 \neq H$) for the preparation of **3-1j**, **3-1k** and **3-1l** as shown in Scheme 3-15 (b), (c) and (d).



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 $[Cp^*RhCl_2]_2$ 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 % $[Cp^*RhCl_2]_2$, 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). By

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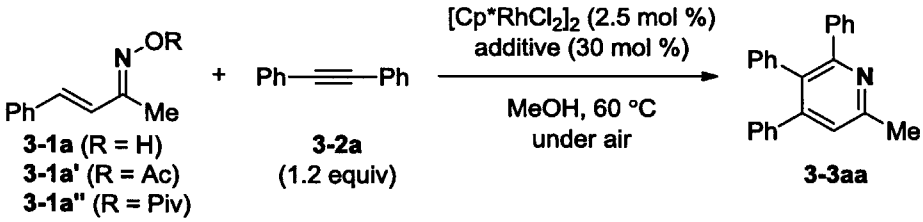
changing acetate (CsOAc) to other carboxylates such as pivalate (CsOPiv), shorter reaction time and higher yield were observed (Table 3-1, entry 3). The reaction with $Cu(OAc)_2$ did not afford the desired pyridine **3-3aa** but resulting in decomposition of *O*-acetyl oxime **3-1a'**, probably due to the Lewis acidity of $Cu(OAc)_2$ (Table 3-1, entry 4).

Table 3-1. Optimization of reaction conditions[a]



3-1a (R = H)
3-1a' (R = Ac)
3-1a" (R = Piv)

3-2a
(1.2 equiv)

3-3aa

entry	oxime **3-1**	additive	time / h	yield of **3-3aa** / %[b]
1	**3-1a'**	NaOAc	24	49
2	**3-1a'**	CsOAc	24	62
3	**3-1a'**	CsOPiv	10	77
4	**3-1a'**	$Cu(OAc)_2$	14	0
5	**3-1a"**	CsOPiv	19	55
6	**3-1a**	CsOPiv	7	79
7[c]	**3-1a**	CsOPiv	24	78
8[d]	**3-1a**	CsOPiv	24	86

[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 $[Cp^*RhCl_2]_2$–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 α,β-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

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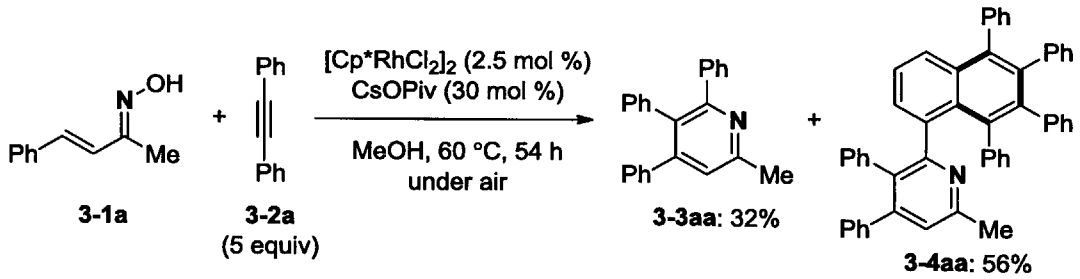
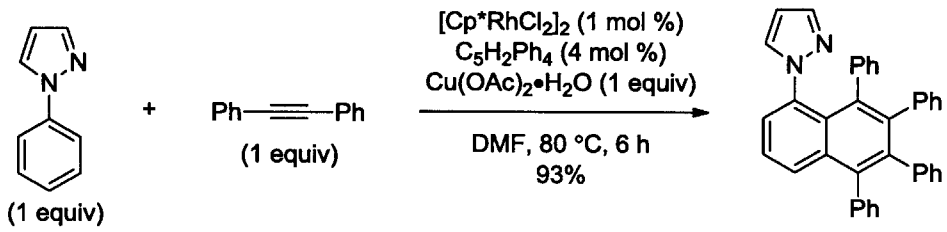
of air (molecular oxygen) may have a crucial role to maintain and accelerate the catalytic turnover. By using 1.5 equiv of α,β-unsaturated oxime **3-1a** with diphenyl acetylene (**3-2a**), pyridine **3-3aa** was formed in 86% yield (based on acetylene **3-2a**) but longer reaction time of 24 h was required (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



*$C_5H_2Ph_4$ = 1,2,3,4-tetraphenylcyclopentadiene

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

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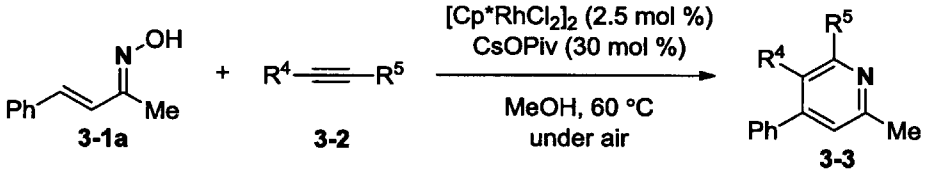
3.2.3 Scope & limitations

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[a]



entry	alkyne **3-2**	R^4	R^5	time / h	yield of **3-3** / %[b]
1	**3-2b**	4-$MeOC_6H_4$	4-$MeOC_6H_4$	24	**3-3ab** 61
2	**3-2c**	4-$TMSC_6H_4$	4-$TMSC_6H_4$	10	**3-3ac** 60[c]
3	**3-2d**	3-BrC_6H_4	3-BrC_6H_4	10	**3-3ad** 77
4	**3-2e**	*n*-Pr	*n*-Pr	8	**3-3ae** 75
5	**3-2f**	CH_2OTBS	CH_2OTBS	30	**3-3af** 69
6	**3-2g**	Me	Ph	8	**3-3ag** 97 (1.5:1)[d]
7[c]	**3-2h**	CO_2Et	Ph	24	**3-3ah** 45 (1.5:1)[d]
8	**3-2i**	4-$MeOC_6H_4$	4-$F_3CC_6H_4$	24	**3-3ai** 87 (2.3:1)[d]

[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.

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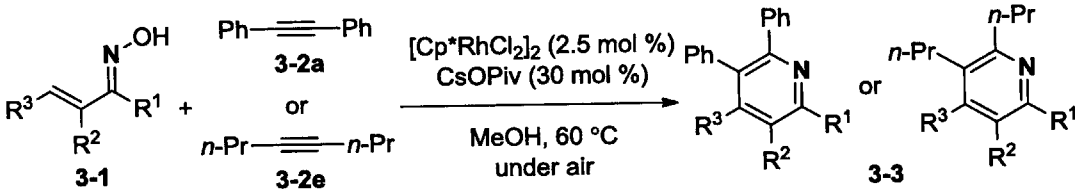
On the other hand, the scope and limitation of α,β-unsaturated oximes **3-1** were studied with alkyne **3-2a** or **3-2e** under the present reaction conditions (Table 3-3). The results showed that benzene ring bearing electron-donating groups such as methoxy and methyl moieties could be introduced as the R^3-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[a]



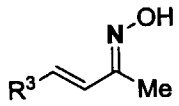
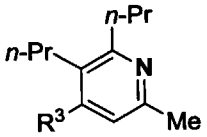
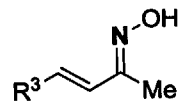
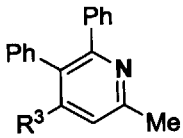
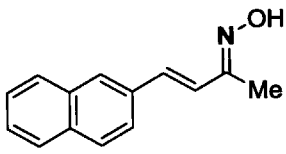
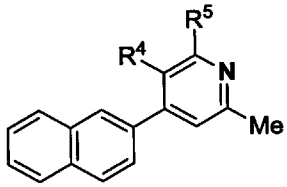
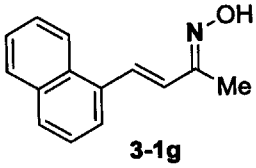
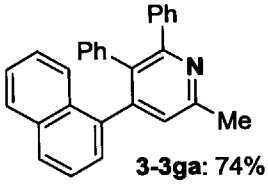
entry	oxime **3-1**	alkyne **3-2**	time	pyridine **3-3** / yield[b]
				
1	**3-1b** (R^3 = 4-OMe-C_6H_4)	**3-2e**	20 h	**3-3be**: 60%
2	**3-1c** (R^3 = 2-OMe-C_6H_4)	**3-2e**	30 h	**3-3ce**: 63%
				
3	**3-1d** (R^3 = 3-Me-C_6H_4)	**3-2a**	30 h	**3-3da**: 68%
4	**3-1e** (R^3 = 4-Br-C_6H_4)	**3-2a**	12 h	**3-3ea**: 87%
				
5	**3-1f**	**3-2a**	24 h	**3-3fa**: 87%
6	**3-1f**	**3-2e**	24 h	**3-3fe**: 77%
7	 **3-1g**	**3-2a**	24 h	 **3-3ga**: 74%

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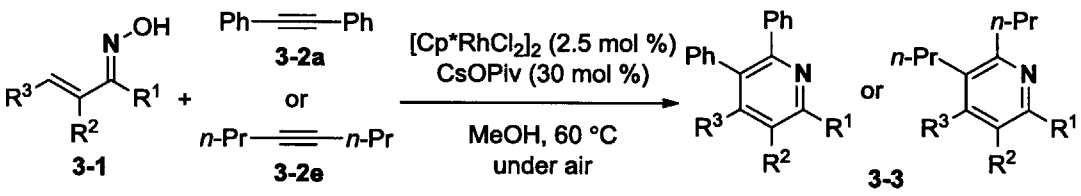
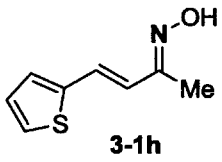
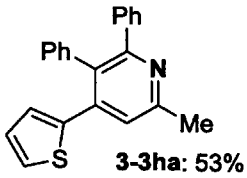
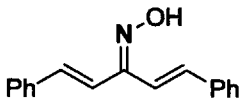
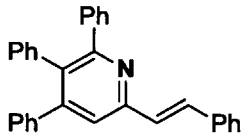
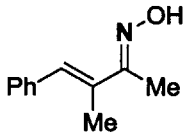
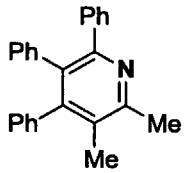
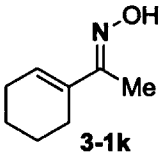
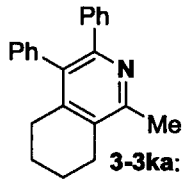
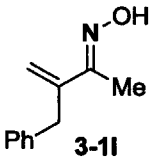
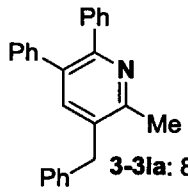
Table 3-3. Scope of α,β-unsaturated oximes (*continue*)[a]



entry	oxime **3-1**	alkyne **3-2**	time	pyridine **3-3** / yield[b]
8	 **3-1h**	**3-2a**	24 h	 **3-3ha**: 53%
9[c]	 **3-1i**	**3-2a**	7 h	 **3-3ia**: 81%
10	 **3-1j**	**3-2a**	7 h	 **3-3ja**: 66%
11	 **3-1k**	**3-2a**	10 h	 **3-3ka**: 68%
12	 **3-1l**	**3-2a**	2 h	 **3-3la**: 88%

[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. [b] Isolated yield. [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**)

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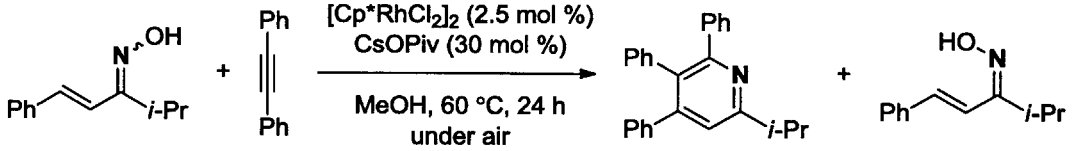
proceeded smoothly to give 6-stylylpyridine **3-3ia** in 81% yield after 7 h (Table 3-3, entry 9). It is worth noting that pentasubstituted pyridines **3-3ja** and **3-3ka** could be synthesized in good yields (Table 3-3, entries 10 and 11).

It is surprising that when 3-benzyl-3-buten-2-one oxime (**3-1l**; 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 **3-1l**.

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]



3-1m
syn:*anti* = 1:1.2

3-2a

3-3ma: 40%

***syn*-3-1m**: 25%

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

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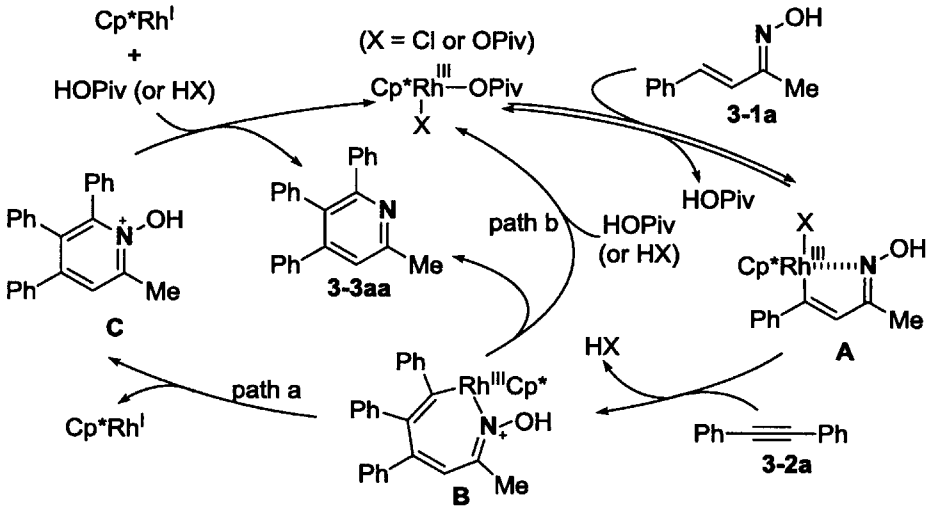
3.2.4 Proposed mechanism

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**.



Scheme 3-19. Proposed catalytic cycle

A proposed catalytic pathway of Rh(III)-catalyzed pyridine synthesis is outlined in Scheme 3-19. It commences with *vinylic* C–H bond activation of α,β-unsaturated oxime **3-1a** with assistance of the directing group, oxime *via* sp^2 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.

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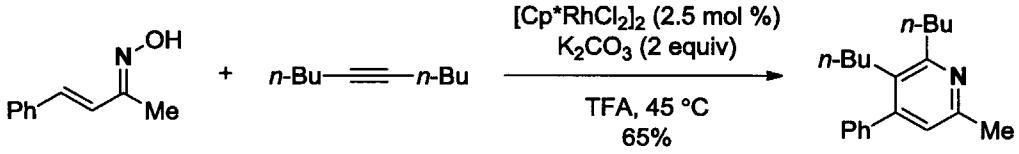
3.3 Conclusion

In summary, we have developed a versatile method for the synthesis of highly substituted pyridines from α,β-unsaturated oximes and internal alkynes using $[Cp^*RhCl_2]_2$–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]



Scheme 3-20. An example of Rh(III)-catalyzed synthesis of pyridines from oximes and alkynes

3.4 References

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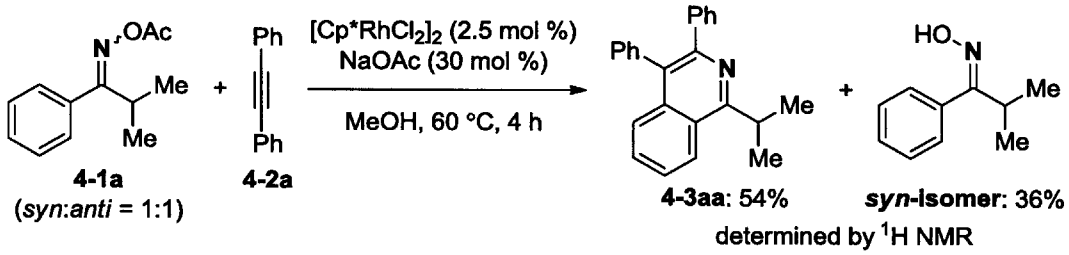
Chapter 4 Synthesis of Azaheterocycles from Aryl Ketone *O*-Acetyl Oximes and Internal Alkynes by Cu–Rh Bimetallic Relay Catalysts

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 % $[Cp^*RhCl_2]_2$, 30 mol % NaOAc, MeOH, 60 °C), 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

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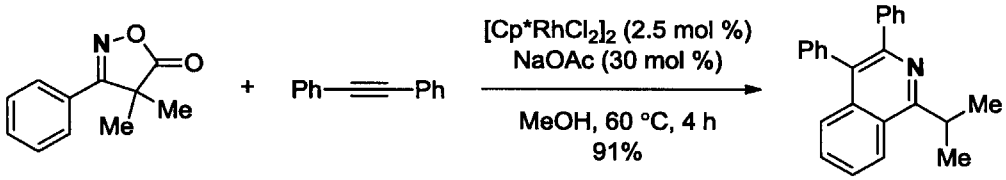
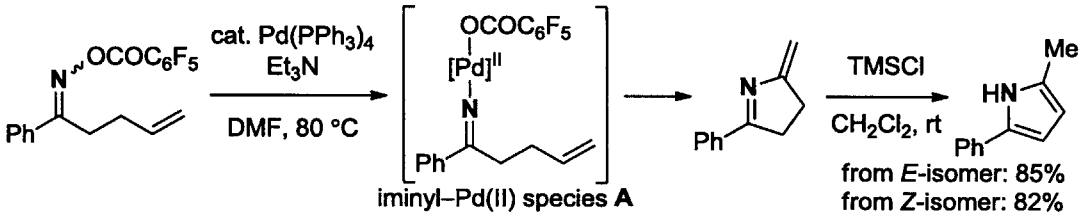
discussed in Chapter 2.2.3.2. However, this method required a multi-step synthesis of substituted 3-phenylisoxazol-5-ones from the corresponding β-keto esters.



Scheme 4-2. An example of synthesis of isoquinolines from 3-phenylisoxazol-5-ones and alkynes

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.



Scheme 4-3. An example of Pd(0)-catalyzed amino-Heck reactions of alkenyl *O*-acyl oximes *via* iminyl–Pd(II) species

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

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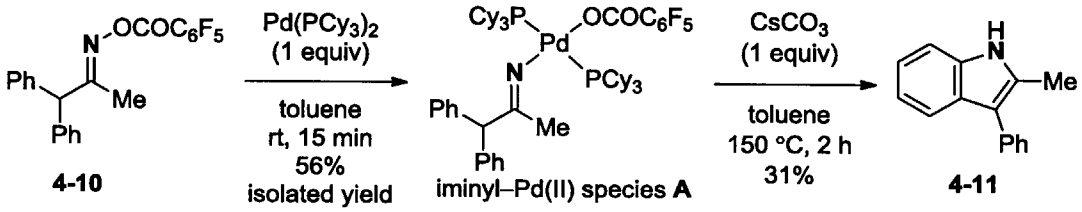
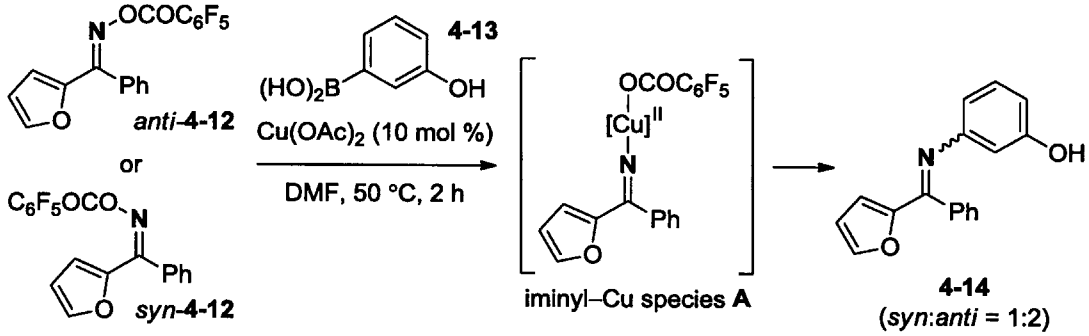
revealed that the bond angle of C=N–Pd(II) is about 120 degrees (Scheme 4-4).[2] Further treatment of isolated complex **A** with 1 equiv of $CsCO_3$ in toluene at 150 °C affords indole **4-11** in 31% yield. In the case, isomerization of (*E*)-isomer of iminyl–Pd(II) complex **A** to (*Z*)-isomer should 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

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.[3] 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

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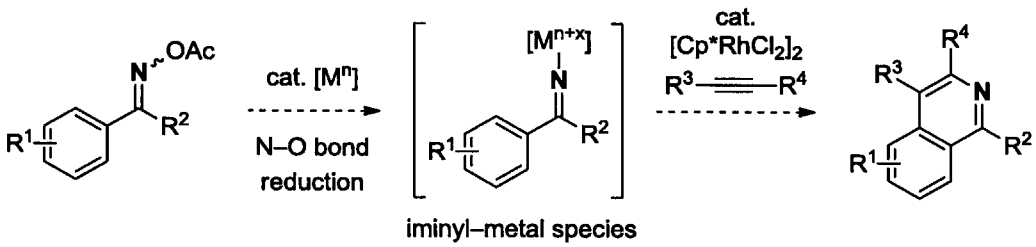
Therefore, we intend to reduce the N–O bond of oximes as an initiation process by using lower valent transition metals [M^n] such as Cu(I) and Pd(0) complexes to generate the corresponding iminyl–metal species (Scheme 4-6). If [M^n] and $[Cp^*RhCl_2]_2$ work independently for two-electron reduction of 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 Cp*Rh(III) species to give iminyl–Cp*Rh(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

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.

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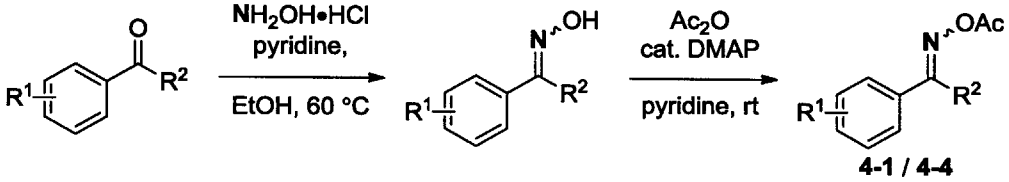
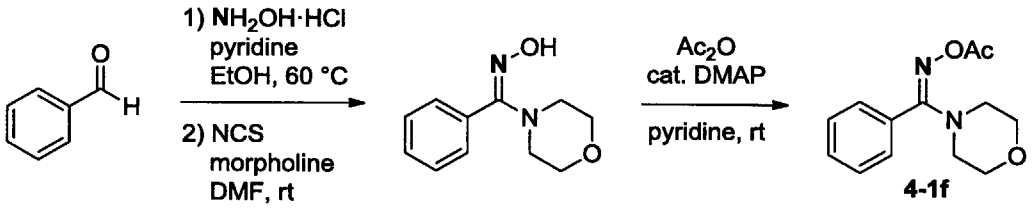


Scheme 4-7. Synthesis of *O*-acetyl oximes from ketones

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 4-8. Synthesis of *anti*-amidoxime from benzaldehyde

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 % $[Cp^*RhCl_2]_2$ (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 $Pd(PPh_3)_4$, no improvement was observed (Table 4-1, entry 2).

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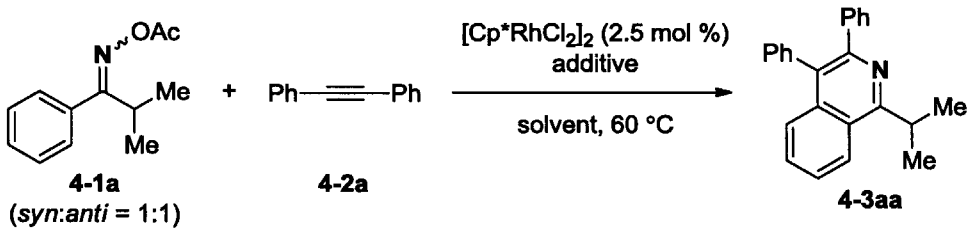
Table 4-1. Optimization of reaction conditions[a]



4-1a (*syn*:*anti* = 1:1) **4-2a** **4-3aa**

entry	additive (mol %)	solvent	time	yield of **4-3aa** / %[b]
1	$Pd(dba)_2$ (20) + NaOAc (30)	DMF	15 h	14[c]
2	$Pd(PPh_3)_4$ (20) + NaOAc (30)	DMF	15 h	19[c]
3	$Cu^{I}OAc$ (10)	DMF	45 min	99
4	$Cu^{II}(OAc)_2$ (10)	DMF	4 h	95
5[d]	$Cu^{II}(OAc)_2$ (10)	DMF	24 h	20[e]
6	$Cu^{II}(OAc)_2$ (10)	MeOH	1 h	80[f]
7	$Cu^{II}(OAc)_2$ (10)	toluene	22 h	0[g]

[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 N_2 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 $Cu^{I}OAc$ 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 $Cu^{I}OAc$ as the reductant. It is worth to note that the use of $Cu^{II}(OAc)_2$ instead of $Cu^{I}OAc$ 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.[4] The speculation could be supported by observation of the sluggish reaction under an air atmosphere (Table 4-1, entry 5); impling 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.

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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 $[Cp^*RhCl_2]_2$, 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).

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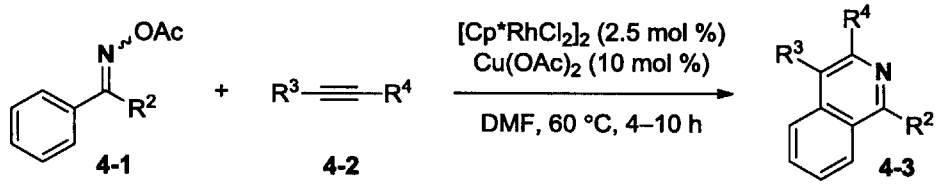
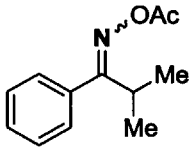
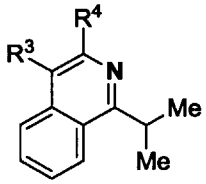
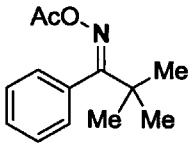
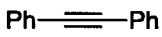
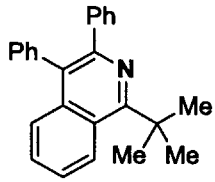
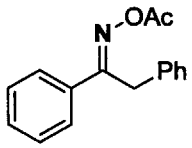
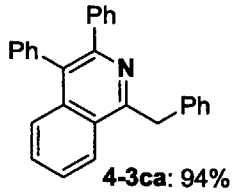
Table 4-2. Synthesis of isoquinolines from *syn*- and/or *anti*-*O*-acetyl oximes and alkynes[a]



entry	oxime **4-1** (*syn*:*anti*)	alkynes **4-2**	isoquinoline **4-3** / yield[b]
			
1	**4-1a** (1:1)	**4-2b** ($R^3 = R^4$ = 4-OMe-C_6H_4)	**4-3ab**: 87%
2	**4-1a** (1:1)	**4-2c** ($R^3 = R^4$ = 4-Br-C_6H_4))	**4-3ac**: 92%
3	**4-1a** (1:1)	**4-2d** ($R^3 = R^4$ = *n*-Pr)	**4-3ad**: 78%
4	**4-1a** (1:1)	**4-2e** ($R^3 = R^4$ = CH_2OTBS)	**4-3ae**: 79%
5	**4-1a** (1:1)	**4-2f** (R^3 = Me, R^4 = Ph)	**4-3af**: 93%
6	**4-1a** (1:1)	**4-2g** (R^3 = CH_2OTBS, R^4 = Ph)	**4-3ag**: 98% (13:1)[c,d]
7	**4-1a** (1:1)	**4-2h** (R^3 = CO_2Et, R^4 = Ph)	**4-3ah**: 75% (1.7:1)[d,e]
8	**4-1a** (1:1)	**4-2i** (R^3 = *n*-hexyl, R^4 = 2-thienyl)	**4-3ai**: 81%
9	 **4-1b** (*syn*)	 **4-2a**	 **4-3ba**: 99%
10	 **4-1c** (*anti*)	**4-2a**	 **4-3ca**: 94%

[a] 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_2 atmosphere. [b] Isolated yield. [c] Isolated as a mixture of 2 regioisomers and the regioselectivity is based on ^{1}H NMR. [d] The structure of major isomer was described. [e] 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

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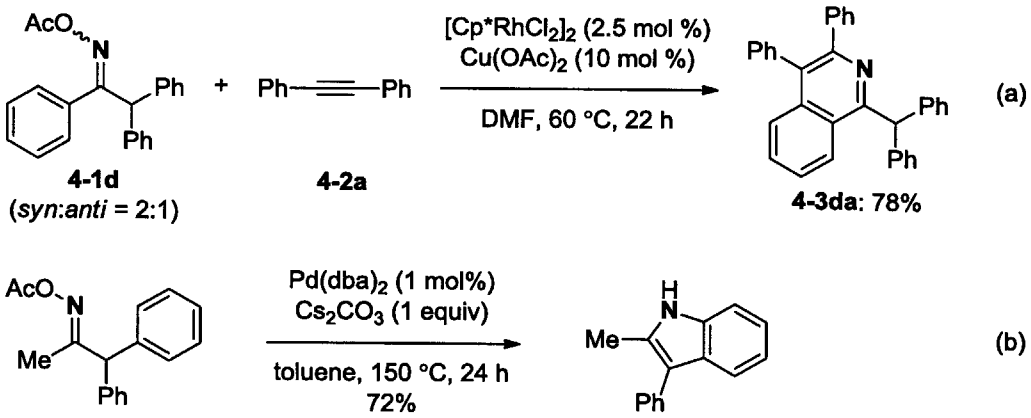
trimethylsilyl moiety (Table 4-2, entry 6); in contrast, low regioselectivity was observed for ethyl 3-phenylpropiolate (**4-2h**) (Table 4-2, entry 7).

It is worth noting that even the reaction of pure *syn*-isomer, *t*-butyl ketone *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 *anti*-isomer, 1,2-diphenylethanone *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 *syn*- and *anti*-oximes could react independently under the present reaction conditions.

In the case of the reaction of 1,2,2-triphenylethanone *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)).[2]



Scheme 4-9. Selective formation of isoquinoline using $[Cp^*RhCl_2]_2$–$Cu(OAc)_2$ catalytic system

When cyclopropyl ketone *O*-acetyl oxime **4-1e** (*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 *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

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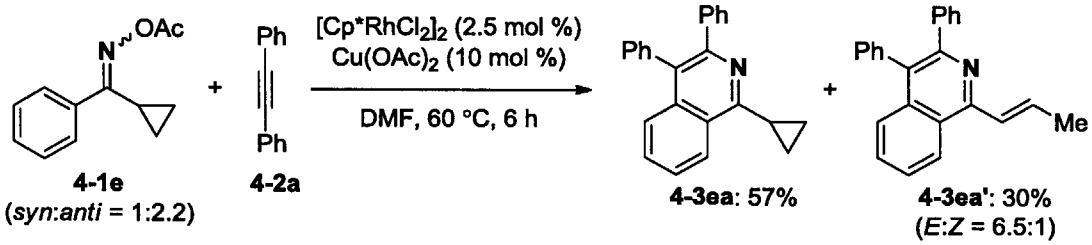
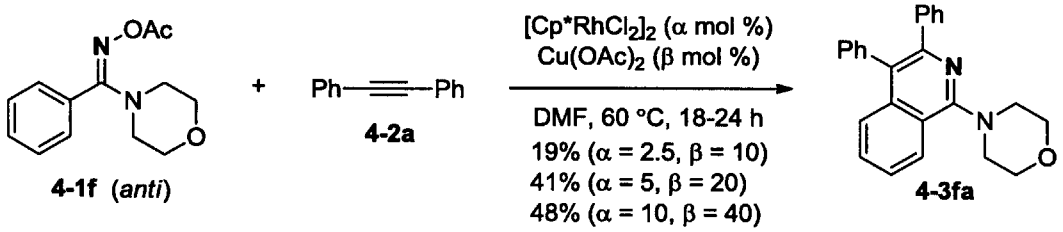
treatment of cyclopropyl isoquinoline **4-3ea** with or without alkyne **4-2a** under the present reaction conditions showed no reactions in both cases, thus, the formation of alkenyl isoquinoline **4-3ea'** is not due to the cyclopropyl ring-opening of isoquinoline **4-3ea**. Secondly, the reactions of cyclopropyl ketone *O*-acetyl oxime **4-1e** and alkyne **4-2a** were conducted in the presence of D_2O or in DMF-d_7; 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.



4-1e (*syn*:*anti* = 1:2.2) + **4-2a** → **4-3ea**: 57% + **4-3ea'**: 30% (*E*:*Z* = 6.5:1)

Scheme 4-10. Formation of cyclopropyl ring-opening product

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 % $[Cp^*RhCl_2]_2$, 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 $[Cp^*RhCl_2]_2$ 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 $[Cp^*RhCl_2]_2$ and 40 mol % of $Cu(OAc)_2$ resulted in the formation of **4-3fa** in 48% yield.



4-1f (*anti*) + **4-2a** → **4-3fa**

Scheme 4-11. Rh(III)-catalyzed synthesis of 1-aminoisoquinoline

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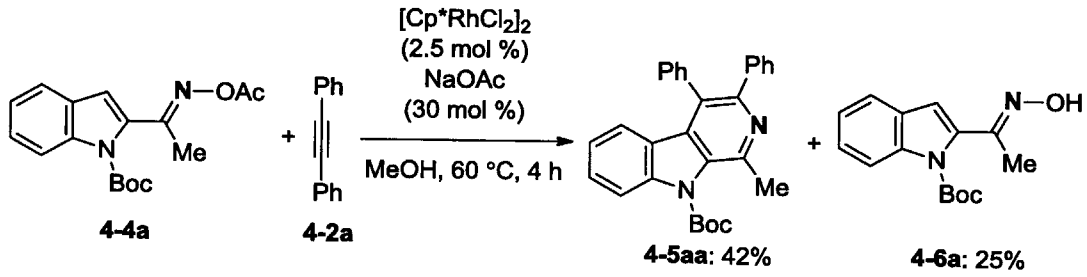
4.2.3.2. Synthesis of β-carbolines and other azaheterocycles

The successful transformation of aryl ketone *O*-acetyl oximes and alkynes to isoquinolines using this $[Cp^*RhCl_2]_2$–$Cu(OAc)_2$ 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 $[Cp^*RhCl_2]_2$ and 30 mol % of $Cu(OAc)_2$ in DMF at 60 °C resulted in the formation of β-carboline **4-5aa** in 82% yield (Table 4-3, entry 1), whereas the reaction under the previous $[Cp^*RhCl_2]_2$–NaOAc catalytic system gave β-carboline **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 $[Cp^*RhCl_2]_2$–NaOAc catalytic system

This finding prompted us to explore the generality of alkynes and indolyl ketone *O*-acetyl oxime derivatives for β-carboline synthesis under the $[Cp^*RhCl_2]_2$–$Cu(OAc)_2$ catalytic system. First of all, the reactivity of various alkynes were examines 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-carboline **4-5ac** in 69% yield (Table 4-3, entry 3), while di(4-methoxyphenyl)acetylene (**4-2b**) give β-carboline **4-5ab** in low yield of 28% (Table 4-3, entry 2). Dialkyl alkyne, 4-octyne (**4-2d**) reacted smoothly to afford β-carboline **4-5ad** in 87% yield (Table 4-3, entry 4).

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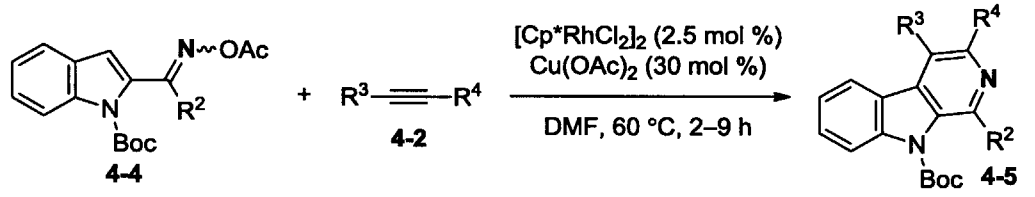
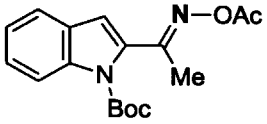
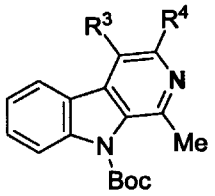
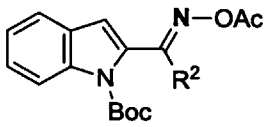
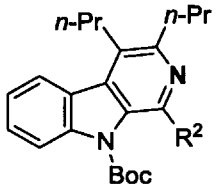
Insertion of unsymmetrical alkynes **4-2f** and **4-2g** proceeded albeit with lower regioselectivity (Table 4-3, entries 5 and 6) compare to that of the isoquinoline formation (see Table 4-2). In the case of methyl 3-phenylpropiolate (**4-2j**), β-carboline **4-5aj** was formed in high yield of 71% with no control of regioselectivity (Table 4-3, entry 7).

Table 4-3. Synthesis of β-carbolines from *O*-acetyl oximes and alkynes[a]



entry	oxime **4-4**	alkyne **4-2**	β-carboline **4-5** / yield[b]
			
1	**4-4a** (*anti*)	**4-2a** ($R^3 = R^4$ = Ph)	**4-5aa**: 82%
2	**4-4a** (*anti*)	**4-2b** ($R^3 = R^4$ = 4-OMe-C_6H_4)	**4-5ab**: 28%[c]
3	**4-4a** (*anti*)	**4-2c** ($R^3 = R^4$ = 4-Br-C_6H_4)	**4-5ac**: 69%[c]
4	**4-4a** (*anti*)	**4-2d** ($R^3 = R^4$ = *n*-Pr)	**4-5ad**: 87%
5	**4-4a** (*anti*)	**4-2f** (R^3 = Me, R^4 = Ph)	**4-5af**: 65% (5:1)[d]
6	**4-4a** (*anti*)	**4-2g** (R^3 = CH_2OTBS, R^4 = Ph)	**4-5ag**: 50% (3:1)[d]
7	**4-4a** (*anti*)	**4-2j** (R^3 = CO_2Me, R^4 = Ph)	**4-5aj**: 71% (1:1)[d]
			
8	**4-4b** (R^2 = *n*-Bu, *anti*)	**4-2d**	**4-5bd**: 91%
9	**4-4c** (R^2 = $CH_2CH_2CH{=}CH_2$, *anti*)	**4-2d**	**4-5cd**: 36%[c,e]
10	**4-4d** (R^2 = CO_2Et, *anti*)	**4-2d**	**4-5dd**: 60%[c]

[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. [c] The reaction was conducted using 5 mol % of $[Cp^*RhCl_2]_2$. [d] The structure of the major isomer was described. [e] Deacetylated product of oxime **4-4c** was observed in 16% yield.

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.

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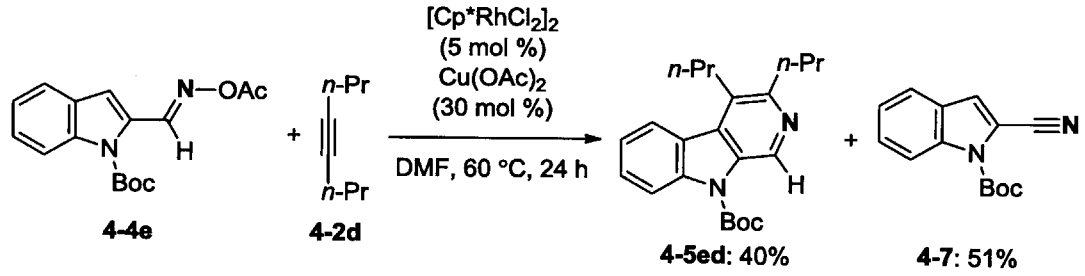
Indolyl ketone *O*-acetyl oxime **4-4** bearing linear alkyl chain and ester moiety reacted smoothly to give β-carbolines **4-5bd** and **4-5dd** in 91% and 60% yield respectively (Table 4-3, entries 8 and 10). Even though *O*-acetyl oxime **4-4c** bearing alkenyl moiety was tolerated under the reaction 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

In addition, other heteroaryl ketone *O*-acetyl oximes bearing benzofuranyl, furanyl, thienyl and pyrrolyl moieties demonstrated high reactivity toward 4-octyne (**4-2d**), providing the corresponding azaheterocycles in high yields (Table 4-4).

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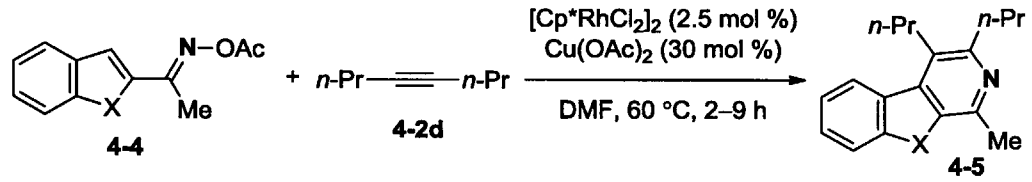
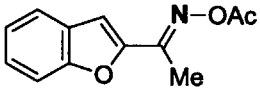
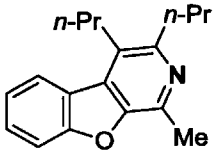
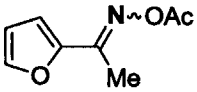
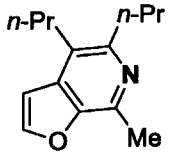
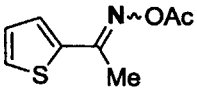
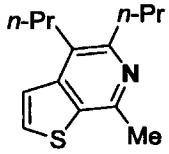
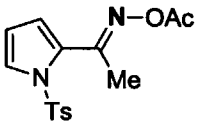
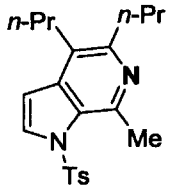
Table 4-4. Synthesis of other azaheterocycles from *O*-acetyl oximes and alkynes[a]



entry	oxime **4-4** (*syn*:*anti*)	azaheterocycles **4-5** / yield[b]
1	 **4-4f** (*anti*)	 **4-5fd**: 86%
2	 **4-4g** (1:20)	 **4-5gd**: 77%
3	 **4-4h** (1:4)	 **4-5hd**: 81%
4	 **4-4i** (*anti*)	 **4-5id**: 91%

[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.

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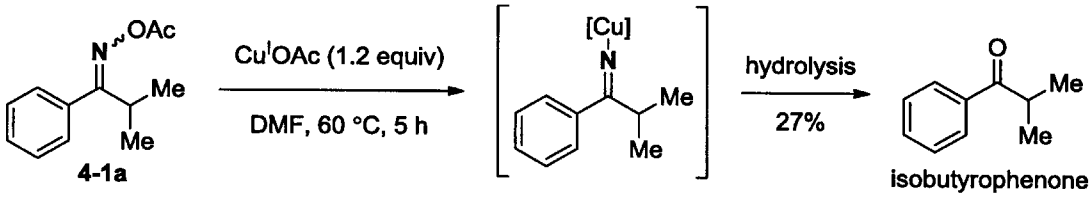
4.2.4 Proposed mechanism

A proposed mechanism of $[Cp^*RhCl_2]_2$–$Cu(OAc)_2$ bimetallic catalytic system is outlined in Scheme 4-14. As an initiation process, $Cu^{II}(OAc)_2$ may be reduced by DMF to form Cu(I) species (Scheme 4-14, step (i)).[6] The proposed initiation step is based on the experimental result where the use of $Cu^{I}OAc$ results in higher yield and shorter reaction time compared to $Cu^{II}(OAc)_2$ (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 iminyl–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 Cp*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 Cp*Rh(III) and Cu(I) species, the final step involves a redox process between Cp*Rh(I) and Cu(II)/Cu(III) (Scheme 4-14, step iv).



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 $Cu^{I}OAc$ in DMF at 60 °C for 5 h (Scheme 4-

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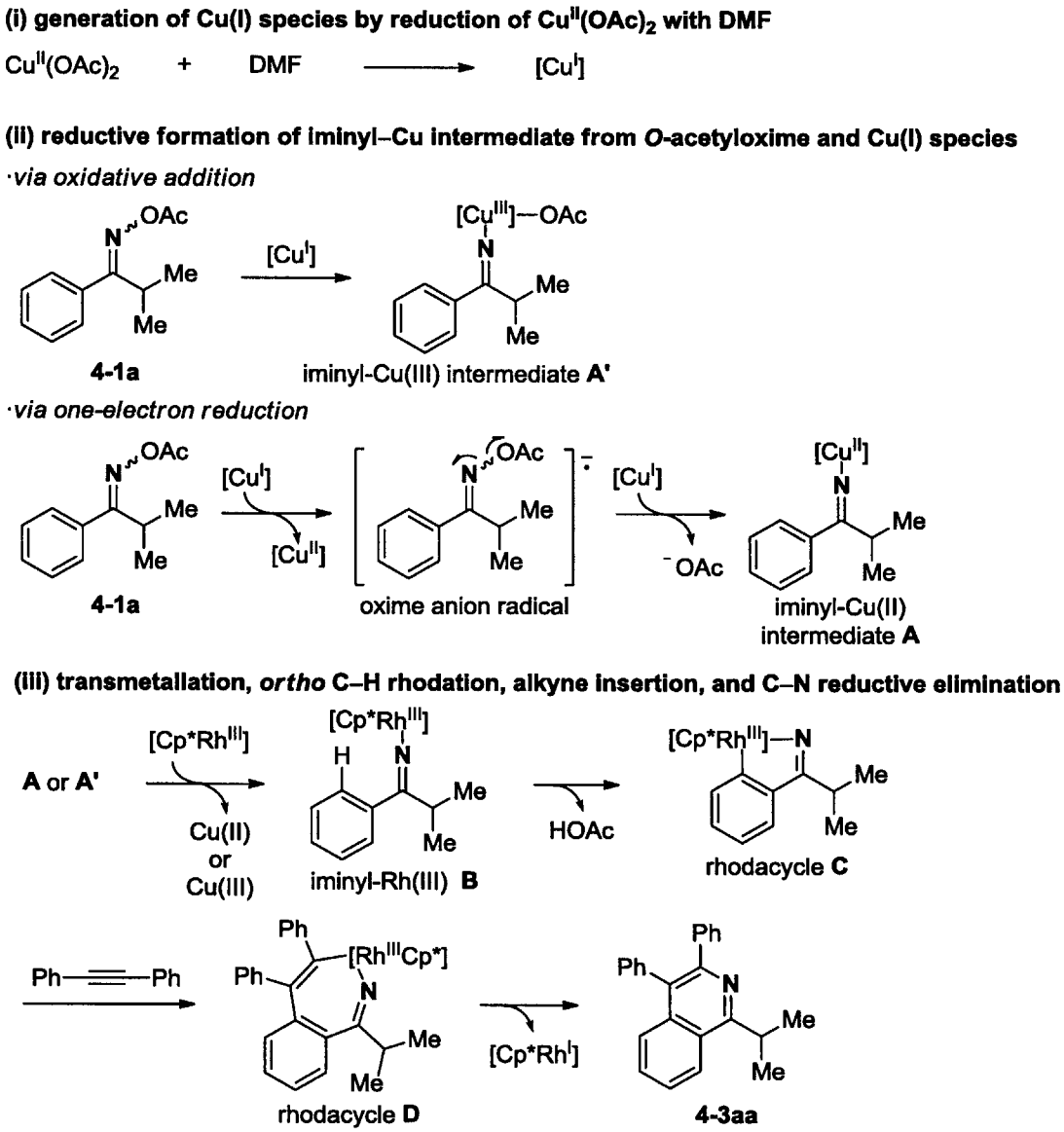
15). The corresponding isobutyrophenone, which could be formed *via* hydrolysis of iminyl–Cu(II)/Cu(III) species, was isolated in 27 % yield.



Scheme 4-14. Proposed Mechanism

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4.3 Application to 1,8-diazapyrene synthesis

Molecular structures with highly π-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 π-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 π-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.

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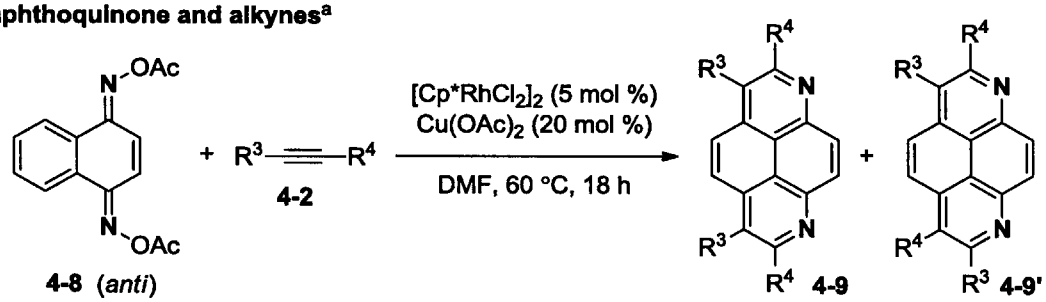
Table 4-5. One step synthesis of 1,8-diazapyrenes from *O,O*-diacetyl dioxime of naphthoquinone and alkynes[a]



entry	alkyne **4-2**	R^3	R^4	1,8-diazapyrene **4-9** / yield[b]
1	**4-2a**	Ph	Ph	**4-9a**: 77%
2	**4-2b**	4-OMe-C_6H_4	4-OMe-C_6H_4	**4-9b**: 34%
3	**4-2c**	4-Br-C_6H_4	4-Br-C_6H_4	**4-9c**: 71%
4	**4-2d**	*n*-Pr	*n*-Pr	**4-9d**: 33%
5	**4-2f**	Me	Ph	**4-9f**: 67% (7.4:1)[c,d]
6	**4-2h**	CO_2Et	Ph	**4-9h**: 59% (1:1.1)[d]

[a] Unless otherwise stated, reactions were carried out on the scale of 0.5 mmol of oxime **4-8** and 2 equiv of alkyne **4-2** in DMF (0.2 M) at 60 °C under N_2 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.[8] 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.[9]

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-

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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.

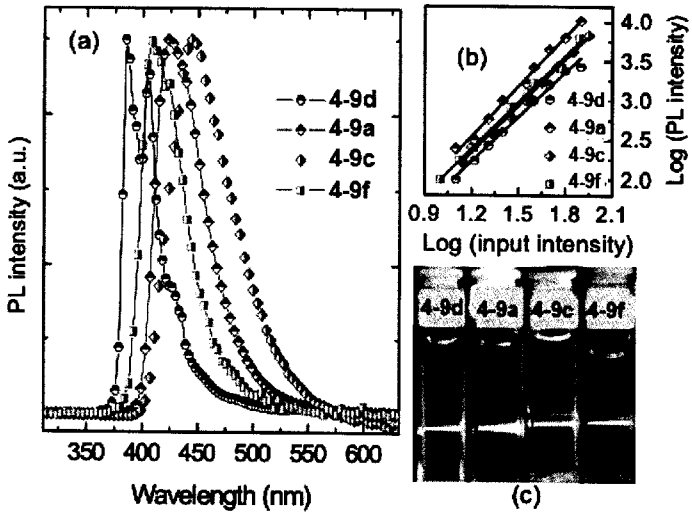

Figure 4-1. (a) TPA excited PL spectra for 1,8-diazapyrenes 4-9; (b) Their PL integrated intensity vs power density at 780 nm. The log–log plots with slope values of around 2 indicate the nature of TPA in all of the compounds. (c) The images of TPA excited PL emission for 1,8-diazapyrenes 4-9 under the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

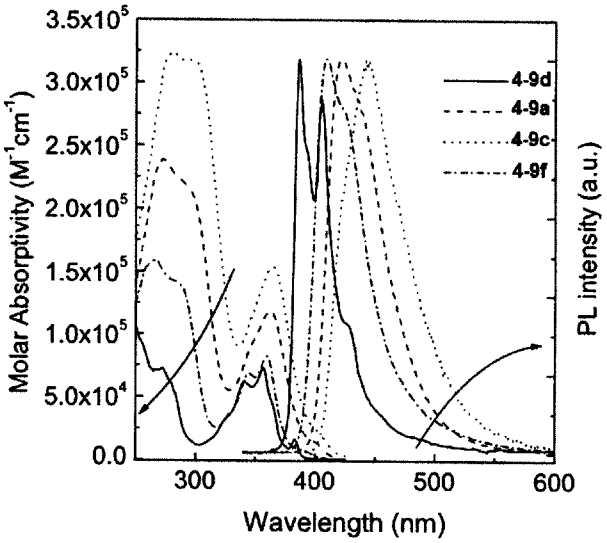

Figure 4-2. UV-Vis and one-photon-excited PL spectra of 1,8-diazapyrenes 4-9

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4.4 Conclusion

We have developed a modified $[Cp^*RhCl_2]_2$–$Cu(OAc)_2$ 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 $[Cp^*RhCl_2]_2$–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

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[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.

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

5.1 Introduction

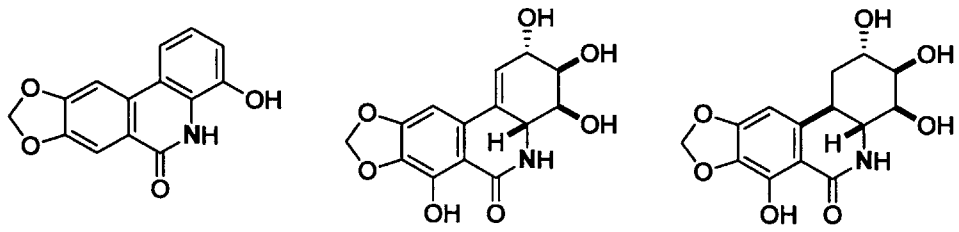
5.1.1 Overview

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.

5-12 **5-13**

Figure 5-1. Benzopyridinone: isoquinolone and quinolone

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]



5-14 **5-15** **5-16**

Figure 5-2. Plant alkaloids with isoquinolone as the basic unit

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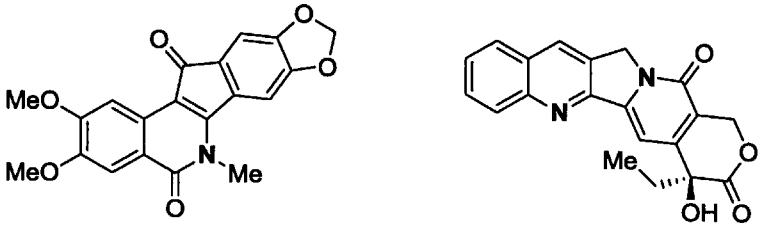
Besides the biologically active plant alkaloids, isoquinolone-derived structures can also be found in pharmaceutical drugs. For example, indenoisoquinoline NSC314622 (**5-17**) and its derivatives both possess significant anti-cancer activity. Cytotoxicity analysis revealed that **5-17** is potential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

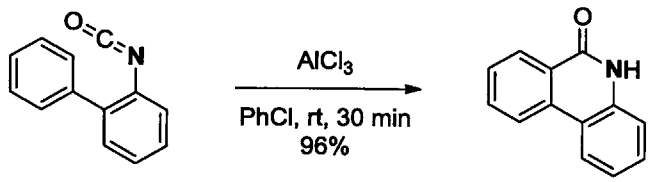


5-17 **5-18**

Figure 5-3. Isoquinolone-derived pharmaceutical drugs

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 $AlCl_3$ as a Lewis acid in chlorobenzene at room temperature (Scheme 5-1).[4]



5-19 **5-20**

Scheme 5-1. $AlCl_3$-catalyzed synthesis of phenanthridone

Later, Agawa and co-workers reported that the cyclization of vinyl isocyanate **5-21** bearing methylthio moiety under heating conditions proceeds to afford 2-

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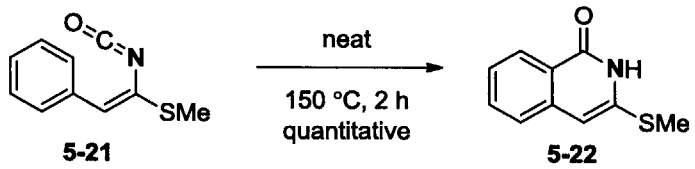
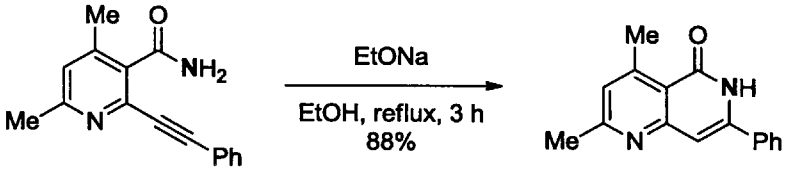
methylthioisoquinolone (**5-22**) in quantitative yield even without Lewis acid (Scheme 5-2).[5]



5-21 **5-22**

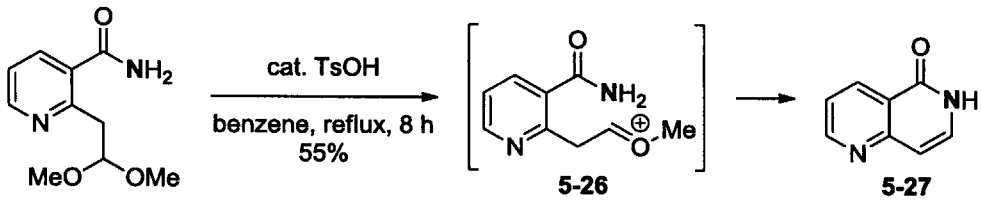
Scheme 5-2. Synthesis of 2-methylthioisoquinolone *via* thermolysis

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).[6] 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.



5-23 **5-24**

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



5-25 **5-26** **5-27**

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.[7] Sch 56036 is a polycyclic xanthone which exhibits high

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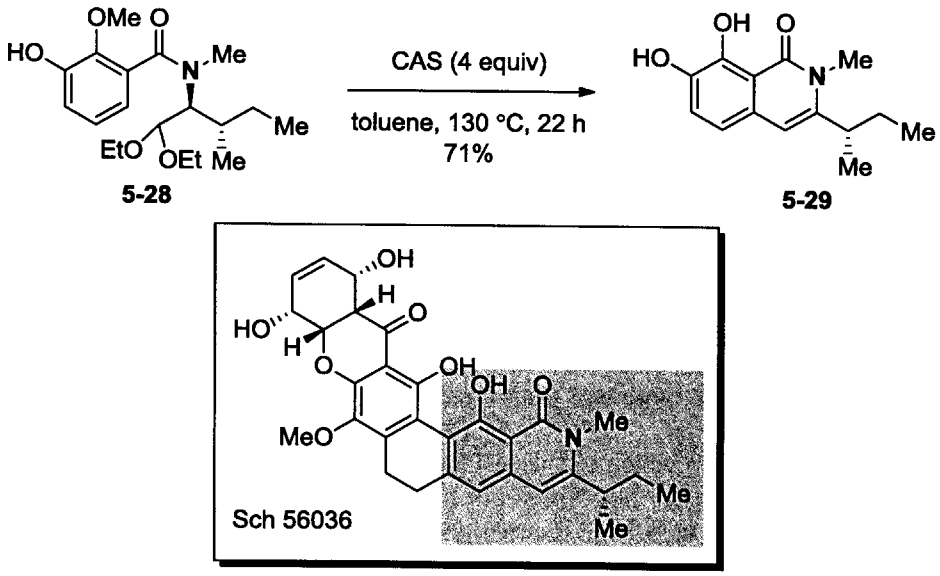
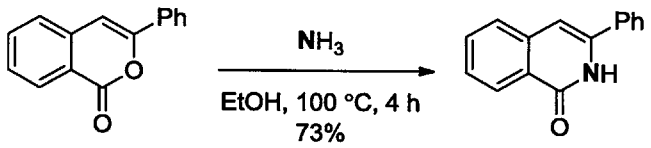
activity against a number of fungal pathogens in antifungal testing.[8] In that case, camphorsulfonic acid is used as the Lewis acid to facilitate Friedel-Craft-tyle cyclization *via* activation of the diethoxymethyl moiety of **5-28** (Scheme 5-5). High temperature required for the cyclization also brought about *O*-demethylation to provide isoquinolone **5-29** without epimerization.



Scheme 5-5. Construction of isoquinolone structure of Sch 56036

In another report, Overberger and Anselme showed that the convertion of 3-phenylisocoumarin to 3-phenylisoquinolone can be achieved using ethanol saturated with ammonia at 100 °C (Scheme 5-6).[9] Similar methodology has been applied by Bach and co-workers for the total synthesis of (±)-fredericamycin A.[10]



Scheme 5-6. Convertion of isocoumarin to isoquinolone

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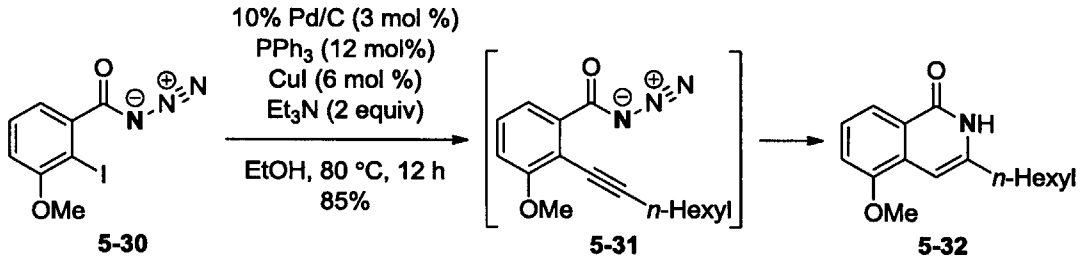
5.1.3 Modern routes in the synthesis of isoquinolones

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).[11]



5-30 **5-31** **5-32**

Scheme 5-7. An intramolecular acetylenic Schmidt reaction under Pd/C–Cu catalysis

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_3N 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

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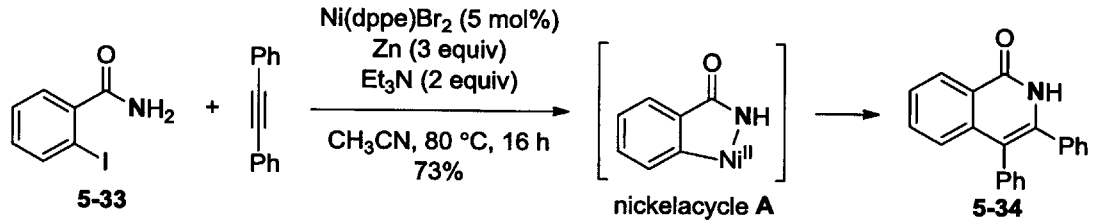
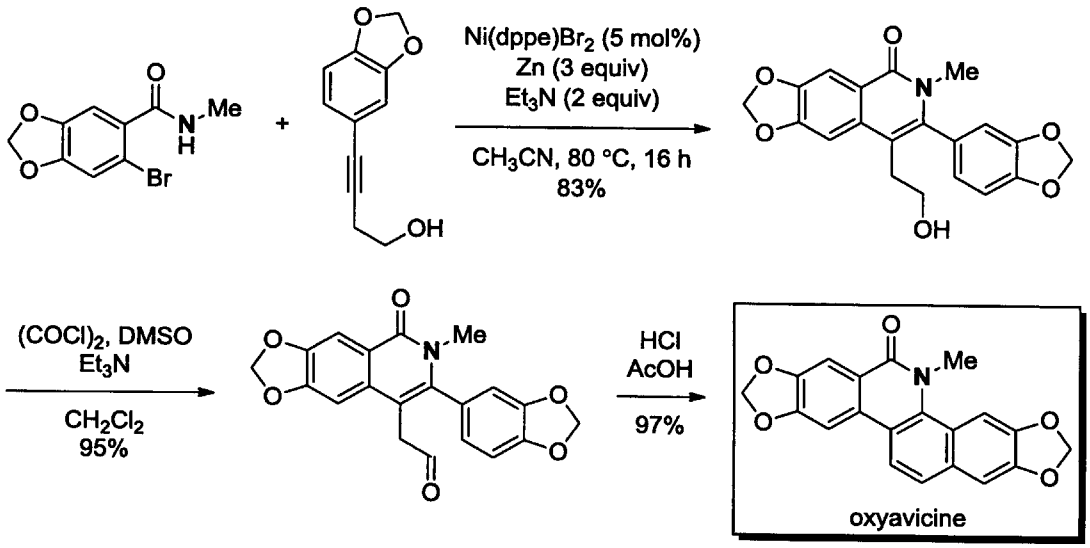
application to the total synthesis of oxyavicine (Scheme 5-9), an alkaloid natural product which exhibits analgesic and anti-inflammatory effects in the biological evaluation[12].



Scheme 5-8. An example of Ni(II)-catalyzed annulation of 2-iodobenzamides with alkynes



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 $Ni(cod)_2$ as a catalyst and PMe_3 (electron-rich phosphine) as a ligand.[13] The reaction mechanism may involve the nucleophilic attack of electron-rich $Ni(PMe_3)_n$ 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.

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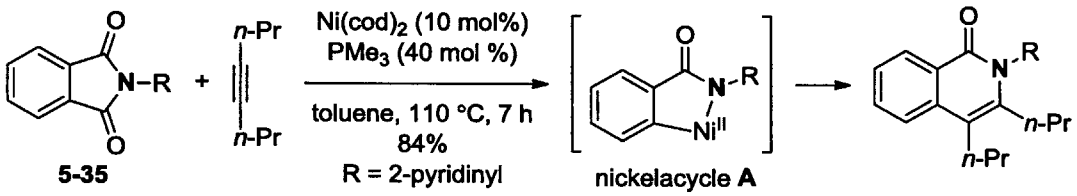
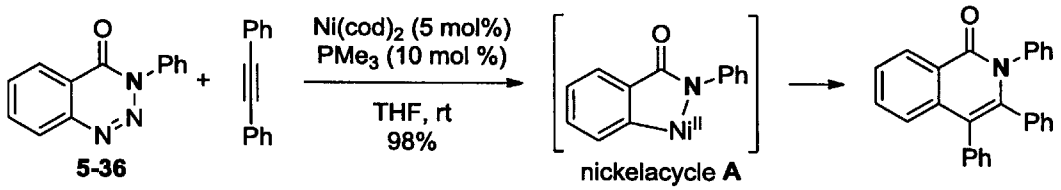


Scheme 5-10. An example of Ni(0)-catalyzed decarbonylative additions of phthalimides to alkynes

Murakami and co-workers showed that similar $Ni(cod)_2$–PMe_3 catalytic system is applicable for the synthesis of isoquinolones from 1,2,3-benzotriazin-4(3*H*)-ones and alkynes (Scheme 5-11).[14] 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.



Scheme 5-11. An example of Ni(0)-catalyzed denitrogenative alkyne insertions of 1,2,3-benzotriazin-4(3*H*)-ones

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.

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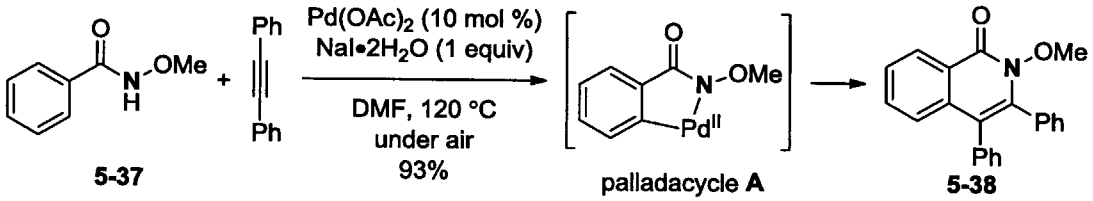
Furthermore, Pd(II)-catalyzed approach has also been successfully applied for the synthesis of isoquinolones. Treatment of *N*-methoxy benzamide (**5-37**) and diphenylacetylene with $Pd(OAc)_2$ and $NaI•2H_2O$ in DMF at 120 °C under an air atmosphere affords isoquinolone **5-38** in high yield (Scheme 5-12).[18] 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

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.[19] Electrophiles such as I_2 (Scheme 5-13), ICl, PhSeCl, and

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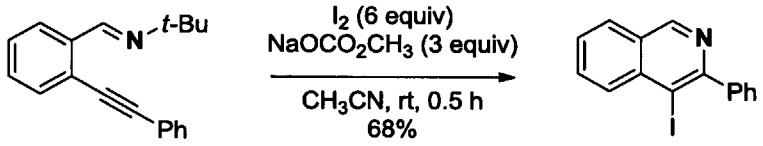
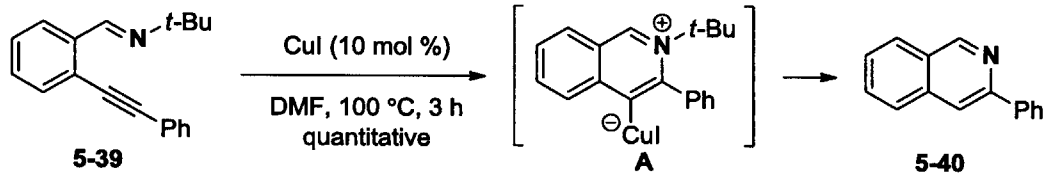
PhSCl have been successfully applied for the synthesis of 4-heterosubstituted isoquinolines. However, in some cases, 5-*exo*-cyclization products are dominant.



Scheme 5-13. An example of isoquinoline synthesis *via* electrophilic ring closure of 2-alkynyl benzaldimines with iodine

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).[20]



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

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.[21] 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**.

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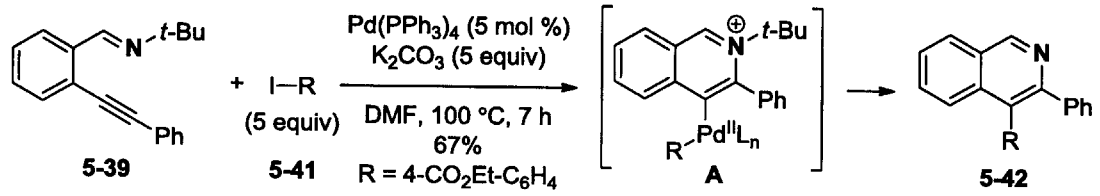
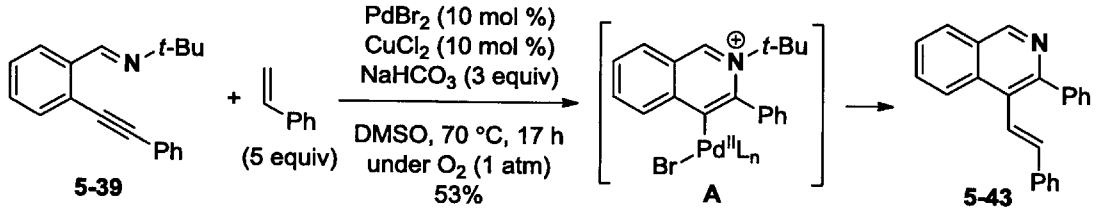


Scheme 5-15. An example of Pd(0)-catalyzed cross-coupling of 2-alkynyl benzaldimines and aryl iodides

To explore the reactivity of the isoquinolinium–Pd(II) complex **A** in a Heck reaction, *N-tert*-butyl-2-alkynyl benzaldimine **5-39** is treated with styrene in the presence of $PdBr_2$ and $CuCl_2$ under an oxygen atmosphere.[22] 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-styrylisoquinoline **5-43** (Scheme 5-16). It is worth noting that oxygen is used as the terminal oxidant to achieve catalytic turnover.



Scheme 5-16. Pd(II)-catalyzed cyclization and followed by a Heck reaction

On the other hand, the C-1 position of isoquinolinium–metal complex can be functionalized *via* addition of an 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.[23] 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

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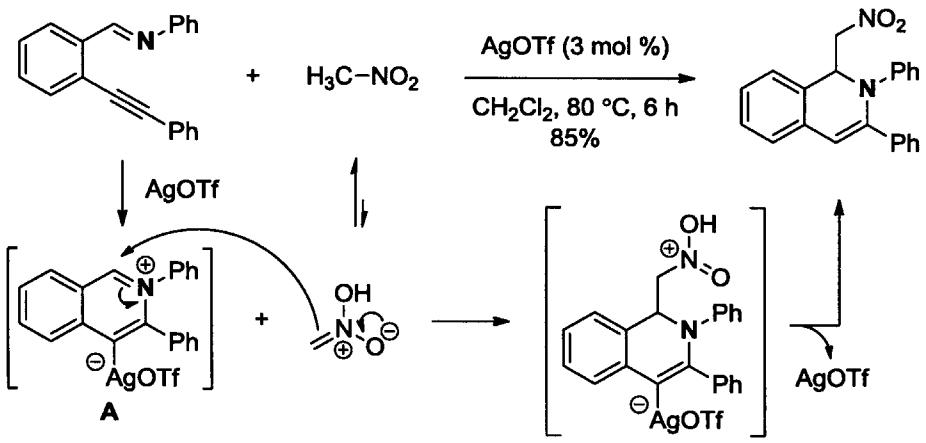
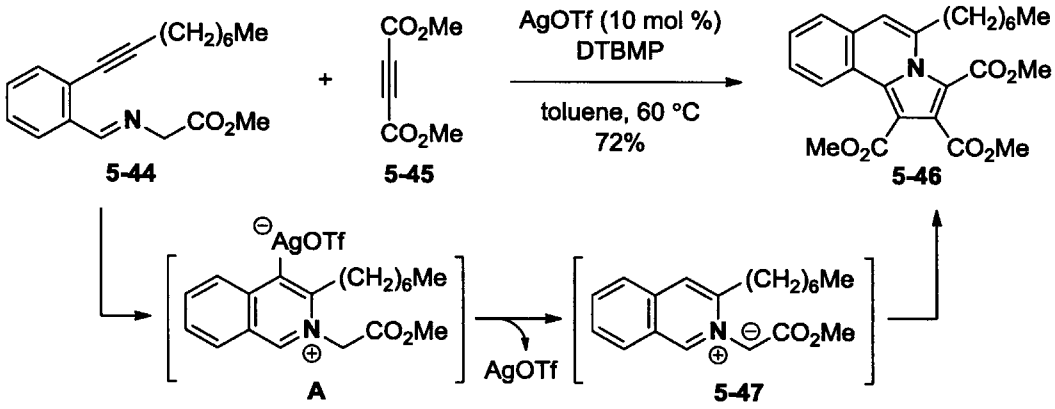
or *N*-alkyl group instead of *N*-*tert*-butyl group is important to stabilize the isoquinolinium–Ag(I) complexes **A** for nucleophilic attack. Further extension of the method to three-component reactions of 2-alkynylbenzaldehydes, amines, and ketones has been reported by Wu and co-workers.[24]



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



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

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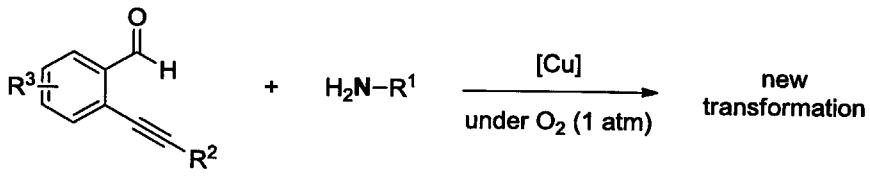
position of **5-47** can be functionalized with dimethylacetylene dicarboxylate (**5-45**) *via* [3+2] dipolar cycloaddition. Subsequent re-aromatization gives pyrroloisoquinoline **5-46**.[25] They believed that Ag(I)-catalyzed cycloisomerization to azomethine ylide **5-47** is the key step for the 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

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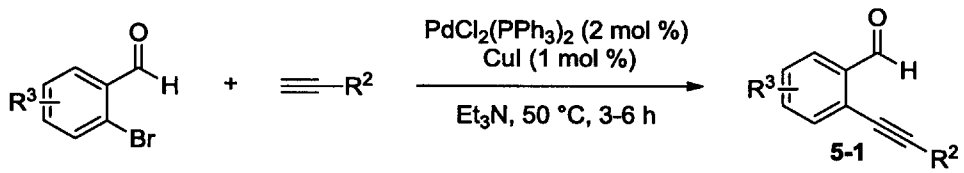
5.2 Results and discussion

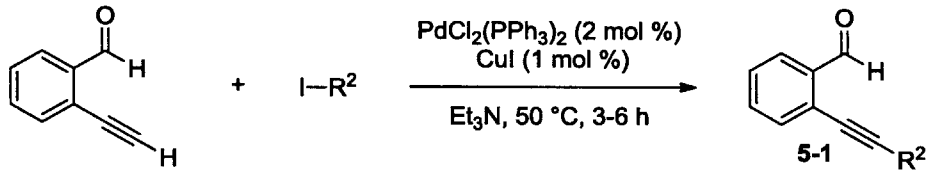
5.2.1 Synthesis of 2-alkynyl benzaldehydes

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_3N 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.



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).



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-(phenylethylnyl)benzaldehyde (**5-1a**) and benzylamine (**5-2a**) using $CuBr{\bullet}SMe_2$ as the initial catalyst under a molecular oxygen atmosphere (Table 5-1).

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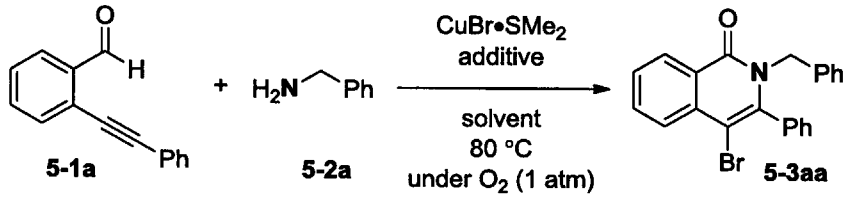
Table 5-1. Optimization of reaction conditions[a]



entry	$CuBr•SMe_2$ (equiv)	additive (0.2 g)	solvent	time (h)	yield of **3aa** (%)[b]
1[c]	0.5	—	toluene	26	19
2[c]	2.2	—	toluene	22	29[d]
3[c]	2.2	SiO_2	toluene	1	34[e]
4	2.2	SiO_2	pyridine	4	56
5	2.2	SiO_2	toluene:pyridine = 5:1	6	64
6	2.2	SiO_2	$ClCH_2CH_2Cl$:pyridine = 5:1	3.5	72
7	2.2	SiO_2	benzene:pyridine = 5:1	4	77 (80)[f]
8	2.2	SiO_2	benzene:pyridine = 10:1	6	70
9	1.1	SiO_2	benzene:pyridine = 5:1	4	39[g]
10	0.2[h]	SiO_2	pyridine	7	2
11[i]	2.2	SiO_2	benzene:pyridine = 5:1	4	49[g]
12	2.2	SiO_2	benzene:Et_3N = 5:1	5	0
13[j]	2.2	SiO_2	benzene	5	0[k]
14[l]	2.2	SiO_2	benzene	5	0

[a] 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 SiO_2 at 80 °C under an O_2 atmosphere, where 0.3 mmol of **5-2a** was added three times at every 1 h interval. [b] Isolated yield. [c] 1.1 equiv of **5-2a** was used and 2.2 equiv of pyridine. [d] **5-1a** was recovered in 31% yield. [e] 4-Bromo-3-phenylisoquinoline (**5-4**) was isolated in 24%. [f] Parenthesis shows the yield of **5-3aa** using 0.5 mmol of **5-1a** with 0.3 g of SiO_2. [g] 1H NMR yield from the crude mixture. [h] 2 equiv of LiBr was added. [i] $CuBr_2$ was used instead of $CuBr•SMe_2$. [j] 2.2 equiv of DABCO was added. [k] 3-Phenylisoquinoline (**5-5**) was isolated in 37% yield. [l] 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 $CuBr•SMe_2$ 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–O_2 system; in contrast, isoquinolines

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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.[26] 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.[27]

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).

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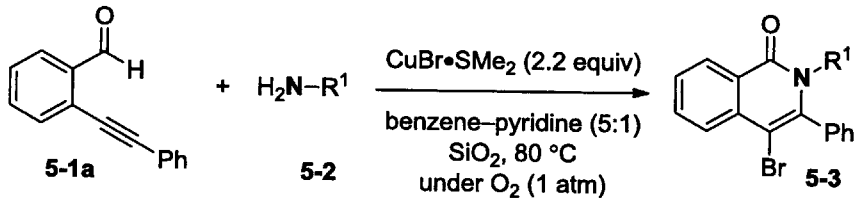
The reactions using other tertiary amines such as triethylamine, DABCO, and 2,2'-bipyridine instead of pyridine did not afford product **5-3aa** at all (Table 5-1, entries 12-14). No 4-bromoisoquinolone formation was observed under a molecular nitrogen atmosphere. These results suggested that the presence 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[a]



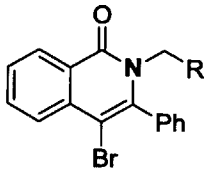
entry	amine **5-2**	4-bromoisoquinolone **5-3** / yield[b]
		
1	**5-2b** (R = 4-OMe-C_6H_4)	**5-3ab**: 64%
2	**5-2c** (R = 4-Me-C_6H_4)	**5-3ac**: 72%
3	**5-2d** (R = 4-F-C_6H_4)	**5-3ad**: 76%
4	**5-2e** (R = CH_2Ph)	**5-3ae**: 55% (51%)[c]
5	**5-2f** (R = $CHPh_2$)	**5-3af**: 56% (42%)[c]
6	**5-2g** (R = *n*-Bu)	**5-3ag**: 59%
7	**5-2h** (R = *cyclo*-C_6H_{11})	**5-3ah**: 57% (53%)[c]
8	**5-2i** (R = *cyclo*-C_3H_5)	**5-3ai**: 57% (52%)[c]

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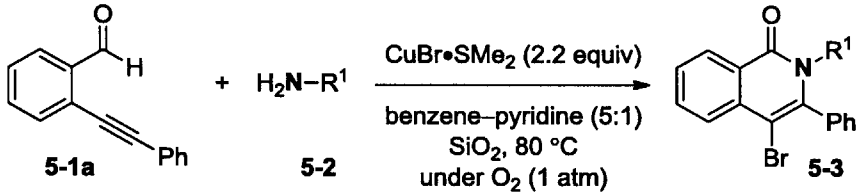
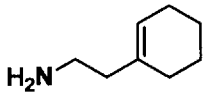
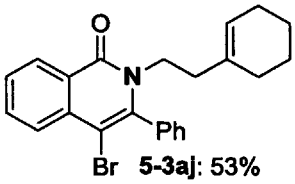
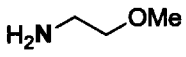
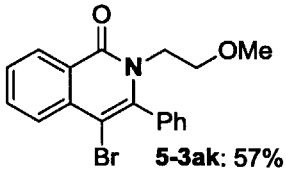
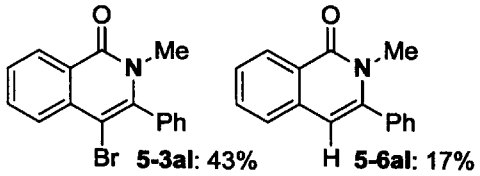
Table 5-2. Scope of primary amines[a] (*continue*)



entry	amine **5-2**	4-bromoisoquinolone **5-3** / yield[b]
9	 **5-2j**	 **5-3aj**: 53%
10	 **5-2k**	 **5-3ak**: 57%
11	H_2N–Me (40 wt % in H_2O) **5-2l**	 **5-3al**: 43% **5-6al**: 17%

[a] Unless otherwise notes, 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. [c] 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_2O) 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_2O), 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

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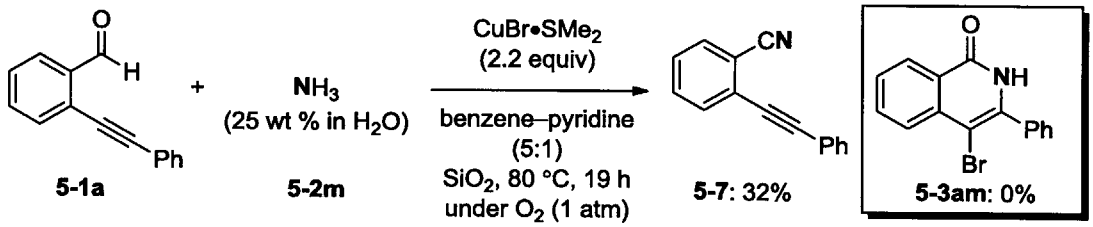
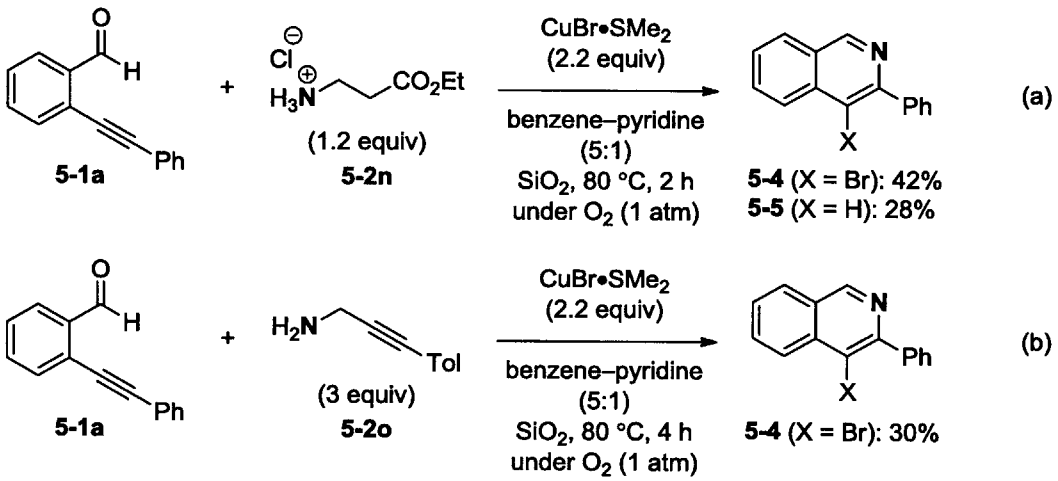
a nitrogen source and MeONa as a base under a molecular oxygen atmosphere in MeOH has been reported by Smit and co-workers.[28] It is noted that aromatic amines (anilines) did not work at all.



Scheme 5-22. Formation of benzonitrile from benzaldehyde

The reaction of β-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

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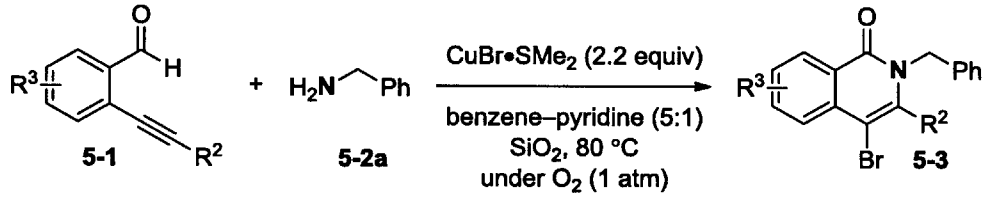
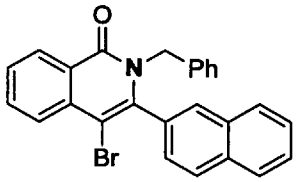
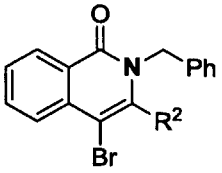
Chart 5-1. Scope of 2-alkynylbenzaldehydes[a,b]



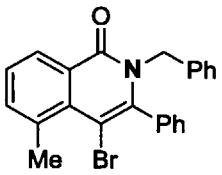
5-3ba (R = 4-OMe): 90%
5-3ca (R = 4-Me): 83%
5-3da (R = 4-F): 73%
5-3ea (R = 4-CO_2Et): 37%
5-3fa (R = 4-CF_3): <47%[c]
5-3ga (R = 3-OMe): 75%
5-3ha (R = 2-OMe): 86%
5-3ia (R = 2-Br): 59%



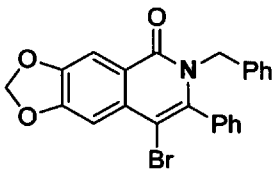
5-3ja: 66%



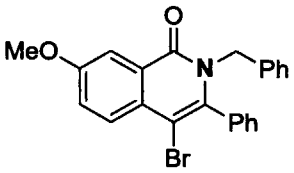
5-3ka (*n*-C_5H_{11}): 72%
5-3la (*cyclo*-C_6H_{11}): 42%
5-3ma (*cyclo*-C_3H_5): 65%



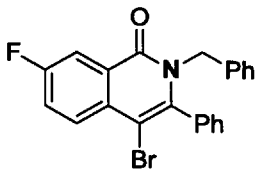
5-3na: 66%



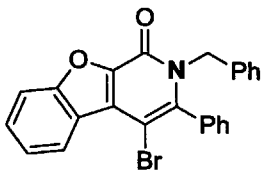
5-3oa: 60%



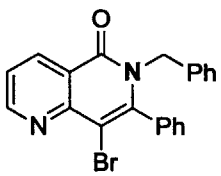
5-3pa: 47%



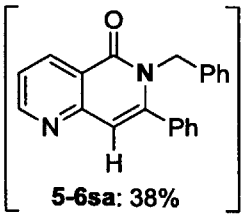
5-3qa: 73%



5-3ra: 29%



5-3sa: 43%



5-6sa: 38%

[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. [b] Isolated yields. [c] The purity of product **5-3fa** is ≤90%.

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 R^2-substituent on the alkyne of **5-1** regardless of the arene substitution pattern to afford

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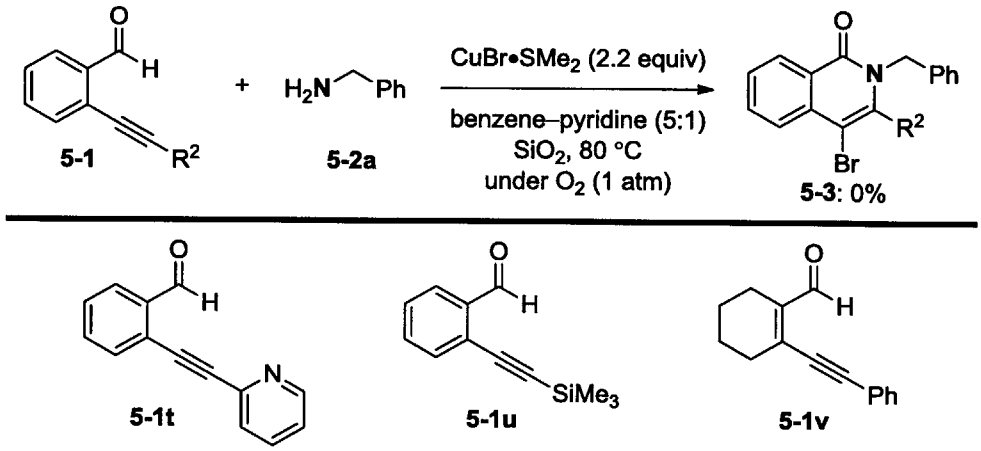
the corresponding 4-bromoisoquinolones **5-3** in good yields. However, aryl groups bearing electron-deficient moieties such as CO_2Et (for **5-3ea**) and CF_3 (for **5-3fa**) at R^2-substituent resulted in the formation of 4-bromoisoquinolones **5-3** in lower yields. Even the linear and cyclic alkyl 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[a]



[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

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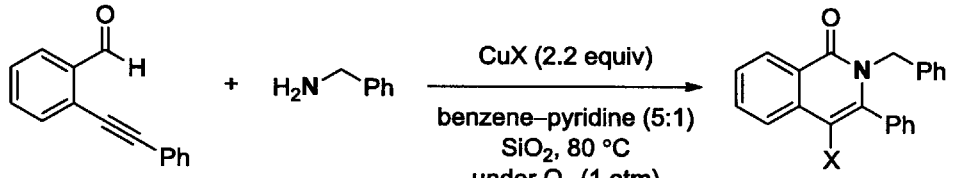
(**5-1u**) moieties at R^2-substituent as well as 2-(phenylethynyl)cyclohex-1-ene carbaldehyde (**5-1v**) were decomposed without the formation of 4-bromoisoquinolones **5-3** (Chart 5-2).

It was found that the treatment of **5-1a** and **5-2a** with CuCl and CuI separately under the same conditions without $CuBr{\bullet}SMe_2$ resulted in the formation of 4-chloroisoquinolone **5-3aa'** and 4-iodoisoquinolone **5-3aa''** in 23% and 39% respectively (Scheme 5-24).



Scheme 5-24. Synthesis of 4-chloroisoquinolone and 4-iodoisoquinolone from CuCl and CuI respectively

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

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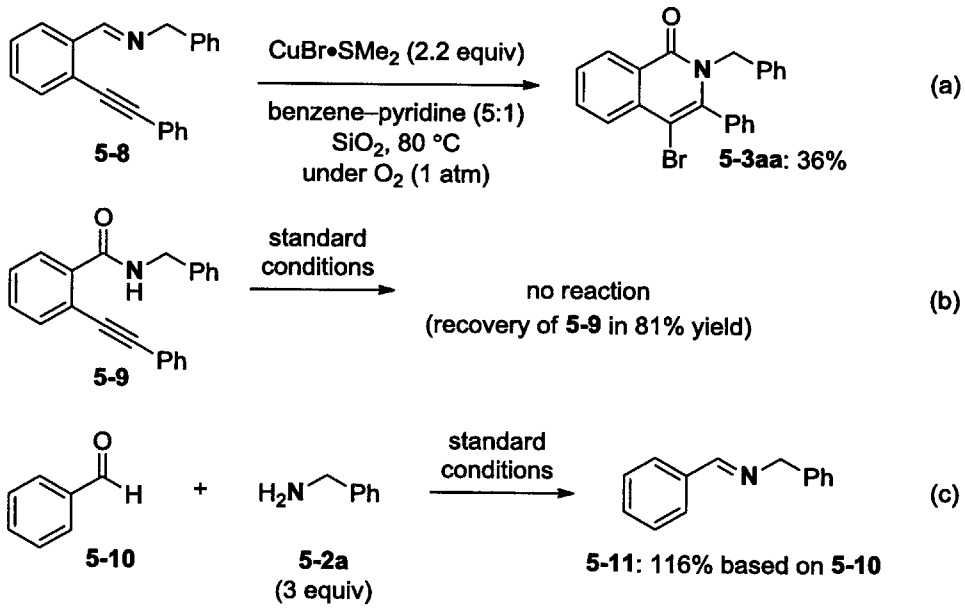
chemical yield of over 100% revealed that **5-11** is not only derived from dehydrative condensation of **5-10** and **5-2a**; however, **5-11** is also partly contributed from dimerization of **5-2a** (Scheme 5-25 (c)). Similar oxidative dimerization of benzylamines has been reported previously by Lee and co-workers.[26]



Scheme 5-25. Elucidation of reaction mechanism–1

Previously, Stahl and-co-workers reported a $CuBr_2$-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 $CuBr_2$ 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 $CuBr•SMe_2$ and SiO_2 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

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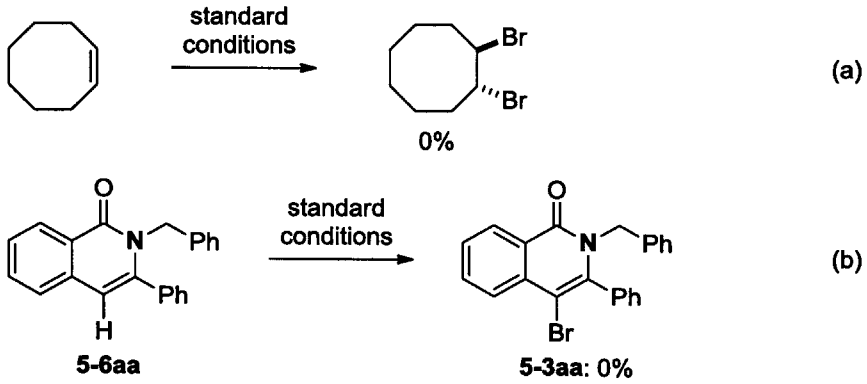
bromonium cation for the electrophilic bromination in the synthesis of 4-bromoisoquinolones.

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.



Scheme 5-26. Elucidation of reaction mechanism–2

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 $[Cu^{n}]Br$ to give vinyl copper species **II** (Scheme 5-27, path a). In the present aerobic conditions, $Cu^{I}Br$ might be oxidized by molecular oxygen to $Cu^{II}Br$ species, which may facilitate the isoquinolone formation.[30]

Alternatively, hemiaminal **I** can undergo dehydrative condensation to provide aldimine **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 aldimine **5-8** as the starting material under the present aerobic conditions

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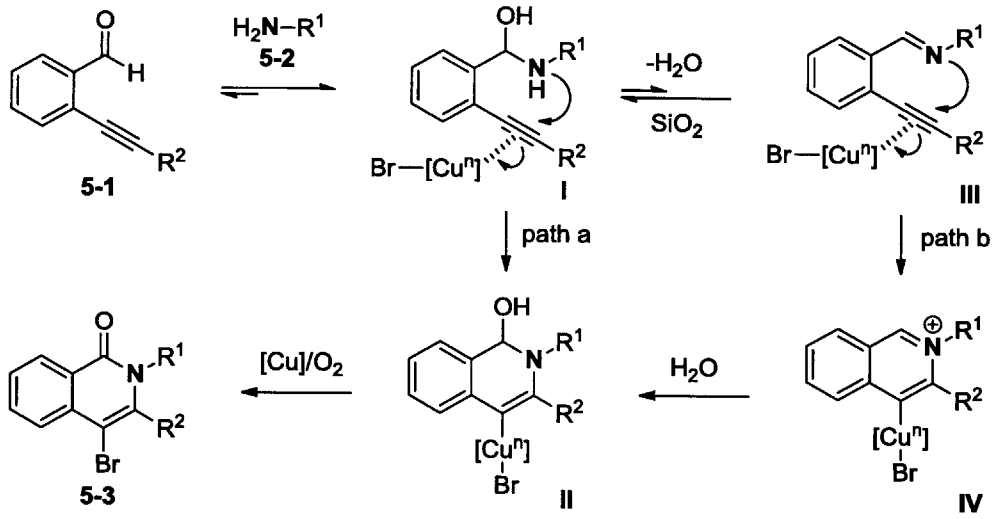
(Scheme 5-25 (a)). SiO_2 may play an important role to drive the equilibrium from aldimine **III** to hemiaminal **I** and lead to shorter reaction time and higher efficiency. From putative intermediate **II**, further C–Br bond reductive elimination[31] and oxidation of the C–O bond under the Cu–O_2 system[32] 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.



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.

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Chapter 6 Experimental

6.1 General

^{1}H NMR (400MHz) spectra [using $(CH_3)_4Si$ (for ^{1}H, δ = 0.00) as internal standard] and ^{13}C NMR (100 MHz) spectra [using $CDCl_3$ (for ^{13}C, δ = 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.

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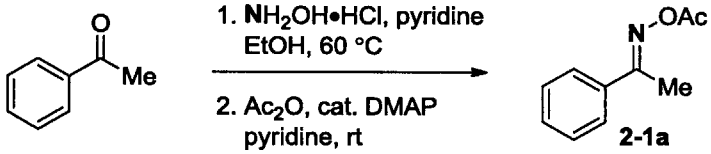
6.2 Experimental section of Chapter 2:

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).



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 NH_2OH•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 $MgSO_4$. 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 Ac_2O (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 $MgSO_4$. 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.

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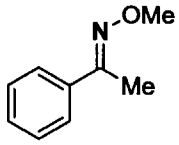
(*E*)-Acetophenone *O*-acetyl oxime (2-1a)

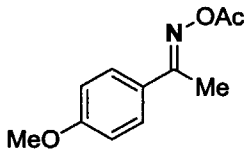
White solid; mp. 56–57 °C; IR (NaCl) 1763, 1616, 1445, 1368, 1310, 935 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.27 (3H, s), 2.39 (3H, s), 7.38-7.47 (3H, m), 7.74 (2H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 19.8, 127.0, 128.5, 130.5, 134.8, 162.4, 169.0; ESI-HRMS: Found: m/z 178.0872. Calcd for $C_{10}H_{12}NO_2$: $(M+H)^+$ 178.0868.

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



Prepared by treatment of acetophenone with $MeONH_2$•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, $CDCl_3$) δ 2.24 (3H, s), 4.01 (3H, s), 7.37-7.39 (3H, m), 7.65-7.68 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) 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, $CDCl_3$) 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); ^{13}C NMR

[1] Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F. G.; Ayala, A. M.; Correa, W.; De Jesus, M. *Org. Lett.* **2007**, *9*, 1793.

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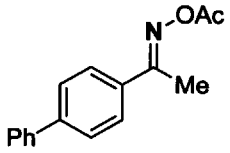
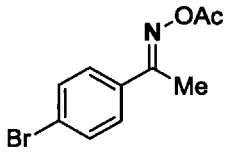
(100 MHz, $CDCl_3$) δ 14.1, 19.9, 55.3, 113.9, 127.1, 128.5, 161.5, 161.9, 169.1; ESI-HRMS: Found: m/z 208.0968. Calcd for $C_{11}H_{14}NO_3$: $(M+H)^+$ 208.0974.

(*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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{16}H_{16}NO_2$: $(M+H)^+$ 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, $CDCl_3$) δ 2.26 (3H, s), 2.36 (3H, s), 7.53 (2H, d, J = 8.8 Hz), 7.61 (2H, d, J = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{10}H_{11}NO_2{}^{79}Br$: $(M+H)^+$ 255.9973.

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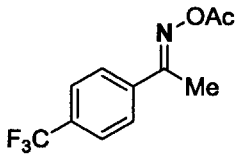
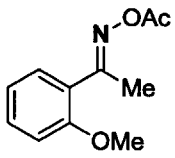
(*E*)-1-(4-(Trifluoromethyl)phenyl)ethanone *O*-acetyl oxime (2-1e)



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, 1317, 1204, 1132, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{11}H_{11}NO_2F_3$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{11}H_{14}NO_3$: $(M+H)^+$ 208.0974.

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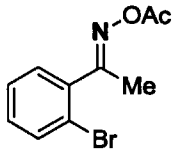
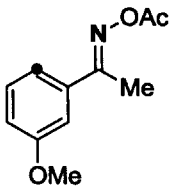
(*E*)-1-(2-Bromophenyl)ethanone *O*-acetyl oxime (2-1g)



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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{10}H_{11}NO_2{}^{79}Br$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{11}H_{14}NO_3$: $(M+H)^+$ 208.0974.

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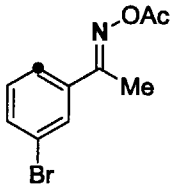
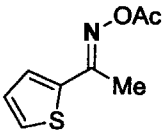
(*E*)-1-(3-Bromophenyl)ethanone *O*-acetyl oxime (2-1i)[2]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



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, 1526, 1429, 1368, 1306 966 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_8H_{10}NO_2S$: $(M+H)^+$ 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.

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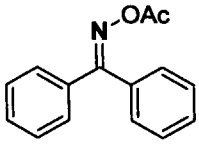
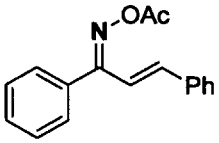
Benzophenone *O*-acetyl oxime (2-1k)[4]



Prepared from benzophenone and purified by recrystallization from hexane-ethyl acetate (one time) in 73% yield; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.11 (3H, s), 7.31-7.38 (4H, m), 7.43-7.49 (4H, m), 7.57-7.59 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 128.2, 128.4, 128.8, 129.0, 129.6, 130.9, 132.5, 134.8, 164.7, 168.8.

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



Prepared from (1*E*,2*E*)-chalcone oxime[5] 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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (3H, s), 6.85 (1H, d, J = 16.4 Hz), 7.37-7.40 (3H, m), 7.43-7.52 (5H, m), 7.56-7.59 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{17}H_{16}NO_2$: $(M+H)^+$ 266.1181.

[4] Liu, S.; Yu, Y.; Liebeskind, L. S. *Org. Lett.* **2007**, *9*, 1947.
[5] Treatment of *trans*-chalcone with hydroxylamine provided an *syn*- and *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. *J. Am. Chem. Soc.* **1991**, *113*, 1364.

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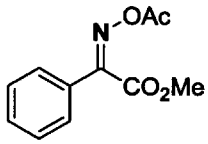
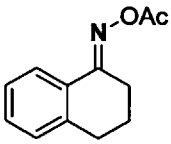
(*Z*)-Methyl 2-(acetoxyimino)-2-phenylacetate (2-1m)



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, 1435, 1368, 1335, 1233, 1186 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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(2*H*)-one *O*-acetyl oxime (2-1n)



Prepared from α-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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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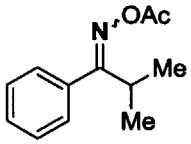
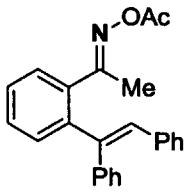
Isobutyrophenone *O*-acetyl oxime (2-1o)



syn:*anti* = 1:1

Colorless oil; IR (NaCl) 2970, 2934, 1626, 1466, 1445, 1366, 1206 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (6H×1, d, J = 6.8 Hz), 1.22 (6H×1, d, J = 7.2 Hz), 1.95 (3H×1, s), 2.23 (3H×1, s), 2.99 (1H×1, septet, J = 6.8 Hz), 3.53 (1H×1, septet, J = 7.2 Hz), 7.13-7.16 (2H×1, m), 7.34-7.45 (3H×1+5H×1, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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; ESI-HRMS: Found: m/z 206.1189. Calcd for $C_{12}H_{16}NO_2$: $(M+H)^+$ 206.1181.

(*E*)-1-(2-((*E*)-1,2-Diphenylvinyl)phenyl)ethanone *O*-acetyl oxime (2-1p)



Prepared from (*E*)-1-(2-(1,2-diphenylvinyl)phenyl)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}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.89 (3H, s), 2.01 (3H, s), 7.00-7.02 (3H, m), 7.11-7.15 (3H, m), 7.24-7.32 (5H, m), 7.36-7.43 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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; ESI-HRMS: Found: m/z 356.1653. Calcd for $C_{24}H_{22}NO_2$: $(M+H)^+$ 356.1651.

[6] Lim, S.-G.; Lee, J. H.; Moon, C. W.; Hong, J.-B.; Jun, C.-H. *Org. Lett.* **2003**, *5*, 2759.

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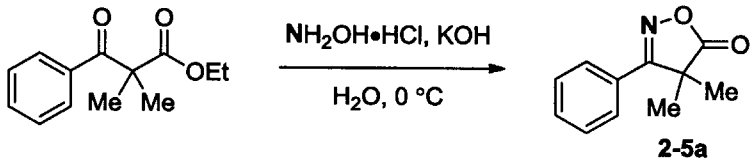
6.2.1.2. Preparation of 4,4-dimethyl-3-phenylisoxazol-5(4*H*)-one (2-5a)[7]



2-5a

To a stirred solution of $NH_2OH•HCl$ (0.87 g, 12.5 mmol) in minimum amount of H_2O at 0 °C was added 8 M of KOH (0.91 g, 22.8 mmol) in H_2O 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_2Cl_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(4*H*)-one (2-5a)

White solid; ^1H 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.

[7] Canonne, P.; Thibeault, D.; Fytas, G. *Tetrahedron* **1986**, *42*, 4203.

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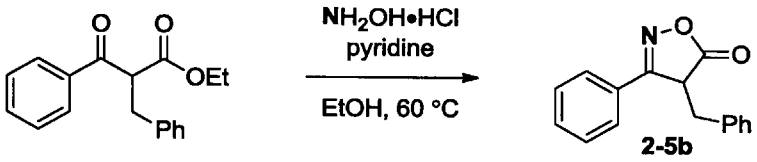
6.2.1.3. Preparation of 3-phenylisoxazol-5-ones 2-5b and 2-5c: a typical procedure for the synthesis of 4,4-dimethyl-3-phenylisoxazol-5(4*H*)-one (2-5b)



2-5b

To a solution of ethyl benzylbenzoylacetate (2.00 g, 7.08 mmol) and pyridine (1.7 mL, 21.3 mmol) in EtOH (7 mL) was added NH_2OH•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(4*H*)-one (2-5b)[8]

75:25
at room temperature

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$_{imine}$, dd, J = 5.2, 14.0 Hz), 3.37 (0.75H$_{imine}$, dd, J = 4.8, 14.0 Hz), 3.78 (0.5H$_{enamine}$, s), 4.15 (0.75H, dd, J = 4.8, 5.2 H), 6.87 (1.5H$_{imine}$, 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.

[8] Risitano, F.; Grassi, G.; Caruso, F.; Foti, F. *Tetrahedron* **1996**, *52*, 1443.

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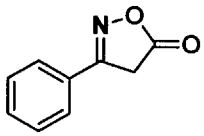
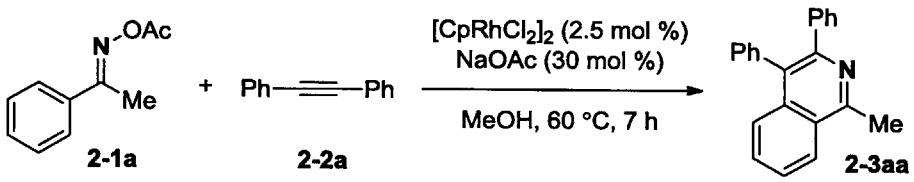
3-Phenylisoxazol-5(4*H*)-one (2-5c)[9]



Prepared from ethyl benzoylacetate and purified by recrystallization from hexane-ethyl acetate (twice) in 74% yield; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.8 (2H, s), 7.46-7.57 (3H, m), 7.67-7.70 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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).



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 $[Cp^*RhCl_2]_2$ (4.6 mg, 0.0075 mmol) and NaOAc (7.4 mg, 0.09 mmol), 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 *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.

[9] Villemin, D.; Martin, B.; Garrigues, B. *Synth. Commun.* **1993**, *23*, 2251.

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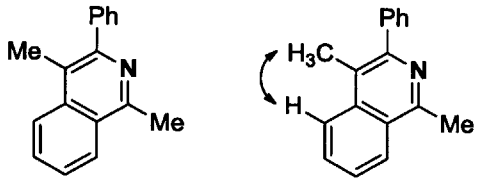
1-Methyl-3,4-diphenylisoquinoline (2-3aa)[10]

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

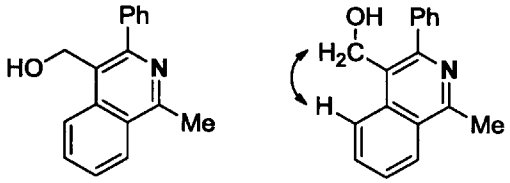
1,4-Dimethyl-3-phenylisoquinoline (2-3ab)[10]



NOESY correlation

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)



NOESY correlation

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, $CDCl_3$) δ 3.01 (3H, s), 5.03 (2H, s), 7.40-7.50 (3H, m),

[10] Parthasarathy, K.; Cheng, C.-H. *J. Org. Chem.* **2009**, *74*, 9359.

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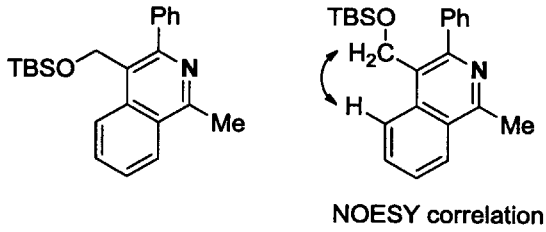
7.62-7.67 (3H, m), 7.79 (1H, ddd, J = 8.4, 6.8, 1.2 Hz), 8.20 (1H, d, J = 8.0 Hz), 8.30 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 59.5, 124.1, 124.4, 126.1, 126.7, 128.0, 128.2, 129.7 (overlapped), 130.6, 135.8, 140.5, 151.8, 158.6; ESI-HRMS: Found: m/z 250.1234. Calcd for $C_{17}H_{16}NO$: $(M+H)^+$ 250.1232.

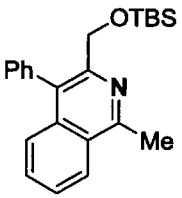
4-((*tert*-Butyldimethylsilyloxy)methyl)-1-methyl-3-phenylisoquinoline (2-3ad)



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}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{30}NOSi$: $(M+H)^+$ 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}; ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.06 (6H, s), 0.83 (9H, s), 3.03 (3H, s), 4.67 (2H, s),

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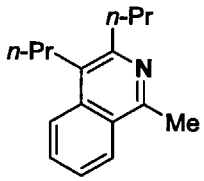
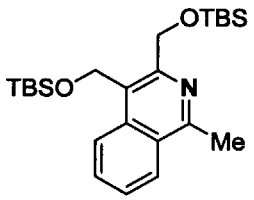
7.33-7.36 (2H, m), 7.44-7.52 (4H, m), 7.53-7.58 (2H, m), 8.14-8.16 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.25, 18.5, 22.4, 26.0, 65.5, 125.4, 126.2, 126.44, 126.48, 127.5, 128.2, 129.6, 130.3, 130.7, 136.0, 136.8, 148.6, 157.6; ESI-HRMS: Found: m/z 364.2097. Calcd for $C_{23}H_{30}NOSi$: $(M+H)^+$ 364.2097.

1-Methyl-3,4-dipropylisoquinoline (2-3ae)[10]



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)



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 $C_{24}H_{42}NO_2Si_2$: $(M+H)^+$ 432.2754.

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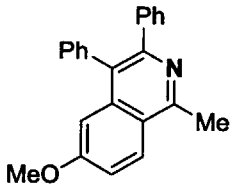
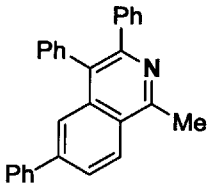
6-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3ba)[10]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)



White solid; mp. 177–179 °C; IR (NaCl) 3059, 2959, 1730, 1616, 1568, 1487, 1447, 1339 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.7, 124.0, 125.2, 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 $C_{28}H_{22}N$: $(M+H)^+$ 372.1752.

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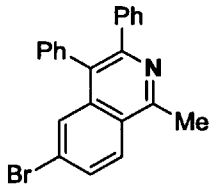
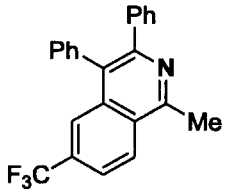
6-Bromo-1-methyl-3,4-diphenylisoquinoline (2-3da)



White solid; mp. 193–195 °C; IR (NaCl) 3059, 2965, 1601, 1566, 1483, 1439, 1393, 1331, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{17}N^{79}Br$: $(M+H)^+$ 374.0544.

1-Methyl-3,4-diphenyl-6-(trifluoromethyl)isoquinoline (2-3ea)[7]



White solid; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

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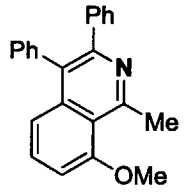
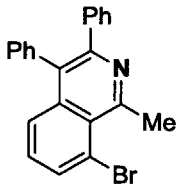
8-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3fa)



White solid; mp. 146–147 °C; IR (NaCl) 3061, 2965, 1610, 1572, 1551, 1456, 1433, 1389, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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)



White solid; mp. 144–147 °C; IR (NaCl) 3061, 2978, 1543, 1499, 1435, 1385, 1356, 1339 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

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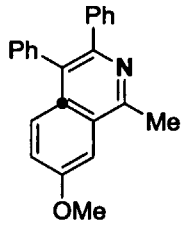
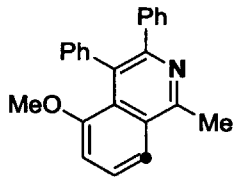
7-Methoxy-1-methyl-3,4-diphenylisoquinoline (2-3ha)[8]



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

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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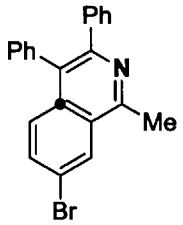
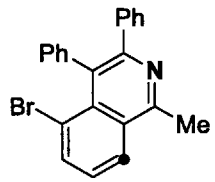
7-Bromo-1-methyl-3,4-diphenylisoquinoline (2-3ia)



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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{17}N^{79}Br$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{17}N^{79}Br$: $(M+H)^+$ 374.0544.

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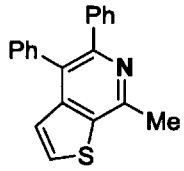
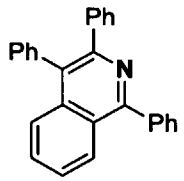
7-Methyl-4,5-diphenylthieno[2,3-*c*]pyridine (2-3ja)[8]



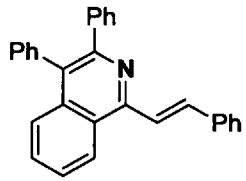
White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.91 (3H, s), 7.18-7.25 (6H, m), 7.29-7.37 (5H, m), 7.61 (1H, d, J = 5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.7, 124.2, 127.0, 127.1, 127.7, 128.18, 128.23, 130.3, 130.5, 130.9, 134.2, 138.3, 140.5, 145.7, 150.9, 151.4.

1,3,4-Triphenylisoquinoline (2-3ka)[8]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



White solid; mp. 172–174 °C; IR (NaCl) 3061, 1632, 1539, 1503, 1449, 1385, 1339 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20-7.27 (5H, m), 7.31-7.48 (8H, m), 7.56-7.62 (2H, m),

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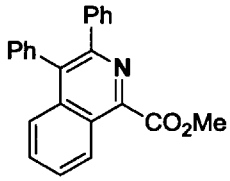
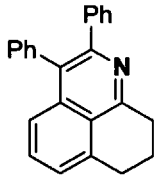
7.69-7.73 (3H, m). 8.08 (1H, d, J = 15.6 Hz), 8.14 (1H. d, J = 15.6 Hz), 8.45 (1H, d, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.9, 124.3, 125.4, 126.3, 126.6, 127.1, 127.2, 127.47, 127.51, 128.3, 128.5, 128.7, 129.78, 129.83, 130.5, 131.4, 136.1, 136.8, 137.1, 137.7, 141.1, 149.8, 153.4; ESI-HRMS: Found: m/z 384.1753. Calcd for $C_{29}H_{22}N$: $(M+H)^+$ 384.1752.

Methyl 3,4-diphenylisoquinoline-1-carboxylate (2-3ma)



White solid; mp. 157–159 °C; IR (NaCl) 3059, 2953, 1724, 1549, 1502, 1439, 1362, 1256 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-7*H*-benzo[*de*]quinoline (2-3na)



White solid; mp. 151–153 °C; IR (NaCl) 3061, 2947, 1607, 1580, 1557, 1443, 1389, 1375 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 23.4, 30.7, 34.8, 123.5, 123.9, 124.7, 126.8, 127.0, 127.6,

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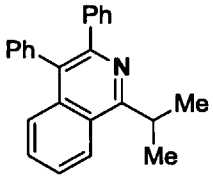
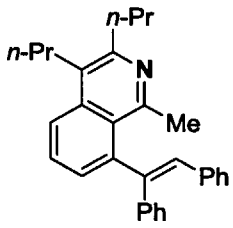
128.1, 129.0, 129.9, 130.2, 131.4, 136.2, 137.8, 138.5, 141.1, 149.5, 159.3; ESI-HRMS: Found: m/z 322.1594. Calcd for $C_{24}H_{20}N$: $(M+H)^+$ 322.1596.

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



White solid; mp. 142–145 °C; IR (NaCl) 3061, 2967, 1551, 1504, 1389, 1323, 1009 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{22}N$: $(M+H)^+$ 324.1752.

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



Yellow oil; IR (NaCl) 2959, 2930, 1597, 1560, 1493, 1445, 1375, 1217 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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), 7.60 (1H, dd, J = 7.2, 8.8 Hz), 8.03 (1H, dd, J = 0.8, 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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,

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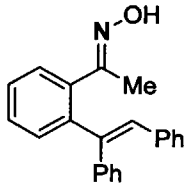
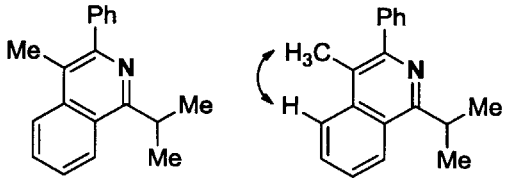
143.9, 151.6, 155.6; ESI-HRMS: Found: m/z 406.2535. Calcd for $C_{30}H_{32}N$: $(M+H)^+$ 406.2535.

(*E*)-1-(2-((*E*)-1,2-diphenylvinyl)phenyl)ethanone oxime (2-4p)



White solid; mp. 133–135 °C; IR (NaCl) 1599, 1491, 1443, 1366, 924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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-Isopropyl-4-methyl-3-phenylisoquinoline (2-6ab)



NOESY correlation

White solid; mp. 92–94 °C; IR (NaCl) 3059, 2967, 1613, 1562, 1506, 1389. 1323 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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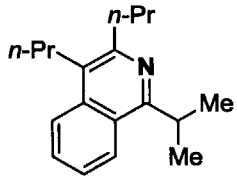
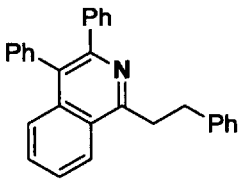
1-Isopropyl-3,4-dipropylisoquinoline (2-6ae)



Colorless oil; IR (NaCl) 3071, 2959, 2930, 1614, 1566, 1456, 1389, 1379, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{18}H_{26}N$: $(M+H)^+$ 256.2065.

1-Phenethyl-3,4-diphenylisoquinoline (2-6ba)[9]



White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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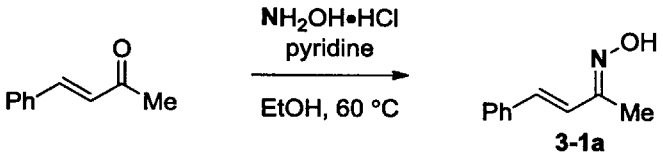
6.3 Experimental section of Chapter 3:

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 (2*E*,3*E*)-4-phenylbut-3-en-2-one oxime (3-1a).



3-1a

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 $NH_2OH•HCl$ (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 $MgSO_4$. 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*E*,3*E*)-4-phenylbut-3-en-2-one oxime (**3-1a**) in quantitative yield.

(2*E*,3*E*)-4-Phenylbut-3-en-2-one oxime (3-1a)[11]

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 9.7, 125.7, 126.9, 128.4, 128.7, 133.4, 136.3, 156.8.

[11] Talapatra, S. K.; Chaudhuri, P.; Talapatra, B. *Heterocycles* **1980**, *14*, 1279.

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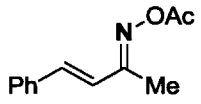
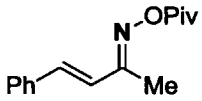
(2*E*,3*E*)-4-Phenylbut-3-en-2-one *O*-acetyl oxime (3-1a')[12]



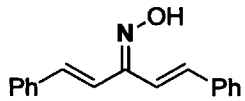
Prepared by treatment of **3-1a** with Ac_2O (2 equiv) in the presence of DMAP (5 mg) in pyridine, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 82% yield; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (6H, s), 7.01 (1H, d, J = 16.4 Hz), 7.08 (1H, d, J = 16.4 Hz), 7.30-7.39 (3H, m), 7.46-7.50 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 19.7, 124.3, 127.2, 128.9, 129.2, 135.5, 137.4, 162.3, 168.4.

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



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_2Cl_2, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 80% yield; White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (9H, s), 2.23 (3H, s), 7.04 (1H, d, J = 16.8 Hz), 7.08 (1H, d, J = 16.8 Hz), 7.30-7.40 (3H, m), 7.49 (2H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 27.3, 38.8, 124.5, 127.2, 128.9, 129.2, 135.6, 137.2, 162.8, 175.0.

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



Prepared from (1*E*,4*E*)-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}H NMR

[12] Wei, Y.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 3756.
[13] Liu, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 6918.

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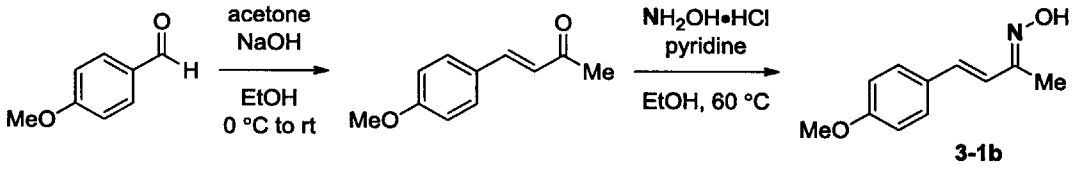
(400 MHz, Acetone-d_6) δ 7.06 (1H, dd, J = 16.4, 0.8 Hz), 7.20 (1H, d, J = 16.4 Hz), 7.28-7.33 (2H, m), 7.34-7.44 (5H, m), 7.49 (1H, dd, J = 16.8, 0.8 Hz), 7.61 (2H, d, J = 7.6 Hz), 7.66 (2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, Acetone-d_6) δ 117.0, 122.9, 126.9, 127.2, 128.1, 128.69, 128.74, 128.8, 133.0, 135.9, 136.8, 137.0, 153.2.

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



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_2O, 25 mL) and the reaction mixture stirred for 2 h (monitored by TLC). The reaction was quenched with H_2O 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 (2*E*,3*E*)-4-(4-methoxyphenyl)but-3-en-2-one oxime (**3-1b**) was obtained in 56% yield (2 steps).

(2*E*,3*E*)-4-(4-Methoxyphenyl)but-3-en-2-one oxime (3-1b)[14]

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 9.6, 55.3, 114.2, 123.6, 128.2, 129.1, 132.9, 156.9, 159.9.

[14] Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Seguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem. Int. Ed.* **2008**, *47*, 1410.

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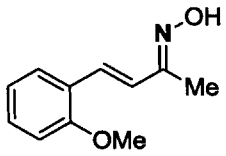
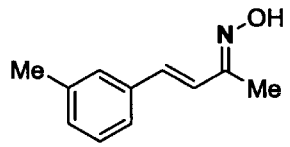
(2*E*,3*E*)-4-(2-Methoxyphenyl)but-3-en-2-one oxime (3-1c)



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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{11}H_{14}NO_2$: $(M+H)^+$ 192.1025.

(2*E*,3*E*)-4-(*m*-Tolyl)but-3-en-2-one oxime (3-1d)[14]



Prepared from 3-methylbenzaldehyde and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in 52% yield; White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 21.4, 124.1, 125.5, 127.5, 128.6, 129.3, 133.6, 136.2, 138.3, 156.8.

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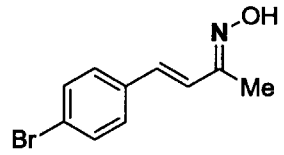
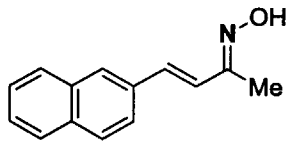
(2*E*,3*E*)-4-(4-Bromophenyl)but-3-en-2-one oxime (3-1e)



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, 1420, 1396, 1373, 1072 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{10}H_{11}NO^{79}Br$: $(M+H)^+$ 240.0024.

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



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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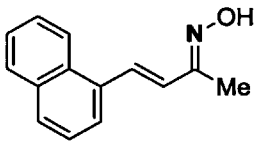
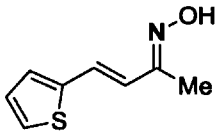
(2*E*,3*E*)-4-(Naphthalen-1-yl)but-3-en-2-one oxime (3-1g)



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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. Calcd for $C_{14}H_{14}NO$: $(M+H)^+$ 212.1075.

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



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 H_2O 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 125.2, 125.7, 126.3, 127.2, 127.7, 141.8, 156.4; ESI-HRMS: Found: m/z 168.0480. Calcd for $C_8H_{10}NOS$: $(M+H)^+$ 168.0483.

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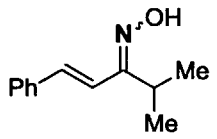
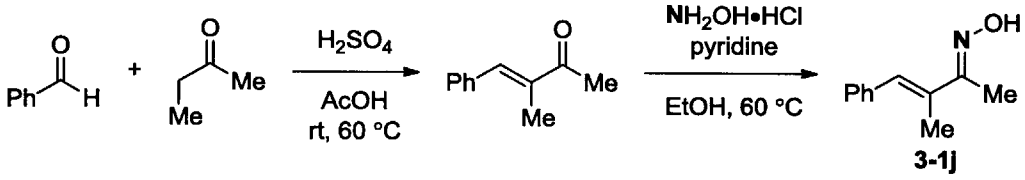
(1*E*)-4-Methyl-1-phenylpent-1-en-3-one oxime (3-1m)



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, 1450, 1335, 972, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (6H×0.55, d, J = 7.2 Hz), 1.26 (6H×0.45, d, J = 7.2 Hz), 3.04 (1H×0.45, sept, J = 7.2 Hz), 3.52 (1H×0.55, sept, J = 7.2 Hz), 6.63 (1H×0.55, d, J = 16.4 Hz), 7.02 (1H×0.45, d, J = 16.4 Hz), 7.06 (1H×0.55, d, J = 16.4 Hz), 7.23-7.40 (3H×0.45+3H×0.55, m), 7.42-7.50 (1H×0.45+2H×0.55, m), 7.54 (2H×0.45, d, J = 6.8 Hz), 9.53 (1H×0.45+1H×0.55, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 α,β-unsaturated oxime 3-1j



3-1j

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_2SO_4 (2.4 g) at room temperature. The reaction was allowed to stirred for 20 h and then quenched with H_2O and neutralized with 25% aqueous NaOH. The residue was extracted with ethyl

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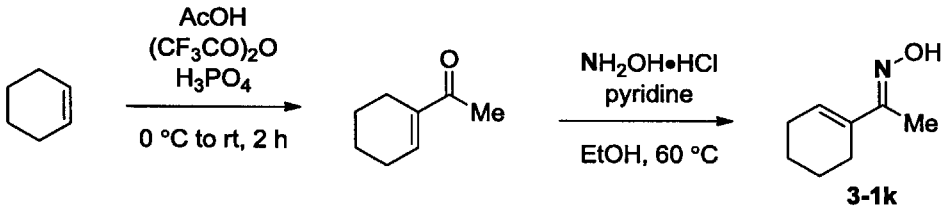
acetate and the combined organic layers were washed with aqueous $NaHCO_3$, brine and dried with $MgSO_4$. After removal of the solvent, the crude material was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) to give the corresponding α,β-unsaturated ketone in 96% yield. The α,β-unsaturated ketone was then subjected to hydroxylamination according to the experimental procedure in Chapter 6.3.1.1. and (2*E*,3*E*)-3-methyl-4-phenylbut-3-en-2-one oxime (**3-1j**) was obtained in 65% yield.

(2*E*,3*E*)-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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{11}H_{14}NO$: $(M+H)^+$ 176.1075.

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



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 CH_2Cl_2. The combined extracts were

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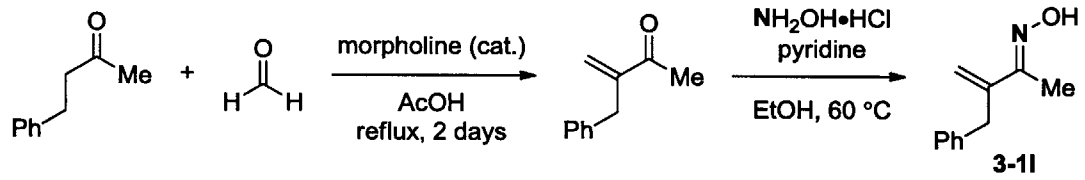
washed with 30% aqueous NaOH and brine, and dried over $MgSO_4$. Volatile materials were removed *in vacuo*. The residue was purified by silica gel column chromatography (hexanes-ethyl acetate = 95:5) to afford 1-(cyclohex-1-en-1-yl)ethanone in 35% yield. 1-(Cyclohex-1-en-1-yl)ethanone was then subjected to hydroxylamination according to the experimental procedure in Chapter 6.3.1.1. and (*E*)-1-(Cyclohex-1-en-1-yl)ethanone oxime (**3-1k**) was obtained in 76% yield.

(*E*)-1-(Cyclohex-1-en-1-yl)ethanone oxime (3-1k)[14]

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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 Hz), 9.60 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.7, 22.0, 22.4, 24.3, 26.0, 130.0, 134.4, 156.8.

6.3.1.5. Preparation of α,β-unsaturated oxime 3-1l



3-1l

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 $NaHCO_3$, brine and dried with $MgSO_4$. 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 13% yield. The α,β-unsaturated ketone was then subjected to hydroxylamination according to the experimental procedure in Chapter

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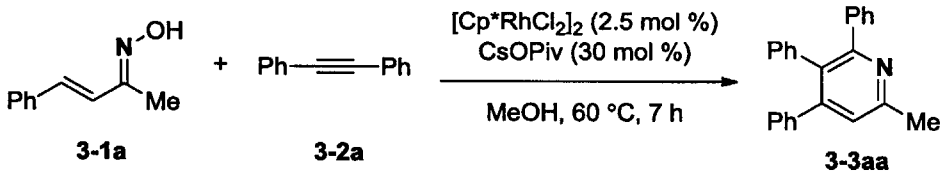
6.3.1.1. and (2*E*,3*E*)-3-methyl-4-phenylbut-3-en-2-one oxime (**3-1l**) was obtained in 91% yield.

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

White solid; mp. 120–122 °C; IR (NaCl) 3287, 2916, 1620, 1605, 1450, 1373, 1018 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{11}H_{14}NO$: $(M+H)^+$ 176.1075.

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



3-1a **3-2a** **3-3aa**

To a MeOH solution (2.5 mL) of (2*E*,3*E*)-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 $[Cp^*RhCl_2]_2$ (7.7 mg, 0.0125 mmol) and CsOPiv (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.

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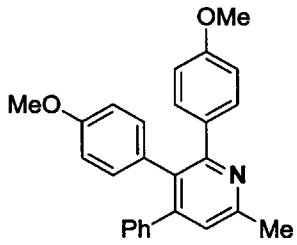
6-Methyl-2,3,4-triphenylpyridine (3-3aa)

White solid; mp. 128–129 °C; IR (NaCl) 3024, 2955, 1574, 1535, 1489, 1443, 1373 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{20}N$: $(M+H)^+$ 322.1596.

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



Colorlesss crystal; mp. 154–155 °C; IR (NaCl) 2940, 2839, 1605, 1512, 1288, 1180, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{26}H_{24}NO_2$: $(M+H)^+$ 382.1807.

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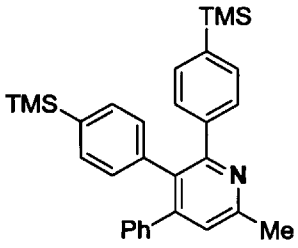
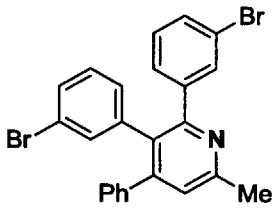
6-Methyl-4-phenyl-2,3-bis(4-(trimethylsilyl)phenyl)pyridine (3-3ac)



White solid; mp. 164–165 °C; IR (NaCl) 2955, 2893, 1582, 1427, 1250, 1111, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. Calcd for $C_{30}H_{36}NSi_2$: $(M+H)^+$ 466.2386.

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



Colorlesss crystal; mp. 128–129 °C; IR (NaCl) 2963, 1582, 1558, 1535, 1474, 887 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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. Calcd for $C_{24}H_{18}N^{79}Br^{81}Br$: $(M+H)^+$ 479.9786.

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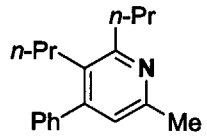
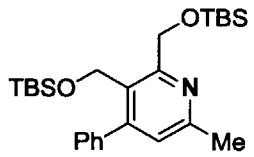
6-Methyl-4-phenyl-2,3-dipropylpyridine (3-3ae)



Yellow oil; IR (NaCl) 2955, 2932, 2870, 1589, 1543, 1497, 1450, 1381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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}C NMR (100 MHz, $CDCl_3$) δ 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; ESI-HRMS: Found: m/z 254.1902. Calcd for $C_{18}H_{24}N$: $(M+H)^+$ 254.1909.

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



White solid; mp. 85–87 °C; IR (NaCl) 2955, 2932, 2855, 1589, 1466, 1258, 1065, 841 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ -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}C NMR (100 MHz, $CDCl_3$) δ -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; ESI-HRMS: Found: m/z 458.2914. Calcd for $C_{26}H_{44}NO_2Si_2$: $(M+H)^+$ 458.2911.

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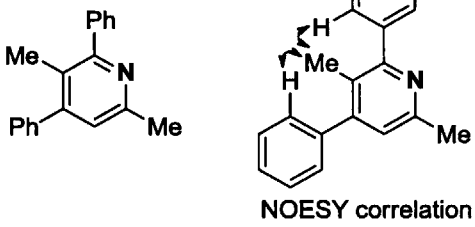
3,6-Dimethyl-2,4-diphenylpyridine (3-3ag)

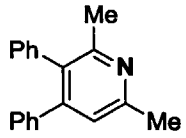


NOESY correlation

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}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.13 (3H, m), 2.59 (3H, m), 7.02 (1H, s), 7.34-7.47 (8H, m), 7.51-7.54 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.2, 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.

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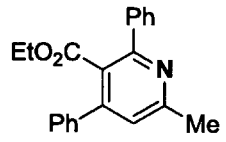
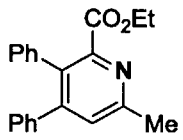
Ethyl 2,4-diphenyl-6-methylpyridine-3-carboxylate (3-3ah)[15]



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

Colourless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)



Yellow oil; IR (NaCl) 2986, 1736, 1589, 1450, 1381, 1342, 1273 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{21}H_{20}NO_2$: $(M+H)^+$ 318.1494.

[15] Bagley, M. C.; Chapaneri, K.; Dale, J. W.; Xiong, X.; Bower, J. *J. Org. Chem.* **2005**, *70*, 1389.

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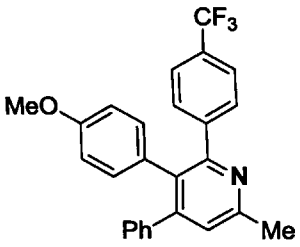
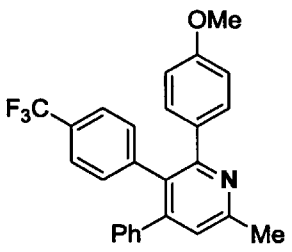
3-(4-Methoxyphenyl)-6-methyl-4-phenyl-2-(4-(trifluoromethyl)phenyl)pyridine (3-3ai)

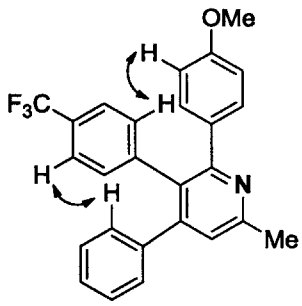


Regioisomer (**3-3ai-minor**) was separated by flash column chromatography.

Colorless oil; IR (NaCl) 2963, 2839, 1612, 1574, 1512, 1327, 1250, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 24.3, 55.0, 113.4, 123.9, 124.2 ($J_{C\text{-}F}$ = 170.3 Hz), 124.6 ($J_{C\text{-}F}$ = 6.7 Hz), 127.3, 127.9, 129.1 ($J_{C\text{-}F}$ = 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 $C_{26}H_{21}NO^{19}F_3$: $(M+H)^+$ 420.1575.

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





NOESY correlation

White solid; mp. 138–140 °C; IR (NaCl) 2963, 2839, 1612, 1589, 1512, 1327, 1126 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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

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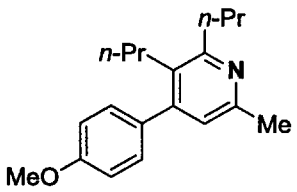
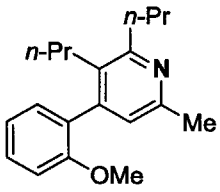
Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.5, 55.2, 113.3, 122.9, 124.1 ($J_{C\text{-}F}$ = 270.3 Hz), 124.6 ($J_{C\text{-}F}$ = 3.7 Hz), 127.5, 128.0, 128.4 ($J_{C\text{-}F}$ = 32.2 Hz), 129.2, 129.9, 131.2, 131.8, 132.9, 139.2, 142.3, 150.0, 157.3, 157.5, 159.1; ESI-HRMS: Found: m/z 420.1575. Calcd for $C_{26}H_{21}NO^{19}F_3$: $(M+H)^+$ 420.1575.

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



Colorlesss 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)



Colorlesss 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,

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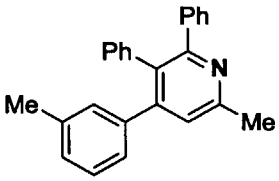
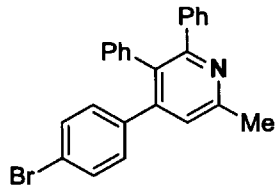
$CDCl_3$) δ 14.4 (overlapped), 23.7, 23.8, 24.0, 31.1, 37.5, 55.3, 110.6, 120.3, 122.4, 129.0, 129.3, 130.4, 131.0, 147.3, 154.1, 155.9, 159.7; ESI-HRMS: Found: m/z 284.2012. Calcd for $C_{19}H_{26}NO$: $(M+H)^+$ 284.2014.

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



White solid; mp. 100–102 °C; IR (NaCl) 2955, 1589, 1535, 1489, 1443, 1427 cm^{-1}; ^1H 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)



Colorlesss crystal; mp. 162–164 °C; IR (NaCl) 2963, 1589, 1574, 1489, 1420, 1373 cm^{-1}; ^1H 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.

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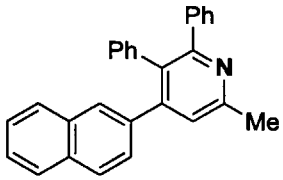
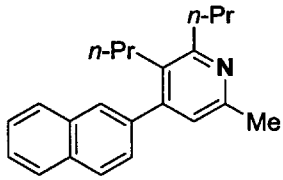
6-Methyl-4-(naphthalen-2-yl)-2,3-diphenylpyridine (3-3fa)



White solid; mp. 159–160 °C; IR (NaCl) 3055, 2955, 1574, 1535, 1504, 1443, 856 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



Yellow oil; IR (NaCl) 2955, 2932, 2870, 1589, 1551, 1505, 1466, 1450 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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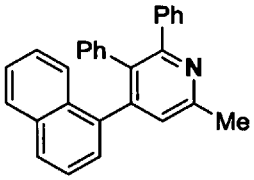
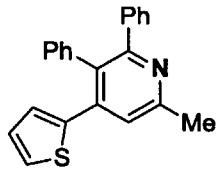
6-Methyl-4-(naphthalen-1-yl)-2,3-diphenylpyridine (3-3ga)



White solid; mp. 122–124 °C; IR (NaCl) 3009, 2963, 1589, 1574, 1535, 1443, 1420, 802 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{28}H_{22}N$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{18}NS$: $(M+H)^+$ 328.1160.

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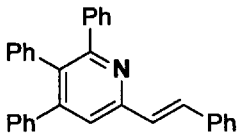
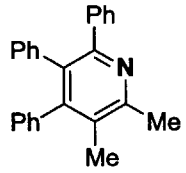
(*E*)-2,3,4-Triphenyl-6-styrylpyridine (3-3ia)



White solid; mp. 184–186 °C; IR (NaCl) 3063, 2970, 1574, 1528, 1497, 1443, 1381, 972 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)[16]



White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

[16] Padwa, A.; Cohen, L. A.; Gingrich, H. L. *J. Am. Chem. Soc.* **1984**, *106*, 1065.

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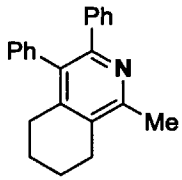
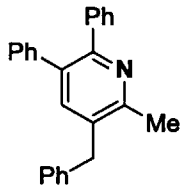
1-Methyl-3,4-diphenyl-5,6,7,8-tetrahydroisoquinoline (3-3ka)



White solid; mp. 142–144 °C; IR (NaCl) 3055, 2940, 2862, 1558, 1427, 1412, 1335 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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 $C_{22}H_{22}N$: $(M+H)^+$ 300.1752.

3-Benzyl-2-methyl-5,6-diphenylpyridine (3-3la)[17]



White solid; ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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.

[17] Kim, S. H.; Kim, K. H.; Kim, H. S.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1948.

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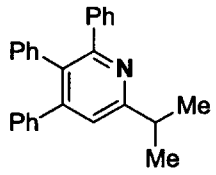
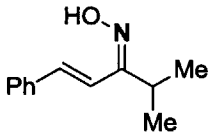
6-Isopropyl-2,3,4-triphenylpyridine (3-3ma)



White solid; mp. 134–136 °C; IR (NaCl) 2963, 2870, 1582, 1566, 1535, 1489, 1381 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (6H, d, J = 7.2 Hz), 3.22 (1H, sept, J = 7.2Hz), 6.86 (2H, d, J = 6.4 Hz), 6.99-7.10 (5H, m), 7.13-7.23 (7H, m), 7.25-7.31 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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; ESI-HRMS: Found: m/z 350.1905. Calcd for $C_{26}H_{24}N$: $(M+H)^+$ 350.1909.

(1*E*,3*Z*)-4-Methyl-1-phenylpent-1-en-3-one oxime (*syn*-3-1m)



White solid; mp. 110–114 °C; IR (NaCl) 3264, 2970, 2932, 2870, 1489, 1450, 1381, 941 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (6H, d, J = 6.8 Hz), 3.04 (1H, sept, J = 6.8 Hz), 7.01 (1H, d, J = 16.8 Hz), 7.32 (1H, d, J = 7.2 Hz), 7.37 (2H, dd, J = 7.2, 7.2 Hz), 7.46 (1H, d, J = 16.8 Hz), 7.54 (2H, d, J = 7.2 Hz), 9.28 (1H, brs); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1, 29.6, 115.9, 127.4, 128.7, 128.9, 135.5, 136.5, 159.9; ESI-HRMS: Found: m/z 190.1240. Calcd for $C_{12}H_{16}NO$: $(M+H)^+$ 190.1232.

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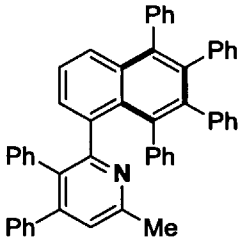
6-Methyl-3,4-diphenyl-2-(5,6,7,8-tetraphenylnaphthalen-1-yl)pyridine (3-4aa)



White solid; mp. 128–130 °C; IR (NaCl) 3055, 3024, 2932, 1582, 1535, 1497, 1443, 1381, 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{52}H_{38}N$: $(M+H)^+$ 676.3004.

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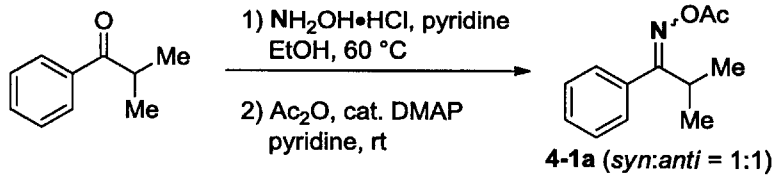
6.4 Experimental section of Chapter 4:

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).



4-1a (*syn*:*anti* = 1:1)

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 $NH_2OH•HCl$ (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 *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_2O (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.

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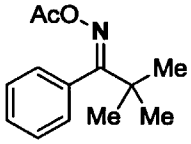
Isobutyrophenone *O*-acetyl oxime (4-1a)[18]

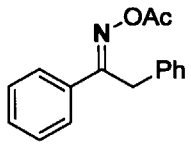
Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (6H×1, d, J = 6.8 Hz), 1.22 (6H×1, d, J = 7.2 Hz), 1.95 (3H×1, s), 2.23 (3H×1, s), 2.99 (1H×1, septet, J = 6.8 Hz), 3.53 (1H×1, septet, J = 7.2 Hz), 7.13-7.16 (2H×1, m), 7.34-7.45 (3H×1+5H×1, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.49, 19.53, 19.77, 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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (9H, s), 1.89 (3H, s), 7.01-7.04 (2H, m), 7.34-7.41 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{13}H_{18}NO_2$: $(M+H)^+$ 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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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

[18] Compound **4-1a** is same as compound **2-1o** in Chapter 2.

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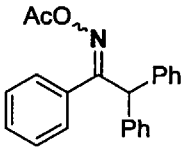
(2H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 34.3, 126.7, 127.5, 128.3, 128.6, 128.8, 130.6, 134.0, 135.3, 163.7, 168.7; ESI-HRMS: Found: m/z 254.1179. Calcd for $C_{16}H_{16}NO_2$: $(M+H)^+$ 254.1181.

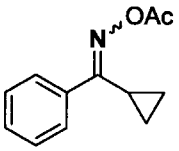
1,2,2-Triphenylethanone *O*-acetyl oxime (4-1d)



syn:*anti* = 2:1

Prepared from 1,2,2-triphenylethanone[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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (3H×0.5, s), 1.98 (3H×1, s), 5.44 (1H×1, s), 6.01 (1H×0.5, s), 7.03-7.05 (2H×1, m), 7.19 (2H×1, d, J = 7.2 Hz), 7.24-7.34 (11H×1+13H×0.5, m), 7.48-7.52 (2H×0.5, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{22}H_{20}NO_2$: $(M+H)^+$ 330.1494.

Cyclopropyl(phenyl)methanone *O*-acetyl oxime (4-1e)



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^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.68-0.72 (2H×1, m), 0.84-0.89 (2H×0.46, m), 0.90-0.95 (2H×0.46, m), 0.98-1.03 (2H×1,

[19] Schmink, J. R.; Leadbeater, N. E. *Org. Lett.* **2009**, *11*, 2575.

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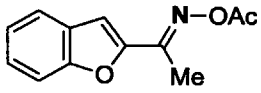
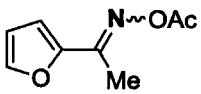
m), 1.92-1.96 (1H×0.46, m), 1.95 (3H×0.46, s), 2.25 (3H×1, s), 2.36-2.42 (1H×1, m), 7.23-7.25 (2H×0.46, m), 7.35-7.41 (5H×1+3H×0.46, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 6.3, 6.4, 10.7, 15.7, 19.5, 19.8, 127.1, 128.06, 128.08, 128.8, 129.1, 129.5, 131.8, 132.3, 168.6, 168.96, 169.01, 169.2; ESI-HRMS: Found: m/z 204.1026. Calcd for $C_{12}H_{14}NO_2$: $(M+H)^+$ 204.1025.

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



Prepared from 1-(benzofuran-2-yl)ethanone and purified by recrystallization from hexane-ethyl acetate (one time) (68% yield); White solid; mp. 101–102 °C; IR (NaCl) 1773, 1607, 1560, 1449, 1368, 1306 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (3H, s), 2.42 (3H, s), 7.25-7.29 (2H, m), 7.38 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.56 (1H, dd, J = 0.8, 8.4 Hz), 7.62 (1H, d, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{12}H_{12}NO_3$: $(M+H)^+$ 218.0817.

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



***syn*:*anti* = 1:20**

Prepared from 1-(furan-2-yl)ethanone and purified by recrystallization from hexane-ethyl acetate (two times) (70% yield); White solid; mp. 99–100 °C; IR (NaCl) 1771, 1609, 1481, 1393, 1368, 1325 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (3H×1, s), 2.28 (3H×0.05), 2.31 (3H×1, s), 2.41 (3H×0.05), 6.49 (1H×1, dd, J = 1.8, 3.6 Hz), 6.59 (1H×0.05, dd, J = 1.6, 3.6 Hz), 6.91 (1H×1, dd, J = 0.4, 3.6 Hz), 7.35 (1H×0.05, dd, J = 0.4, 3.6 Hz), 7.54 (1H×1, dd, J = 0.6, 1.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 19.6,

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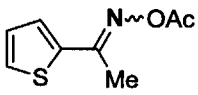
111.7, 113.2, 145.0, 148.3, 153.8, 168.4; ESI-HRMS: Found: m/z 168.0656. Calcd for $C_8H_{10}NO_3$: $(M+H)^+$ 168.0661.

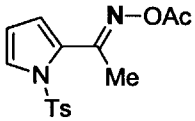
1-(Thiophen-2-yl)ethanone *O*-acetyl oxime (4-4h)



syn:*anti* = 1:4

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, $CDCl_3$) δ 2.26 (3H×1, 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_8H_{10}NO_2S$: $(M+H)^+$ 184.0432.

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



Prepared from 1-(1-tosyl-1H-pyrrol-2-yl)ethanone[20] 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$)

[20] Song, C.; Knight, D. W.; Whatton (neé Fagan), M. A. *Tetrahedron Lett.* **2004**, *45*, 9573.

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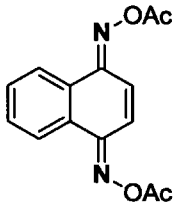
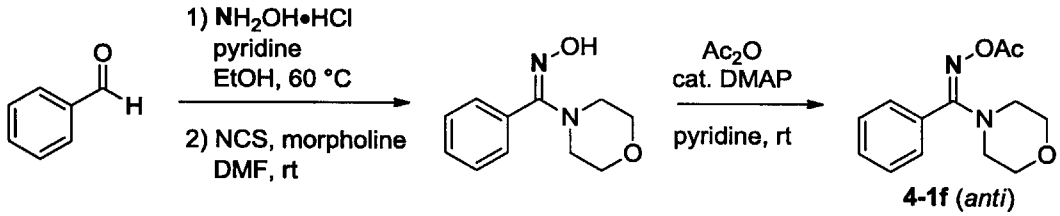
δ 19.2, 19.6, 21.6, 113.1, 117.9, 125.4, 127.5, 129.7, 129.8, 135.2, 145.3, 158.9, 168.1; ESI-HRMS: Found: m/z 321.0904. Calcd for $C_{15}H_{17}N_2O_4S$: $(M+H)^+$ 321.0909.

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



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}; ^1H 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 $C_{14}H_{13}N_2O_4$: $(M+H)^+$ 273.0875.

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



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_2OH•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

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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. $NaHCO_3$, brine, and dried over $MgSO_4$. 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 Ac_2O (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 $MgSO_4$. The solvents were removed under reduced pressure and the crude was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 80:20) to 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{13}H_{17}N_2O_3$: $(M+H)^+$ 249.1239.

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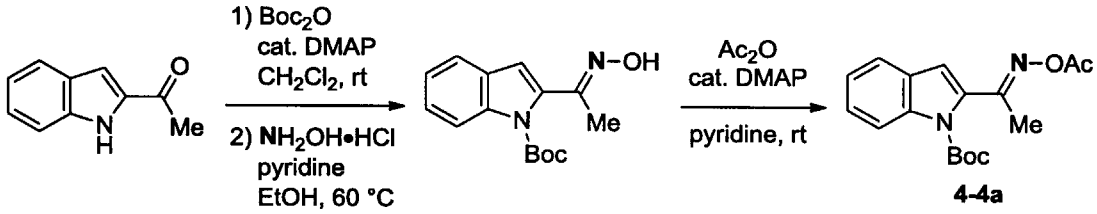
6.4.1.3. Preparation of indolyl ketone *O*-acetyl oximes 4-4a to 4-4e: a typical procedure for synthesis of (*E*)-*tert*-butyl 2-(1-(acetoxyimino)ethyl)-1*H*-indole-1-carboxylate (4-4a).



To a solution of 1-(1*H*-indol-2-yl)ethanone[21] (1.75 g, 11.0 mmol) in CH_2Cl_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_2Cl_2. The combined organic extracts were washed with water and brine, as well as dried over anhydrous $MgSO_4$. Volatile materials were removed *in vacuo* and *tert*-butyl 2-acetyl-1*H*-indole-1-carboxylate was used for the next step without purification. To a solution of *tert*-Butyl 2-acetyl-1*H*-indole-1-carboxylate in EtOH (5 mL) was added pyridine (2.5 ml, 30.4 mmol) and NH_2OH•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 temperatrue for 1 h. The reaction mixture was then quenched with water and

[21] Akimoto, H.; Kawai, A.; Nomura, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 123.

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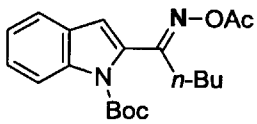
extracted twice with ethyl acetate. The combined organic extracts were washed with 1 M aqueous HCl, brine and dried over anhydrous $MgSO_4$. Volatile materials were removed *in vacuo* and the crude was purified by flash column chromatography (Silica gel, hexane:ethyl acetate = 90:10) to afford the indole *O*-acetyl oxime **4-4a** (2.72 g, 8.60 mmol) in 78% yield.

(*E*)-*tert*-Butyl 2-(1-(acetoxyimino)ethyl)-1*H*-indole-1-carboxylate (4-4a)

White solid; mp. 62–64 °C; IR (NaCl) 1767, 1734, 1618, 1566, 1452, 1327 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.7, 28.0, 84.8, 111.8, 115.5, 121.4, 123.3, 125.5, 128.6, 133.9, 136.9, 149.4, 159.5, 168.5; ESI-HRMS: Found: m/z 317.1504. Calcd for $C_{17}H_{21}N_2O_4$: $(M+H)^+$ 317.1501.

(*E*)-*tert*-Butyl 2-(1-(acetoxyimino)pentyl)-1*H*-indole-1-carboxylate (4-4b)



Prepared from 1-(1*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; IR (NaCl) 2961, 1769, 1732, 1614, 1452, 1329 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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; ESI-HRMS: Found: m/z 359.1964. Calcd for $C_{20}H_{27}N_2O_4$: $(M+H)^+$ 359.1971.

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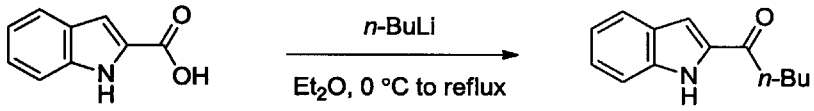
Synthesis of 1-(1*H*-indol-2-yl)pentan-1-one



To a solution of 1*H*-indole-2-carboxylic acid (1.2 g, 7.5 mmol) in 25 mL of diethyl ether at 0 °C, was added *n*-BuLi solution (14.0 ml, 22.4 mmol, 1.6 M in hexane) dropwise. The reaction mixture was allowed to stir for 1.5 h at reflux, then quenched with 1 M aqueous HCl and extracted thrice with diethyl ether. The combined organic extracts were washed with water and brine, and dried over anhydrous $MgSO_4$. Volatile materials were removed under reduced pressure and the resultant crude was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to afford 1-(1*H*-indol-2-yl)pentan-1-one in 63% yield.

1-(1*H*-Indol-2-yl)pentan-1-one

Yellow solid; mp. 113–115 °C; IR (NaCl) 3321, 3019, 1651, 1524, 1414, 1341, 1167, 1144 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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; ESI-HRMS: Found: m/z 202.1241. Calcd for $C_{13}H_{16}NO$: $(M+H)^+$ 202.1232.

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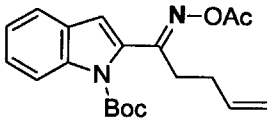
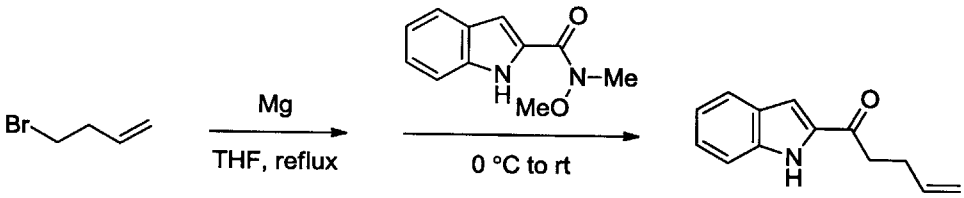
(*E*)-*tert*-Butyl 2-(1-(acetoxyimino)pent-4-enyl)-1*H*-indole-1-carboxylate (4-4c)



Prepared from 1-(1*H*-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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{20}H_{25}N_2O_4$: $(M+H)^+$ 357.1814.

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



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

[22] Mouloud, D.; Dodd, R. H. *Tetrahedron* **1994**, *50*, 6299.

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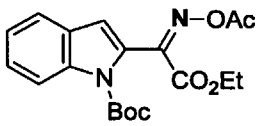
brine, and dried over anhydrous $MgSO_4$. Volatile materials were removed *in vacuo* and the resultant crude was purified by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) to afford the desired ketone in 52 % yield.

1-(1*H*-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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{13}H_{14}NO$: $(M+H)^+$ 200.1075.

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



Prepared from *tert*-butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{23}N_2O_6$: $(M+H)^+$ 375.1556.

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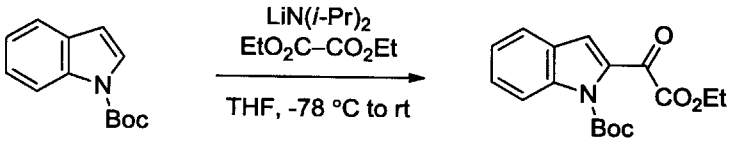
Synthesis of *tert*-butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-indole-1-carboxylate



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 1*H*-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-(1*H*-indol-2-yl)-2-oxoacetate in 67 % yield.

***tert*-Butyl 2-(2-ethoxy-2-oxoacetyl)-1*H*-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, $CDCl_3$) δ 1.39 (3H, t, J = 7.2 Hz), 1.65 (9H, s), 4.37 (2H, q, J = 7.1 Hz), 7.30 (1H, ddd, J = 0.8, 6.4, 8.8 Hz), 7.48 (1H, ddd, J = 1.2, 7.2, 8.4 Hz), 7.67 (1H, d, J = 7.6 Hz), 8.02 (1H, dd, J = 0.8, 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

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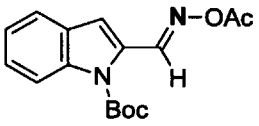
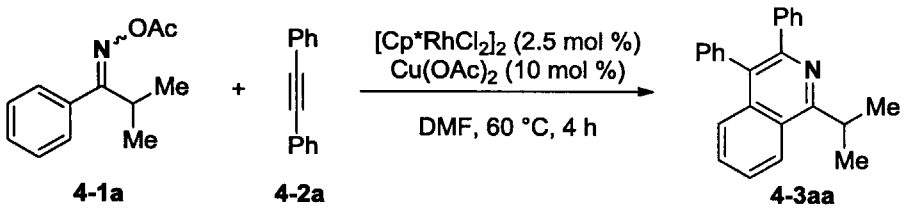
(*E*)-*tert*-Butyl 2-((acetoxyimino)methyl)-1*H*-indole-1-carboxylate (4-4e)



Prepared from 1*H*-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}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.71 (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 Hz), 7.60 (1H, d, J = 7.6 Hz), 8.08 (1H, dd, J = 0.4, 8.4 Hz), 9.05 (1H, d, J = 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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; 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).



4-1a *syn*:*anti* = 1:1 **4-2a** **4-3aa**

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 $[Cp^*RhCl_2]_2$ (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

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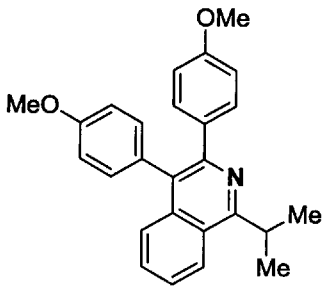
extracted three times with ethyl acetate. The combined extracts were washed with water (three times) and brine, and dried over $MgSO_4$. The solvents were removed under reduced pressure and the crude was purified by flash column chromatography (hexane : ethyl acetate = 8 : 92) to afford 1-isopropyl-3,4-diphenylisoquinoline (**4-3aa**) (92.4 mg, 0.286 mmol) in 95% yield.

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

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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)



White solid; mp. 127–129 °C; IR (NaCl) 2965, 1609, 1514, 1439, 1389, 1287, 1246, 1177 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 **2-3oa** in Chapter 2.

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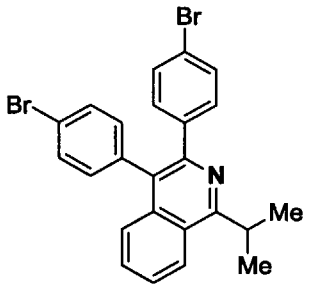
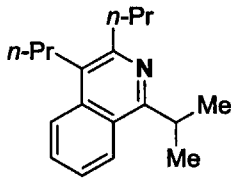
137.0, 148.2, 158.5, 158.6, 164.6; ESI-HRMS: Found: m/z 384.1969. Calcd for $C_{26}H_{26}NO_2$: $(M+H)^+$ 384.1964.

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}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{20}N^{79}Br^{81}Br$: $(M+H)^+$ 481.9942.

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



Colorless oil; ^1H NMR (400 MHz, $CDCl_3$) 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.

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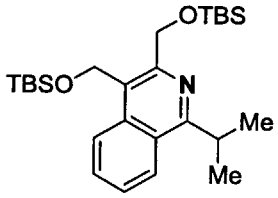
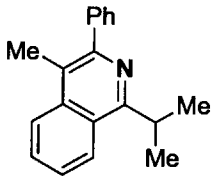
J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.7, 22.3, 23.0, 24.0, 29.8, 30.8, 37.1, 123.8, 124.5, 124.9, 125.0, 125.4, 128.8, 135.7, 151.5, 162.7.

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



Pale yellow oil; IR (NaCl) 2955, 2928, 2857, 1566, 1472, 1462, 1389, 1360, 1254 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ -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 $C_{26}H_{46}NO_2Si_2$: $(M+H)^+$ 460.3067.

1-Isopropyl-4-methyl-3-phenylisoquinoline (4-3af)[25]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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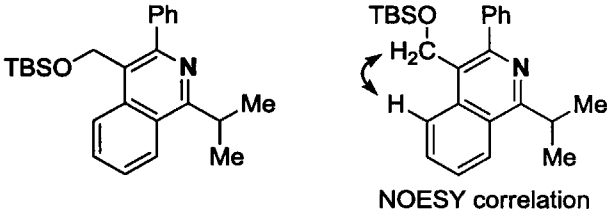
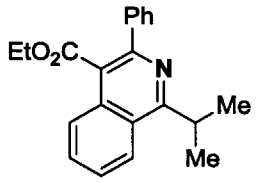
4-((*tert*-Butyldimethylsilyloxy)methyl)-1-isopropyl-3-phenylisoquinoline (4-3ag)



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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.3, 18.4, 22.2, 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 $C_{25}H_{34}NOSi$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.1, 31.5,

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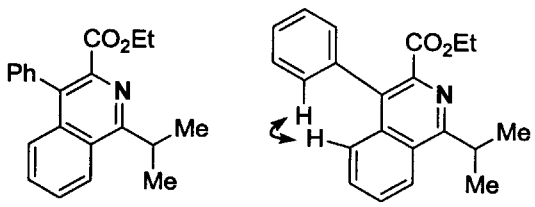
61.6, 121.3, 124.3, 124.85, 124.88, 127.0, 128.2, 128.3, 129.0, 130.6, 133.9, 140.7, 149.2, 167.3, 169.5; ESI-HRMS: Found: m/z 320.1647. Calcd for $C_{21}H_{22}NO_2$: $(M+H)^+$ 320.1651.

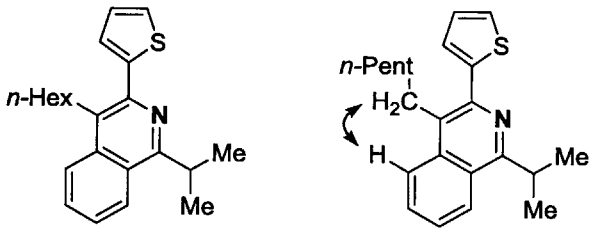
Ethyl 1-isopropyl-4-phenylisoquinoline-3-carboxylate (4-3ah-minor)



NOESY correlation

White solid; mp. 92–93 °C; IR (NaCl) 2968, 2934, 1506, 1404, 1389, 1373, 1323, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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)



NOESY correlation

Yellow oil; IR (NaCl) 2961, 2928, 1560, 1506, 1468, 1447, 1431, 1387 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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),

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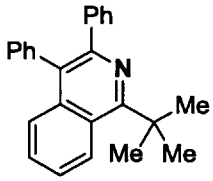
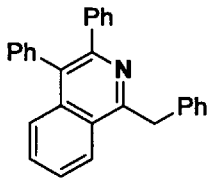
7.55 (1H, ddd, J = 0.8, 6.8, 8.0 Hz), 7.70 (1H, ddd, J = 1.2, 6.8, 8.4 Hz), 8.09 (1H, d, J = 8.4 Hz), 8.22 (1H, d, J = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.2, 22.7, 28.5, 29.8, 30.2, 31.3, 31.7, 124.4, 125.1, 125.2, 125.3, 125.4, 125.9, 127.1, 127.5, 129.5, 136.3, 142.6, 147.1, 163.1; ESI-HRMS: Found: m/z 338.1944. Calcd for $C_{22}H_{28}NS$: $(M+H)^+$ 338.1942.

1-*tert*-Butyl-3,4-diphenylisoquinoline (4-3ba)



White solid; mp. 165–167 °C; IR (NaCl) 2984, 2968, 1547, 1506, 1476, 1396, 1368, 1194 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 31.3, 40.2, 124.5, 125.1, 126.8, 126.9, 127.06, 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 $C_{25}H_{24}N$: $(M+H)^+$ 338.1909.

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



White solid; mp. 123–124 °C; IR (NaCl) 3063, 1553, 1506, 1495, 1379, 1339, 1265 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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,

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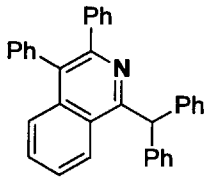
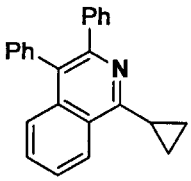
130.4, 131.3, 136.7, 137.5, 139.7, 140.9, 149.4, 159.2; ESI-HRMS: Found: m/z 372.1755. Calcd for $C_{28}H_{22}N$: $(M+H)^+$ 372.1752.

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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{34}H_{26}N$: $(M+H)^+$ 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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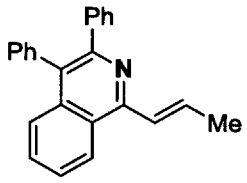
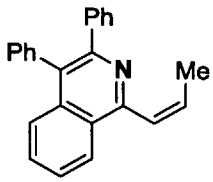
(*E*)-3,4-Diphenyl-1-(prop-1-enyl)isoquinoline ((*E*)-4-3ea')



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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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')



White solid; mp. 125–127 °C; IR (NaCl) 1653, 1543, 1504, 1445, 1385, 963 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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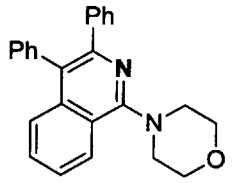
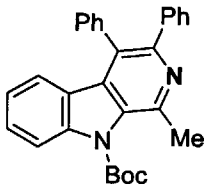
4-(3,4-Diphenylisoquinolin-1-yl)morpholine (4-3fa)



White solid; mp. 145–147 °C; IR (NaCl) 2967, 2855, 1612, 1568, 1551, 1504, 1410, 1115 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{23}N_2O$: $(M+H)^+$ 367.1810.

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



White solid; mp. 155–156 °C; IR (NaCl) 1730, 1605, 1570, 1300, 1246, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{29}H_{27}N_2O_2$: $(M+H)^+$ 435.2073.

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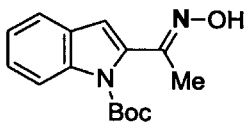
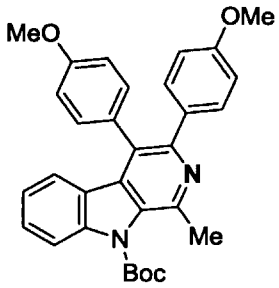
(*E*)-tert-Butyl 2-(1-(hydroxyimino)ethyl)-1*H*-indole-1-carboxylate (4-6a)



Yellow solid; mp. 148–151 °C; IR (NaCl) 3019, 1730, 1454, 1371, 1331, 1161, 1136 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{15}H_{19}N_2O_3$ $(M+H)^+$ 275.1396.

***tert*-Butyl 3,4-bis(4-methoxyphenyl)-1-methyl-9*H*-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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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,

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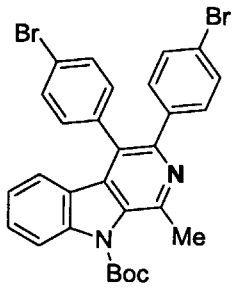
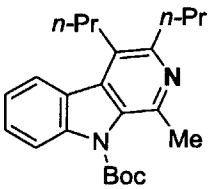
144.9, 150.5, 151.0, 158.7, 159.1; ESI-HRMS: Found: m/z 495.2284. Calcd for $C_{31}H_{31}N_2O_4$: $(M+H)^+$ 495.2284.

***tert*-Butyl 3,4-bis(4-bromophenyl)-1-methyl-9*H*-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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{29}H_{25}Br_2N_2O_2$: $(M+H)^+$ 591.0283.

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



Yellow oil; IR (NaCl) 1732, 1609, 1578, 1246, 1121, 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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,

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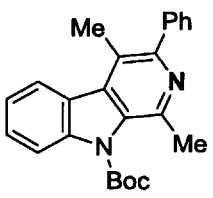
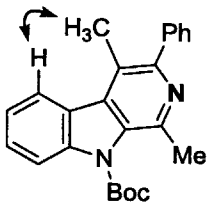
t, J = 7.6 Hz), 8.00 (1H, d, J = 7.6 Hz), 8.15 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 14.5, 23.0, 24.1, 24.5, 28.2, 30.9, 36.7, 84.4, 115.3, 123.17, 123.24, 124.8, 126.2, 128.2, 131.8, 132.9, 140.8, 143.0, 150.5, 153.4; ESI-HRMS: Found: m/z 367.2391. Calcd for $C_{23}H_{31}N_2O_2$: $(M+H)^+$ 367.2386.

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



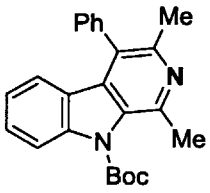


NOESY correlation

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}; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{25}N_2O_2$: $(M+H)^+$ 373.1916.

***tert*-Butyl 1,3-dimethyl-4-phenyl-9*H*-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}; ^{1}H NMR (400 MHz, $CDCl_3$) 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 =

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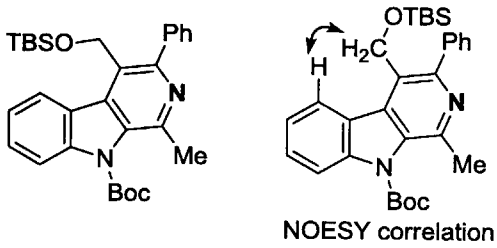
1.2, 7.2, 8.4 Hz), 7.52-7.58 (3H, m), 8.08 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.1, 24.6, 28.2, 84.5, 115.1, 122.8, 123.1, 124.5, 127.3, 127.9, 128.7, 129.1, 129.4, 132.1, 132.6, 138.0, 141.0, 144.6, 149.2, 150.5; ESI-HRMS: Found: m/z 373.1910. Calcd for $C_{24}H_{25}N_2O_2$: $(M+H)^+$ 373.1916.

tert-Butyl 4-((_tert_-butyldimethylsilyloxy)methyl)-1-methyl-3-phenyl-9_H_-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 $C_{30}H_{39}N_2O_3Si$: $(M+H)^+$ 503.2730.

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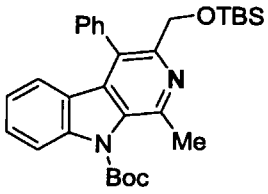
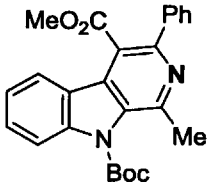
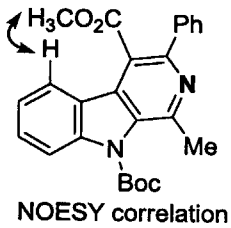
***tert*-Butyl 3-((*tert*-butyldimethylsilyloxy)methyl)-1-methyl-4-phenyl-9*H*-pyrido[3,4-*b*]indole-9- carboxylate (4-5ag-minor)**



Yellow solid; m.p. 118–120 °C; IR (NaCl) 1732, 1607, 1578, 1254, 1146, 1072 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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-HRMS: Found: m/z 503.2730. Calcd for $C_{30}H_{39}N_2O_3Si$: $(M+H)^+$ 503.2730.

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





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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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,

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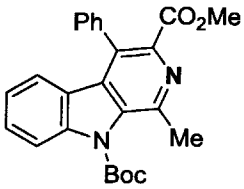
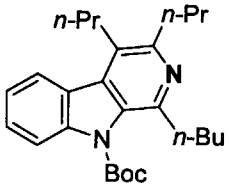
147.6, 150.0, 150.3, 169.4; ESI-HRMS: Found: m/z 417.1798. Calcd for $C_{25}H_{25}N_2O_4$: $(M+H)^+$ 417.1814.

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



Pale yellow solid; m.p. 154–155 °C; IR (NaCl) 1734, 1607, 1570, 1233, 1217,1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, 7.2, 8.1 Hz), 7.38-7.40 (2H, m), 7.49 (1H, ddd, J = 1.2, 7.6, 8.8 Hz), 7.52-7.56 (3H, m), 8.09 (1H, d, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.9, 28.1, 52.4, 85.4, 114.8, 123.2, 123.4, 123.9, 128.2, 128.7, 128.8, 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. Calcd for $C_{25}H_{25}N_2O_4$: $(M+H)^+$ 417.1814.

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



Yellow oil; IR (NaCl) 2959, 2930, 2870, 1732, 1607, 1572, 1464, 1431, 1391, 1369, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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,

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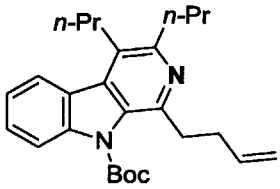
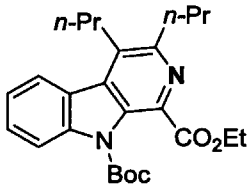
140.9, 147.0, 150.7, 153.3; ESI-HRMS: Found: m/z 409.2849. Calcd for $C_{26}H_{37}N_2O_2$: $(M+H)^+$ 409.2855.

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



Yellow oil; IR (NaCl) 3019, 2961, 2932, 2872, 1728, 1639, 1607, 1572, 1464, 1431, 1371, 1153, 1121 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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), 4.90 (1H, dd, J = 0.8, 10.0 Hz), 5.02 (1H, dd, J = 1.6, 17.2 Hz), 5.81-5.91 (1H, m), 7.38 (1H, 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, $CDCl_3$) δ 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 $C_{26}H_{35}N_2O_2$: $(M+H)^+$ 407.2699.

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



Yellow solid; m.p. 43–45 °C; IR (NaCl) 3019, 2965, 1736, 1609, 1574, 1464, 1396, 1371, 1344, 1314, 1153, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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

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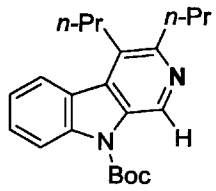
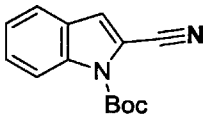
(100 MHz, $CDCl_3$) δ 14.2, 14.3, 14.5, 22.6, 23.8, 28.1, 31.1, 36.5, 61.5, 84.9, 115.9, 123.3, 123.5, 124.1, 128.8, 131.3, 131.5, 132.5, 136.7, 140.1, 150.6, 153.6, 166.8; ESI-HRMS: Found: m/z 425.2438. Calcd for $C_{25}H_{33}N_2O_4$: $(M+H)^+$ 425.2440.

tert-Butyl 3,4-dipropyl-9*H*-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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{29}N_2O_2$: $(M+H)^+$ 353.2229.

tert-Butyl 2-cyano-1*H*-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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{15}N_2O_2$: $(M+H)^+$ 243.1134.

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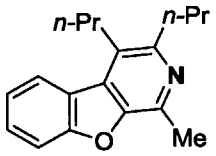
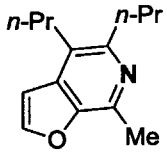
1-Methyl-3,4-dipropylbenzofuro[2,3-*c*]pyridine (4-5fd)



White solid; m.p. 60–62 °C; IR (NaCl) 2959, 2930, 2870, 1628, 1599, 1464, 1435, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 14.4, 18.5, 23.2, 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 $C_{18}H_{22}NO$: $(M+H)^+$ 268.1701.

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



Yellow oil; IR (NaCl) 2961, 2932, 2870, 1614, 1587, 1450, 1377, 1192, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{20}NO$: $(M+H)^+$ 218.1545.

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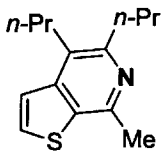
7-Methyl-4,5-dipropylthieno[2,3-*c*]pyridine (4-5hd)



Yellow oil; IR (NaCl) 2959, 2930, 2870, 1557, 1454, 1425, 1379, 1362, 1165 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{14}H_{20}NS$: $(M+H)^+$ 234.1316.

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

White solid; mp. 78–80 °C; IR (NaCl) 2961, 2932, 1576, 1454, 1445, 1368, 1173, 1132 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{27}N_2O_2S$: $(M+H)^+$ 371.1793.

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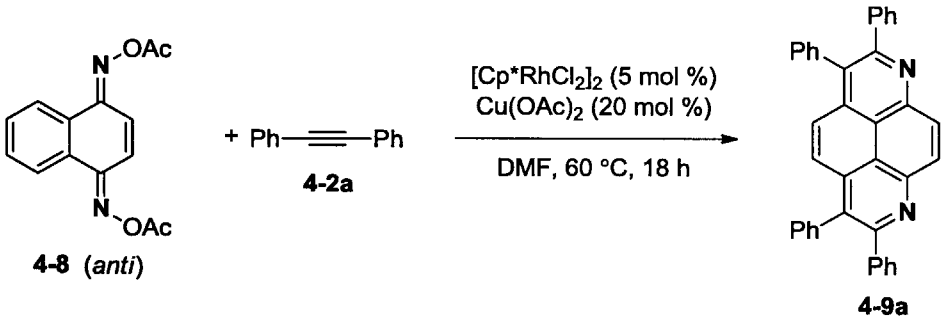
6.4.3 Synthesis of 1,8-diazapyrenes by Cu–Rh catalytic system: a typical procedure for the reaction of (1*E*,4*E*)-naphthalene-1,4-dione *O*,*O*-diacetyl dioxime (4-8) and diphenylacetylene (4-2a) (Table 4-5, entry 1)



To a DMF solution (2.5 mL) of (1*E*,4*E*)-naphthalene-1,4-dione *O*,*O*-diacetyl dioxime (**4-8**) (136.1 mg, 0.50 mmol) and diphenylacetylene (**4-2a**) (178.2 mg, 1.00 mmol) were added $[Cp^*RhCl_2]_2$ (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 CH_2Cl_2. The combined extracts were washed with water (three times) and brine, and dried over $MgSO_4$. 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{38}H_{25}N_2$: $(M+H)^+$ 509.2018.

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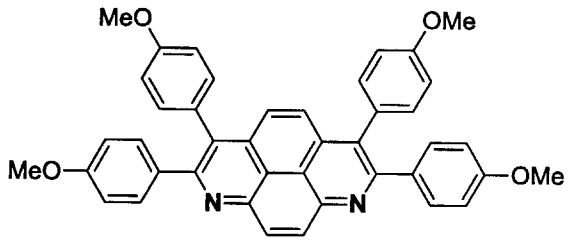
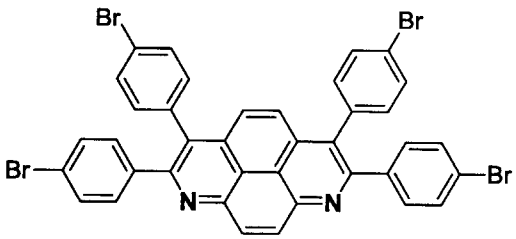
2,3,6,7-Tetrakis(4-methoxyphenyl)benzo[*lmn*][2,9]phenanthroline (4-9b)



Yellowish green solid; mp. 242–244 °C; IR (NaCl) 2953, 1607, 1553, 1514, 1377, 1248, 1177, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. Calcd for $C_{42}H_{33}N_2O_4$: $(M+H)^+$ 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. Calcd for $C_{38}H_{21}N_2{}^{79}Br_2{}^{81}Br_2$: $(M+H)^+$ 824.8397.

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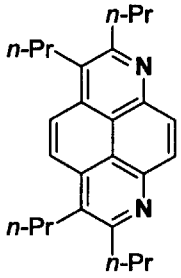
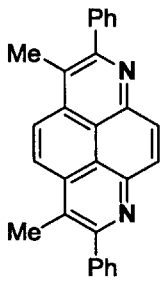
2,3,6,7-Tetrapropylbenzo[*lmn*][2,9]phenanthroline (4-9d)



Brownish red solid; mp. 77–78 °C; IR (NaCl) 2961, 2932, 2872, 1562, 1477, 1456, 1391, 1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{26}H_{33}N_2$: $(M+H)^+$ 373.2644.

3,6-Dimethyl-2,7-diphenylbenzo[*lmn*][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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{28}H_{21}N_2$: $(M+H)^+$ 385.1705.

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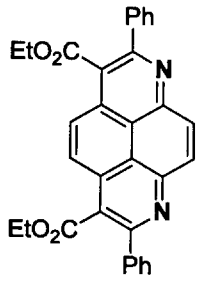
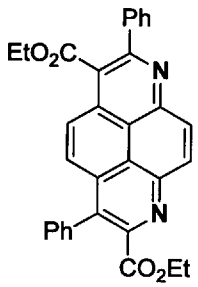
Diethyl 2,7-diphenylbenzo[*lmn*][2,9]phenanthroline-3,6-dicarboxylate (4-9h)



Regioisomer (**4-9h'**) 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{32}H_{25}N_2O_4$: $(M+H)^+$ 501.1814.

Diethyl 2,7-diphenylbenzo[*lmn*][2,9]phenanthroline-3,6-dicarboxylate (4-9h')



White solid; mp. 199–201 °C; IR (NaCl) 2982, 1732, 1722, 1557, 1472, 1302, 1244, 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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

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(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 $C_{32}H_{25}N_2O_4$: $(M+H)^+$ 501.1814.

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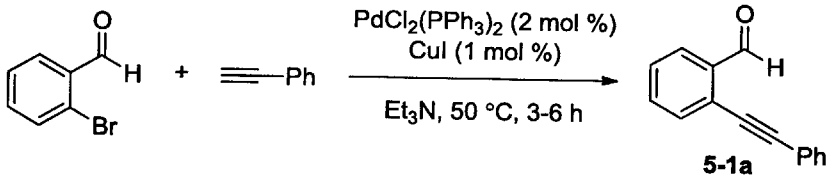
6.5 Experimental section of Chapter 5:

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).



5-1a

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_3N 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 × 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.

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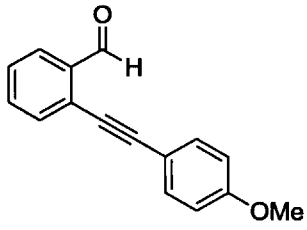
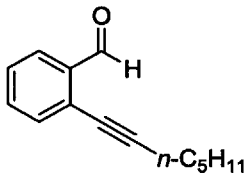
2-[2-(4-Methoxyphenyl)ethynyl]benzaldehyde (5-1b)[27]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)[28]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

[27] Obika, S.; Kono, H.; Yasui, Y.; Yanada, R.; Takemoto, Y. *J. Org. Chem.* **2007**, *72*, 4462.
[28] Hamze, A.; Provot, O.; Alami, M.; Brion, J.-D. *Org. Lett.* **2005**, *7*, 5625.

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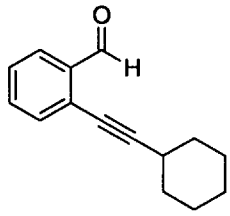
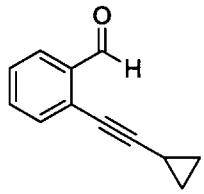
2-(Cyclohexylethynyl)benzaldehyde (5-1l)[29]



Prepared from 2-bromobenzaldehyde and cyclohexylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in quantitative yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)[26]



Prepared from 2-bromobenzaldehyde and cyclopropylacetylene, and purified by flash column chromatography (Si gel, hexane:ethyl acetate = 95:5) in quantitative yield; Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.3, 8.9, 71.4, 101.2, 126.9, 127.7, 127.8, 133.2, 133.6, 136.0, 192.1.

[29] Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691.

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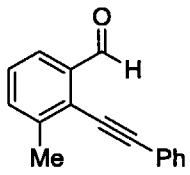
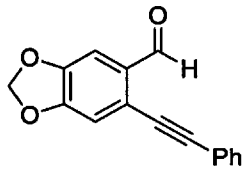
3-Methyl-2-(phenylethynyl)benzaldehyde (5-1n)



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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 (5-1o)[26]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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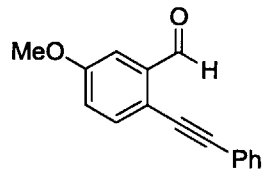
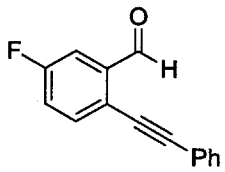
5-Methoxy-2-(phenylethynyl)benzaldehyde (5-1p)[26]



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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.88 (3H, s), 7.14 (1H, dd, J = 2.8, 8.8 Hz), 7.35-7.39 (3H, m), 7.43 (1H, d, J = 2.8 Hz), 7.53-7.58 (3H, m), 10.62 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)[26]



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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (1H, dt, 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, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.8, 96.0, 113.7 (d, J = 22.9 Hz), 121.3 (d, J = 22.5 Hz), 122.1, 123.0 (d, J = 3.6 Hz), 128.5, 129.1, 131.6, 135.2 (d, J = 7.6 Hz), 137.7 (d, J = 6.5 Hz), 162.3 (d, J = 251.2 Hz), 190.4.

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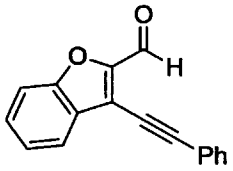
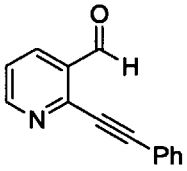
3-(Phenylethynyl)benzofuran-2-carbaldehyde (5-1r)



Prepared from 3-bromobenzofuran-2-carbaldehyde[30] 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{17}H_{11}O_2$: $(M+H)^+$ 247.0759.

2-(Phenylethynyl)nicotinaldehyde (5-1s)[27]



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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

[30] Zhao, H.; Dankwardt, J. W.; Koenig, S. G.; Singh, S. P. *Tetrahedron Lett.* **2012**, *53*, 166.

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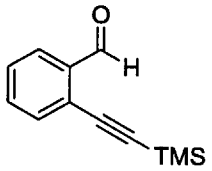
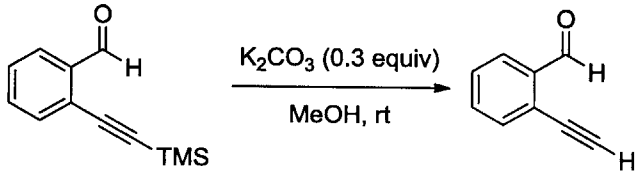
2-(2-Trimethylsilylethynyl)benzaldehyde (5-1u)[26]



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, $CDCl_3$) δ 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, $CDCl_3$) δ -0.3, 100.0, 102.4, 126.7, 126.8, 128.8, 133.5, 133.6, 136.1, 191.8.

Preparation of 2-ethynylbenzaldehyde



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_2CO_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_2Cl_2 (50 mL × 3). The combined organic layer was washed with 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 = 90:10) to give 2-ethynylbenzaldehyde in 71% yield.

2-Ethynylbenzaldehyde[26]

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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,

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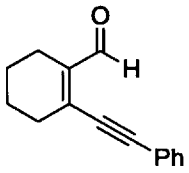
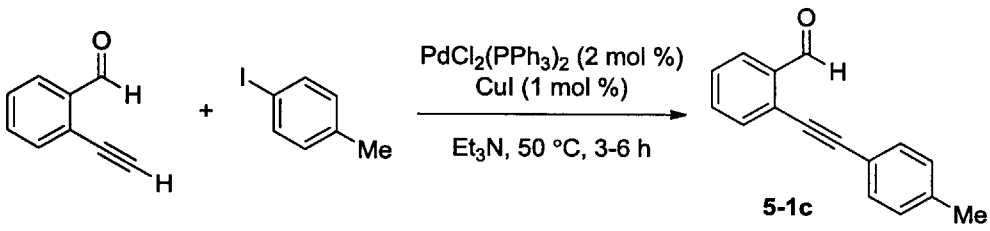
7.6 Hz), 10.54 (1H, d, J = 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.2, 84.2, 125.5, 127.2, 129.2, 133.7, 133.9, 136.5, 191.4.

2-(Phenylethynyl)cyclohex-1-enecarbaldehyde (5-1v)[31]



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).



To a solution of 2-ethynylbenzaldehyde (195 mg, 1.5 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), and CuI (2.9 mg, 0.015 mmol) in 6 mL of Et_3N was added the 1-iodo-4-

[31] Garcia-Garcia, P.; Martinez, A.; Sanjuan, A. M.; Fernandez-Rodriguez, M. A.; Sanz, R. *Org. Lett.* **2011**, *13*, 4970.

[32] Lian, J.-J.; Chen, P.-C.; Lin, Y.-P.; Ting, H.-C.; Liu, R.-S. *J. Am. Chem. Soc.* **2006**, *128*, 11372.

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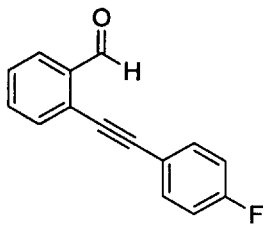
methylbenzene (393 mg, 1.8 mmol). The resulting mixture was heated under nitrogen atmosphere at 50 °C. After the reaction was completed, the reaction mixture was quenched with distilled water and extracted with ethyl acetate (50 mL × 3). Volatile materials were removed *in vacuo* and the crude material 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)[33]

Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, 7.6Hz), 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, $CDCl_3$) δ 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)



Prepared from 2-ethynylbenzaldehyde and 4-fluoroiodobenzene, 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, $CDCl_3$) δ 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, $CDCl_3$) δ 84.6, 95.2, 155.9 (d, J = 21.9 Hz), 118.4 (d, J = 3.5 Hz),

[33] Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499.

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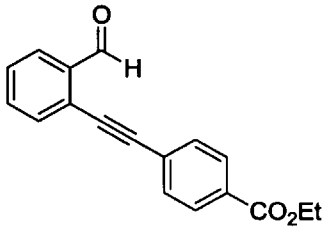
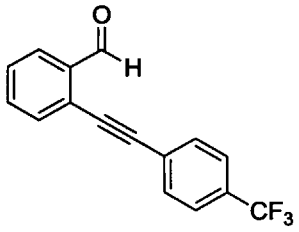
126.6, 127.4, 128.7, 133.2, 133.6 (d, J = 8.5 Hz), 133.8, 135.8, 162.9 (d, J = 249.6 Hz), 191.5; ESI-HRMS: Found: m/z 225.0711. Calcd for $C_{15}H_{10}FO$: $(M+H)^+$ 225.0716.

Ethyl 4-((2-formylphenyl)ethynyl)benzoate (5-1e)[34]



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, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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)[27]



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, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.2, 94.5, 123.8 (q, J = 270.6 Hz), 125.5 (q, J =

[34] Allen, C. P.; Benkovics, T.; Turek, A. K.; Yoon, T. P. *J. Am. Chem. Soc.* **2009**, *131*, 12560.

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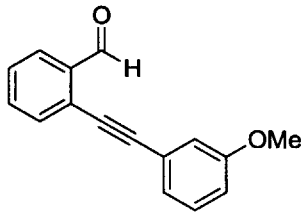
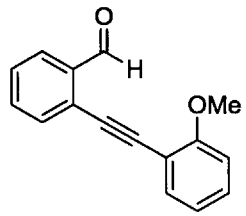
3.7 Hz), 125.8, 126.1, 127.6, 129.2, 130.7 (q, J = 32.7 Hz), 131.9, 133.4, 133.8, 136.0, 191.2.

2-[2-(3-Methoxyphenyl)ethynyl]benzaldehyde (5-1g)[35]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)[36]



Prepared from 2-ethynylbenzaldehyde and 1-bromo-2-methoxybenzene, and purified by by flash column chromatography (Si gel, hexane:ethyl acetate = 90:10) in 87% yield; Pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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

[35] Patil, N. T.; Konala, A.; Singh, V.; Reddy, V. V. N. *Eur. J. Org. Chem.* **2009**, 5178.
[36] Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem.* **2009**, 2852.

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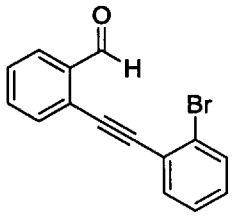
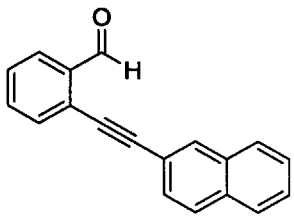
= 1.6, 7.2 Hz), 7.56 (1H, dt, J = 1.2, 7.6 Hz), 7.65 (1H, dd, J = 0.4, 8.0 Hz), 7.95 (1H, dd, J = 0.8, 7.6 Hz), 10.74 (1H, d, J = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.8, 89.0, 93.0, 110.6, 111.6, 120.5, 126.9, 127.4, 128.3, 130.5, 132.9, 133.2, 133.6, 135.8, 160.4, 192.5.

2-[2-(2-Bromophenyl)ethynyl]benzaldehyde (5-1i)[37]



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; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (1H, dt, J = 1.6, 7.6 Hz), 7.34 (1H, dt, J = 1.2, 7.6 Hz), 7.48 (1H, t, J = 7.6 Hz), 7.58-7.63 (2H, m), 7.64 (1H, dd, J = 0.8, 8.0 Hz), 7.70 (1H, dd, J = 0.8, 8.0 Hz), 7.97 (1H, dd, J = 1.2, 8.0 Hz), 10.76 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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-Naphthyl)ethynyl]benzaldehyde (5-1j)



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; mp. 73–75 °C; IR (neat) 743, 758, 1263, 1506, 1591, 1653, 1690 cm^{-1}; ^{1}H NMR (400

[37] Iwaniuk, D. P.; Wolf, C. *Org. Lett.* **2011**, *13*, 2602.

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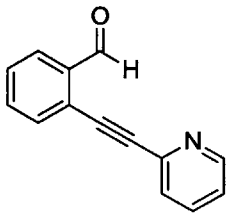
MHz, $CDCl_3$) δ 7.48 (1H, t, J = 7.6 Hz), 7.51-7.56 (2H, m), 7.58-7.64 (2H. m), 7.70 (1H, dd, J = 0.8, 8.0 Hz), 7.83-7.88 (3H, m), 7.98 (1H, dd, J = 0.8, 8.0 Hz), 8.11 (1H, s), 10.73 (1H, d, J = 0.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.2, 96.8, 119.5, 126.8, 126.9, 127.1, 127.3, 127.8, 127.9, 128.0, 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 $C_{19}H_{13}O$: $(M+H)^+$ 257.0966.

2-(Pyridin-2-ylethynyl)benzaldehyde (5-1t)[38]



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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 **5-2n**[39] and **5-2o**[40] which were known compounds and synthesized according to the reported literatures.

[38] Zhao, J.; Li, P.; Wu, C.; Chen, H.; Ai, W.; Sun, R.; Ren, H.; Larock, R. C.; Shi, F. *Org. Biomol. Chem.* **2012**, *10*, 1922.
[39] Rayan, A.; Falah, M. *U.S. Pat. Appl. Publ.* 20100284959, **2010**.

[40] Lemhadri, M.; Doucet, H.; Santelli, M. *Synthesis* **2005**, 1359.

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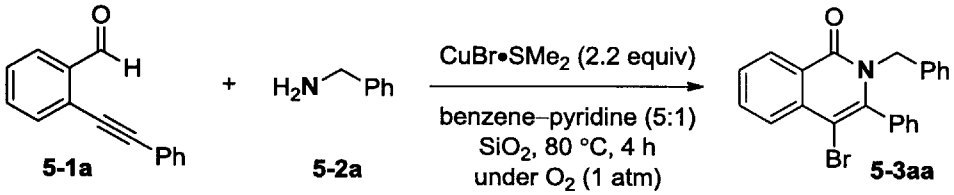
6.5.2 CuBr-mediated synthesis of 4-bromoisoquinolones: a typical procedure for the reaction of 2-(phenylethynyl)benzaldehyde (5-1a) and benzylamine (5-2a) (Table 5-1, entry 7).



To a stirred solution of 2-alkynylbenzaldehyde (**5-1a**) (105.0 mg, 0.509 mmol), $CuBr{\cdot}SMe_2$ (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}; ^1H 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 $C_{22}H_{17}NO\ ^{79}Br$: $(M+H)^+$ 390.0494.

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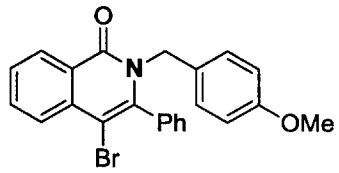
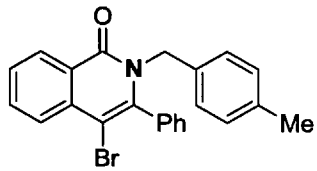
4-Bromo-2-(4-methoxybenzyl)-3-phenylisoquinolin-1(*2H*)-one (5-3ab)



Yellow oil; IR (neat) 748, 1032, 1177, 1246, 1510, 1582, 1607, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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: $(M+H)^+$ 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{23}H_{19}NO$ ^{79}Br: $(M+H)^+$ 404.0650.

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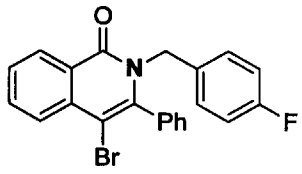
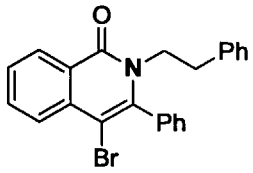
4-Bromo-2-(4-fluorobenzyl)-3-phenylisoquinolin-1(*2H*)-one (5-3ad)



Yellow solid; mp. 149–151 °C; IR (neat) 750, 1219, 1335, 1508, 1582, 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{16}NOF\ ^{79}Br$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{19}NO\ ^{79}Br$: $(M+H)^+$ 404.0650.

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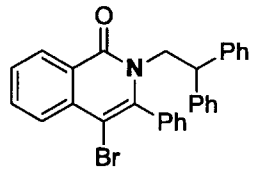
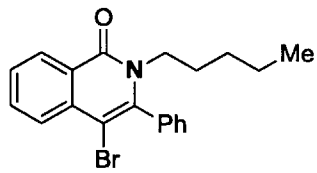
4-Bromo-2-(2,2-diphenylethyl)-3-phenylisoquinolin-1(*2H*)-one (5-3af)



Yellow solid; mp. 159–161 °C; IR (neat) 698, 756, 1508, 1636, 1645, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{29}H_{23}NO\,^{79}Br$: $(M+H)^+$ 480.0963.

4-Bromo-2-pentyl-3-phenylisoquinolin-1(*2H*)-one (5-3ag)



Yellow oil; IR (neat) 762, 1092, 1339, 1474, 1582, 1647, 2930, 2955 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{20}H_{21}NO\,^{79}Br$: $(M+H)^+$ 370.0807.

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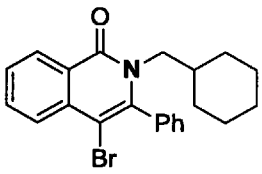
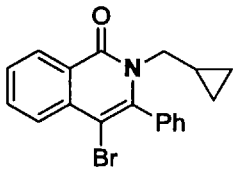
4-Bromo-2-(cyclohexylmethyl)-3-phenylisoquinolin-1(*2H*)-one (5-3ah)



White solid; mp. 140–145 °C; IR (neat) 1335, 1506, 1578, 1645, 1717, 2849, 2926 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{23}NO\ ^{79}Br$: $(M+H)^+$ 396.0963.

4-Bromo-2-(cyclopropylmethyl)-3-phenylisoquinolin-1(*2H*)-one (5-3ai)



Orange solid; mp. 102–104 °C; IR (neat) 694, 764, 1474, 1607, 1645, 2851, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{19}H_{17}NO\ ^{79}Br$: $(M+H)^+$ 354.0494.

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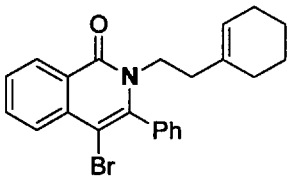
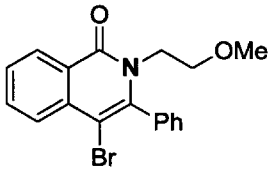
4-Bromo-2-(2-(cyclohex-1-en-1-yl)ethyl)-3-phenylisoquinolin-1(*2H*)-one (5-3aj)



White solid; mp. 107–109 °C; IR (neat) 752, 1578, 1609, 1636, 1647, 2859, 2924 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{23}NO$ ^{79}Br: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{18}H_{17}NO_2$ ^{79}Br: $(M+H)^+$ 358.0443.

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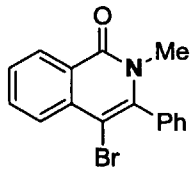
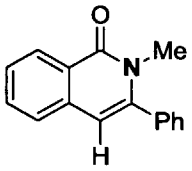
4-Bromo-2-methyl-3-phenylisoquinolin-1(*2H*)-one (5-3al)



White solid; mp. 132–134 °C; IR (neat) 745, 756, 1117, 1339, 1474, 1636, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. Calcd for $C_{16}H_{13}NO\ ^{79}Br$: $(M+H)^+$ 314.0181.

2-Methyl-3-phenylisoquinolin-1(*2H*)-one (5-6al)[41]



White solid; ^1H NMR (400 MHz, $CDCl_3$) δ 3.43 (3H, s), 6.46 (1H, 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, $CDCl_3$) δ 34.1, 107.5, 124.9, 125.8, 126.6, 127.8, 128.6, 128.7, 128.9, 132.2, 136.2, 136.3, 143.9, 163.3.

[41] Couture, A.; Cornet, H.; Grandclaudon, P. *J. Organomet. Chem.* **1992**, *440*, 7.

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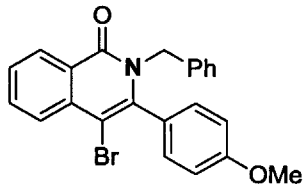
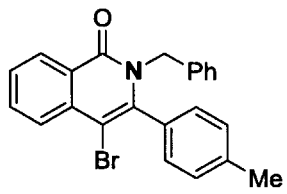
2-Benzyl-4-bromo-3-(4-methoxyphenyl)isoquinolin-1(*2H*)-one (5-3ba)



Sticky yellow oil; IR (neat) 750, 1032, 1173, 1248, 1508, 1609, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

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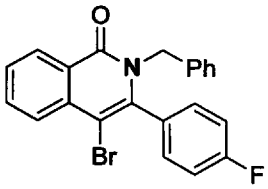
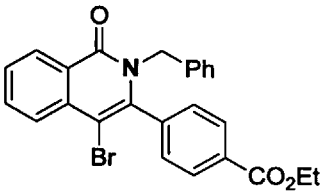
2-Benzyl-4-bromo-3-(4-fluorophenyl)isoquinolin-1(*2H*)-one (5-3da)



White solid; mp. 131–133 °C; IR (neat) 1223, 1238, 1373, 1506, 1636, 1717, 1734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{16}NOF\ ^{79}Br$: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{25}H_{21}NO_3\ ^{79}Br$: $(M+H)^+$ 462.0705.

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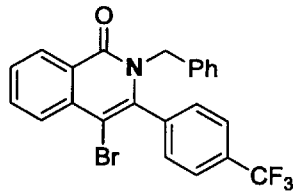
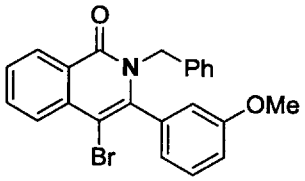
2-Benzyl-4-bromo-3-(4-trifluoromethylphenyl)isoquinolin-1(*2H*)-one (5-3fa)



Yellow oil; IR (neat) 760, 1067, 1128, 1167, 1321, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{16}NOF_3$ ^{79}Br: $(M+H)^+$ 458.0367.

2-Benzyl-4-bromo-3-(3-methoxyphenyl)isoquinolin-1(*2H*)-one (5-3ga)



Sticky oil; IR (neat) 1040, 1215, 1261, 1456, 1489, 1578, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{19}NO_2$ ^{79}Br: $(M+H)^+$ 420.0599.

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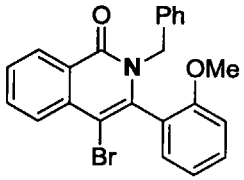
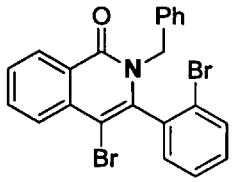
2-Benzyl-4-bromo-3-(2-methoxyphenyl)isoquinolin-1(*2H*)-one (5-3ha)



Yellow solid; mp. 108–110 °C; IR (neat) 758, 1256, 1495, 1578, 1599, 1636, 2965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{19}NO_2$ ^{79}Br: $(M+H)^+$ 420.0599.

2-Benzyl-4-bromo-3-(2-bromophenyl)isoquinolin-1(*2H*)-one (5-3ia)



Yellow oil; IR (neat) 692, 752, 1026, 1327, 1472, 1607, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{16}NO$ ^{79}Br ^{81}Br: $(M+H)^+$ 469.9578.

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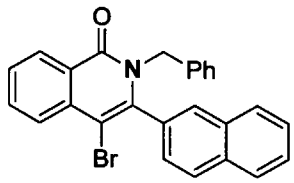
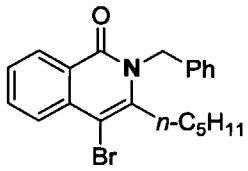
2-Benzyl-4-bromo-3-(2-naphthyl)isoquinolin-1(*2H*)-one (5-3ja)



Yellow oil; IR (neat) 748, 1337, 1506, 1582, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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. Calcd for $C_{26}H_{19}NO\ ^{79}Br$: $(M+H)^+$ 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}; ^1H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 13.9, 22.2, 27.9, 31.7, 33.6, 48.1, 102.3, 124.6, 125.9, 126.1, 127.0,

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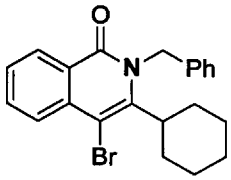
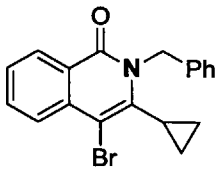
127.3, 128.5, 128.8, 133.2, 135.8, 137.0, 142.4, 162.5; ESI-HRMS: Found: m/z 384.0969. Calcd for $C_{21}H_{23}NO\,^{79}Br$: $(M+H)^+$ 384.0963.

2-Benzyl-4-bromo-3-cyclohexylisoquinolin-1(*2H*)-one (5-3la)



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, 1653cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) 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. Calcd 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, $CDCl_3$) 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, $CDCl_3$) δ 12.1, 15.3, 47.5, 105.5, 125.1, 126.0,

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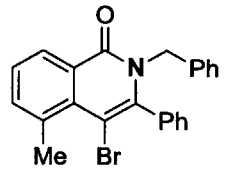
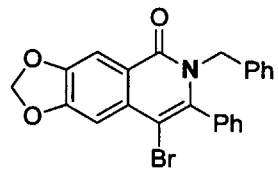
126.3, 127.0, 127.3, 128.3, 128.6, 133.0, 135.8, 137.6, 141.3, 162.5; ESI-HRMS: Found: m/z 354.0497. Calcd for $C_{19}H_{17}NO\ ^{79}Br$: $(M+H)^+$ 354.0494.

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^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{23}H_{19}NO\ ^{79}Br$: $(M+H)^+$ 404.0650.

6-Benzyl-8-bromo-7-phenyl-[1,3]dioxolo[4,5-*g*]isoquinolin-5(*6H*)-one (5-3oa)



Sticky yellow oil; IR (neat) 696, 1036, 1231, 1406, 1472, 1568, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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 $C_{23}H_{17}NO_3\ ^{79}Br$: $(M+H)^+$ 434.0392.

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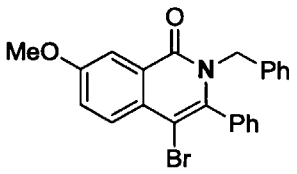
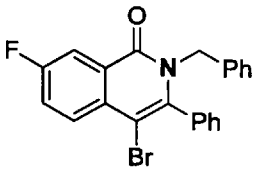
2-Benzyl-4-bromo-7-methoxy-3-phenylisoquinolin-1(*2H*)-one (5-3pa)



Yellow solid; mp. 161–163 °C; IR (neat) 698, 939, 1038, 1406, 1474, 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{23}H_{19}NO_2$ ^{79}Br: $(M+H)^+$ 420.0599.

2-Benzyl-4-bromo-7-fluoro-3-phenylisoquinolin-1(*2H*)-one (5-3qa)



Yellow solid; mp. 104–106 °C; IR (neat) 696, 752, 941, 1341, 1489, 1585, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{16}NOF$ ^{79}Br: $(M+H)^+$ 408.0399.

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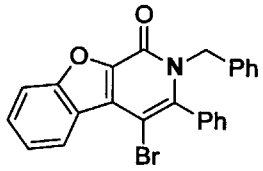
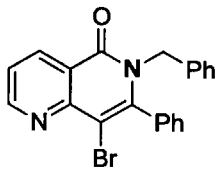
2-benzyl-4-bromo-3-phenylbenzofuro[2,3-*c*]pyridin-1(*2H*)-one (5-3ra)



White solid; mp. 182–184 °C; IR (neat) 743, 1038, 1456, 1474, 1647, 1668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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, dd, J = 0.4, 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{24}H_{17}NO_2$ ^{79}Br: $(M+H)^+$ 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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{16}N_2O$ ^{79}Br: $(M+H)^+$ 391.0446.

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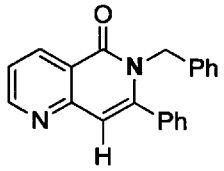
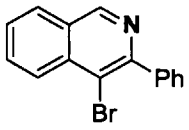
6-Benzyl-7-phenyl-1,6-naphthyridin-5(*6H*)-one (5-6sa)



Yellow solid; mp. 113–115 °C; IR (neat) 704, 839, 1358, 1437, 1506, 1558, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{21}H_{17}N_2O$: $(M+H)^+$ 313.1341.

4-Bromo-3-phenylisoquinoline (5-4)[42]



White solid; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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.

[42] Zhang, H.-P.; Yu, S.-C.; Liang, Y.; Peng, P.; Tang, B.-X.; Li, J.-H. *Synlett* **2011**, 982.

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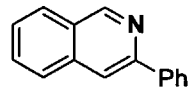
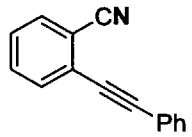
3-Phenylisoquinoline (5-5)[43]



White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.5, 126.8, 126.9, 127.0, 127.5, 127.7, 128.4, 128.7, 130.4, 136.5, 139.5, 151.2, 152.3.

2-(Phenylethynyl)benzonitrile (5-7)[44]



Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, dd, J = 0.8, 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

[43] Niu, Y.-N.; Yan, Z.-Y.; Gao, G.-L.; Wang, H.-L.; Shu, X.-Z.; Ji, K.-G.; Liang, Y.-M. *J. Org. Chem.* **2009**, *74*, 2893.

[44] Pu, X.; Li, H.; Colacot, T. J. *J. Org. Chem.* **2013**, *78*, 568.

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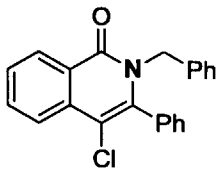
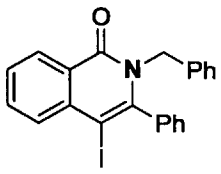
6.5.3 The reactions with CuCl and CuI (Scheme 5-24)

2-Benzyl-4-chloro-3-phenylisoquinolin-1(*2H*)-one (5-3aa')



Synthesized from 2.2 equiv of CuCl; Yellow oil; IR (neat) 696, 752, 1477, 1495, 1585, 1611, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{17}NOCl$: $(M+H)^+$ 346.0999.

2-Benzyl-4-iodo-3-phenylisoquinolin-1(*2H*)-one (5-3aa'')



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, $CDCl_3$) 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); ^{13}C NMR (100 MHz, $CDCl_3$) 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 $C_{22}H_{17}NOI$: $(M+H)^+$ 438.0355.

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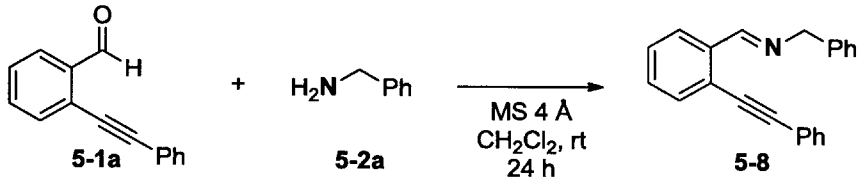
6.5.4 Control experiments to elucidate the reaction mechanism (Scheme 2-25 & 2-26)

6.5.4.1. Preparation of *N*-benzylaldimines 5-8



To a solution of 2-(2-phenylethynyl)benzaldehyde (**5-1a**) (206 mg, 1.0 mmol) in 1 mL of CH_2Cl_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 *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)**[27]

Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.90 (2H, s), 7.36-7.40 (10H, m), 7.50-7.57 (3H, m), 8.14 (1H, d, J = 6.8 Hz), 8.99 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 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.

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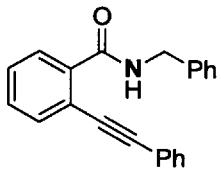
6.5.4.2. Preparation of 2-alkynylbenzamide 5-9

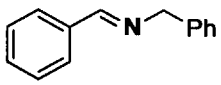
_N_-Benzyl-2-(phenylethynyl)benzamide (5-9)[45]



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, $CDCl_3$) δ 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, $CDCl_3$) δ 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)[46]



Prepared from benzaldehyde and benzylamine; Brown oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 65.0, 126.9, 127.9, 128.18, 128.22, 128.4, 128.5, 129.0, 130.7, 161.9.

[45] Liu, G.; Zhou, Y.; Ye, D.; Zhang, D.; Ding, X.; Jiang, H.; Liu, H. *Adv. Synth. Catal.* **2009**, *351*, 2605.
[46] Marinescu, L. G.; Pedersen, C. M.; Bols, M. *Tetrahedron* **2004**, *61*, 123.

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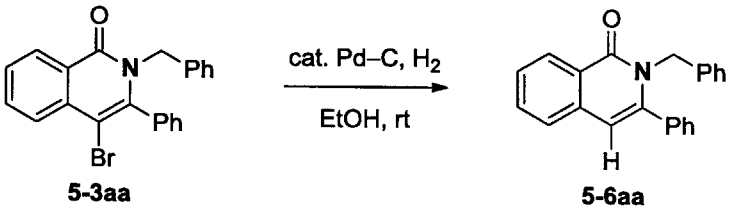
6.5.4.3. Preparation of 2-benzyl-3-phenylisoquinolin-1(2*H*)-one (5-6aa)



5-3aa **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(2*H*)-one (5-6aa)[47]

White solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

[47] Couture, A.; Grandclaudon, P. *Synthesis* **1986**, 576.