博士論文

Development of New Cobalt(III)-Precursors for Expanding the Scope of C-H Bond Functionalization

(新規 Co(III)前駆体の開拓と C−H 官能基化の基質一般性拡張)

Bo Sun

孫　博

Contents

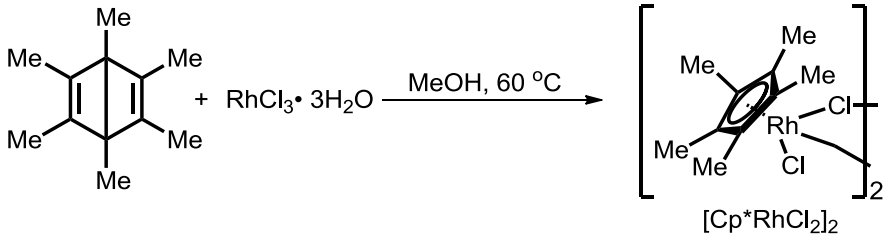
Abbreviation

Ac	acetyl
acac	acetylacetonate
Ar	aryl
Bu	butyl
Cat.	catalyst
Co	cobalt
Cp*	pentamethylcyclopentadienyl
Cs	cesium
DCE	1,2-dichloroethane
equiv.	equivalent
Et	ethyl
h	hour
HRMS	high resolution mass spectrometry
Ir	iridium
IR	infrared spectroscopy
L	ligand
M	metal or mol/L
Me	methyl
NMR	nuclear magnetic resonance
Ph	phenyl
Piv	pivaloyl
R	alkyl or general substituent
Rh	rhodium
Ru	ruthenium
Temp.	temperature
THF	tetrahydrofuranyl
Ts	tosyl

Chapter 1
Introduction

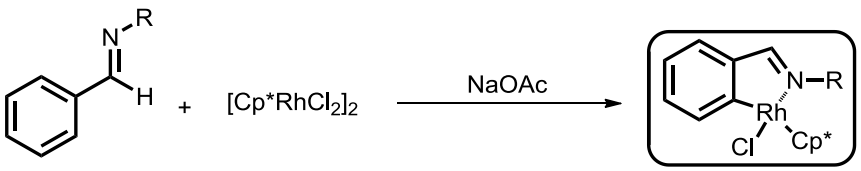
The traditional methods for nucleophilic addition of organometallic reagents to electrophiles are very important in organic chemistry. Generally, the generation of nucleophilic organometallic reagents needs stoichiometric amounts of strong bases and/or reducing metals, such as, *n*BuLi and Mg; therefore, inevitably producing stoichiometric salt waste. Thus, the development of atom-economical processes involving the catalytic generation of nucleophilic organometallic species and their addition to polar electrophiles without additional activating reagents is highly desirable.

Transition metal-catalyzed directed C-H bond functionalization has emerged as a powerful synthetic methodology[1] in the last decades, that is potentially superior to traditional organic reactions using stoichiometric amounts of activating reagents. Among the various transition metal catalysts suitable for directed C-H bond functionalization, rhodium(III) catalysts, in particular $[Cp^*RhCl_2]_2$ (Cp*=pentamethylcyclopentadienyl) and $[Cp^*Rh(MeCN)_3]^{2+}$ have an established role.[2] $[Cp^*RhCl_2]_2$ was firstly synthesized by Maitlis and coworkers[3] in 1969 **(Scheme 1.1)**.



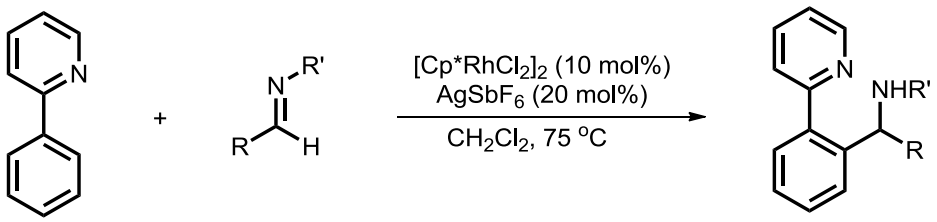
Scheme 1.1 Preparation of Cp*Rh(III) Complex

In 2003, Davies and coworkers[4] reported Cp*Rh(III) for directed cyclometallation with imines under base condition **(Scheme 1.2)**.



Scheme 1.2 Cp*Rh(III) for directed cyclometallation

In 2011, Ellman group[5] and Shi group[6] almost at the same time reported that $[Cp^*RhCl_2]_2$, in combination with $AgSbF_6$, can promote the addition of 2-phenylpyridine to imines in good yields. These are the first examples of rhodium(III)-catalyzed arylation of imines through catalytic generation of a nucleophilic Rh-aryl species *in situ* via C-H bond functionalization **(Scheme 1.3)**.

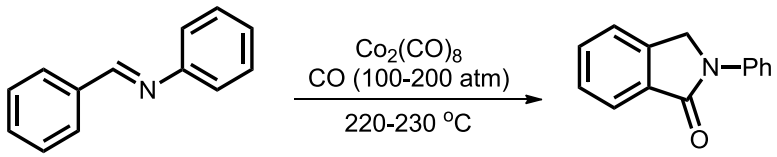


Scheme 1.3 Cp*Rh(III)-catalyzed arylation of imines

Now, Miura, Fagnou, Glorius, Ellman, Shi, Li, Ackermann, Chang, Rovis and many other groups are investigating cationic Cp^*Rh^{III} complexes for various C-C, C-N, and many other C-X bond-formations and applications in the synthesis of natural products, useful building blocks, and organic materials, showing high efficiency, selectivity, and functional group tolerance. Despite their utilities in C-H functionalization, however, the need for expensive and precious rhodium sources is economically and environmentally disadvantageous, especially for future industrial applications. Therefore, the development of an inexpensive base metal catalyst as an alternative to cationic Cp^*Rh^{III} catalysts is highly desired.

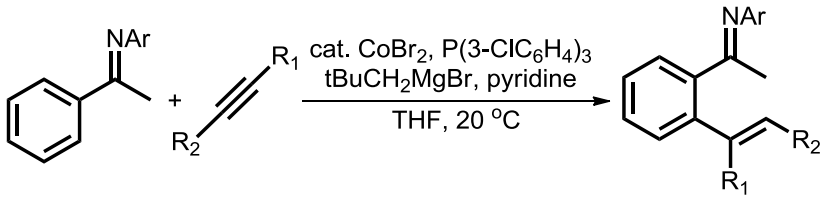
In the last few decades, cheap and commercially available first-row transition metals were commonly utilized to the various C-H bond functionalization reactions. Cobalt is the same group with rhodium. Cobalt catalyst was the first catalyst to be used in chelation-assisted C-H bond functionalization. The first example was reported by Murahashi[7] in 1955. Under the catalysis of dicobalt octacarbonyl,

N-benzylideneaniline coordinated with high pressure CO gas and gave isoindoline derivative **(scheme 1.4)**.



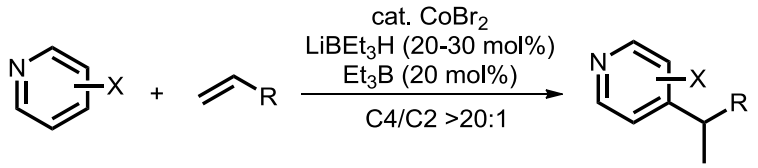
Scheme 1.4 Cobalt-catalyzed formation of isoindoline derivative

In the past 10 years, there has been a rise in the interest of low-valent cobalt catalysts for C-H bond functionalization. In Yoshikai group[8], they used a ternary catalytic system consisting of a cobalt precatalyst, a phosphine ligand, and a reducing agent for hydroarylation reactions of alkynes and alkenes under mild conditions. These examples show that with appropriate ligands and reducing agents, low-valent cobalt catalysts can emulate the reactivity of noble second- and third-row late-transition metal catalysts for C−H bond functionalization. Low-valent cobalt catalysts exhibited unique reactivity and selectivity in C−H bond functionalization **(Scheme 1.5)**.



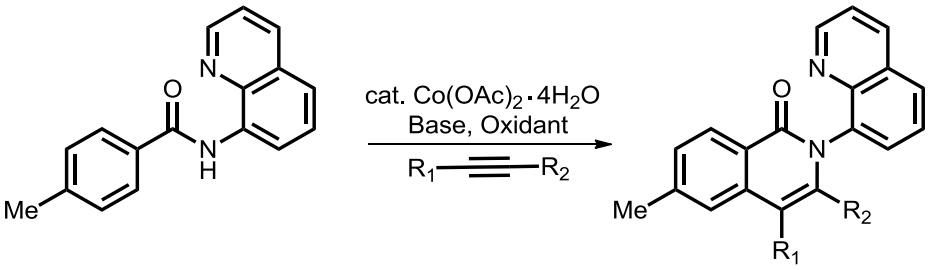
Scheme 1.5 Cobalt-catalyzed alkenylation reaction

In 2013, Our group[9] reported that the combined use of $CoBr_2$ and $LiBEt_3H$ catalyzed the reaction of pyridines with 1-alkenes to give alkylation products with C4/C2 ratios of >20:1 **(Scheme 1.6)**.



Scheme 1.6 Cobalt-catalyzed C4-Selective direct alkylation of pyridines

In contrast, studies on the corresponding high-valent cobalt catalysis were rare when I started my Ph.D works. Last year, Daugulis group[10] reported cobalt-catalyzed aminoquinoline-directed C-H bond alkenylation by alkynes, showing excellent functional-group tolerance and both internal and terminal alkynes were competent substrates for the coupling. The reaction used a $Co(OAc)_2 \cdot 4H_2O$ catalyst, $Mn(OAc)_2$ and oxygen as a terminal oxidant, and the authors proposed *in situ* generation of Co(III) species under the reaction conditions **(Scheme 1.7)**.



Scheme 1.7 Cobalt-catalyzed aminoquinoline-directed C-H bond alkenylation

I only listed small numbers of low-valent cobalt catalyst-catalyzed C-H bond functionalization reactions. The cobalt catalysts worked well, how about high-valent cobalt catalyst? Whether it has similar reactivity with noble transition metal rhodium(III) catalyst? As my Ph.D work, I investigate to develop readily available high-valent Cp^*Co^{III} complexes for C-H bond functionalization and expand the scopes of Cp^*Co^{III} catalysis.

References

[1] Recent reviews on C-H bond functionalization: a) *C-H Activation*, *Topics in Current Chemistry*, vol. *292*, (Eds.: J. Q. Yu, Z. J. Shi, Springer, **2010**); b) D. A. Colby, R. G. Bergman, J. A. Ellman, *Chem. Rev.* **2010**, *110*, 624; c) I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890; d) T. W. Lyons, M. S. Sanford, *Chem. Rev.* **2010**, *110*, 1147; e) J. Wencel-Delord, T. Dröge, F. Liu, F. Glorius, *Chem. Soc. Rev.* **2011**, *40*, 4740; f) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068; g) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315; h) C. Zhu, R. Wang, J. R. Falck, *Chem. Asian J.* **2012**, *7*, 1502; i) N. Kuhl, M. N. Hopkinson, J. Wencel-Delord, F. Glorius, *Angew. Chem. Int. Ed.* **2012**, *51*, 10236; j) K. M. Engle, T.-S. Mei, M. Wasa, J. Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; k) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; l) B. J. Li, Z. J. Shi, *Chem. Rev.* **2012**, *112*, 5879; m) P. Beatrice Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; n) J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369; (o) G. Rouquet, N. Chatani, *Angew. Chem. Int. Ed.* **2013**, *52*, 11726.

[2] Reviews on Cp^*Rh^{III} catalysis: a) T. Satoh, M. Miura, *Chem.-Eur. J.* **2010**, *16*, 11212; b) F. W. Patureau, J. Wencel-Delord, F. Glorius, *Aldrichimica Acta* **2012**, *45*, 31; c) G. Song, F. Wang, X. Li, *Chem. Soc. Rev.* **2012**, *41*, 3651; d) S. Chiba, *Chem. Lett.* **2012**, *41*, 1554.

[3] J. W. Kang, K. Mose;ey, P. M. Maitlis, *J. Am. Chem. Soc*. **1969**, *91*, 5970.

[4] D. L. Davies, O. Al-Duaij, J. Fawcett, M. Giardiello, S. T. Hilton, D. R. Russell, *Dalton Trans.* **2003**, 4132.

[5] A. S. Tsai, M. E. Tauchert, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc*. **2011**, *133*, 1248.

[6] Y. Li, B. J. Li, W. H. Wang, W. P. Huang, X. S. Zhang, K. Chen, Z. J. Shi, *Angew. Chem. Int. Ed.* **2011**, *50*, 2115.

[7] S. Murahashi, *J. Am. Chem. Soc.* **1955**, *77*, 6403.

[8] a) P. S. Lee, T. Fujita, N. Yoshikai, *J. Am. Chem. Soc*. **2011**, *133*, 17283; b) K. Gao, N. Yoshikai, *Acc. Chem. Res*. **2014**, *47*, 1208.

[9] T. Andou, Y. Saga, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 3213.

[10] L. Grigorjeva, O. Daugulis, *Angew. Chem. Int. Ed.* **2014**, *53*, 10209.

Chapter 2

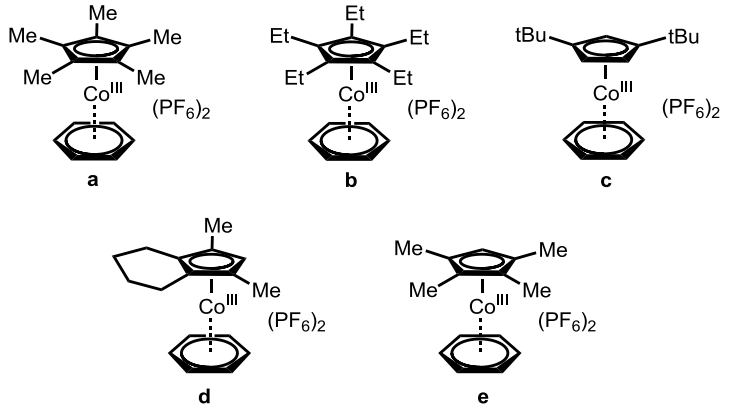
Air-Stable $Cp^*Co(CO)I_2$ Complex as a Precursor for Cationic Cp^*Co^{III} Catalysis: Application for Directed C2-Selective C-H Amidation of Indoles

2.1 Introduction

Cationic Cp^*Rh^{III} complexes are widely utilized for various C-C, C-N, and many other C-X bond-formations. Despite their utility in C-H functionalization, however, the need for expensive and precious rhodium sources is economically and environmentally disadvantageous, especially for future industrial applications. Therefore, the development of an inexpensive base metal catalyst as an alternative to cationic Cp^*Rh^{III} catalysts is highly desired[1]. As part of ongoing studies on first-row transition metal-catalysis, Dr. Yoshino in Kanai/Matsunaga group, a co-worker of mine, recently reported the utility of a cationic $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex for the addition of 2-phenylpyridines[2] and indoles[3] to imines. Herein, I described my efforts to expand the scope of Cp^*Co^{III} catalysis. A readily available $Cp^*Co(CO)I_2$ complex was successfully utilized as the precursor of a cationic Co^{III} active catalyst in a directed C2-selective amidation of indoles.

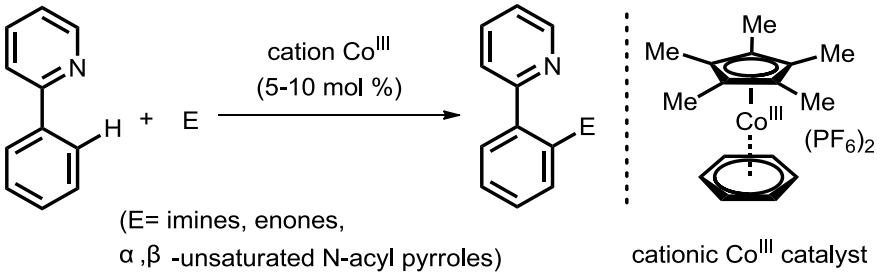
2.1.1 Precedents of Cp*Co(III)-catalyzed C-H bond functionalization

In 2013, Dr. Yoshino[2] reported, for the first time, the utility of a cationic high-valent cobalt complex and the structure–activity relationship of various Cp^*Co^{III} complexes **(Scheme 2.1)** for the catalytic generation of nucleophilic organometallic species.



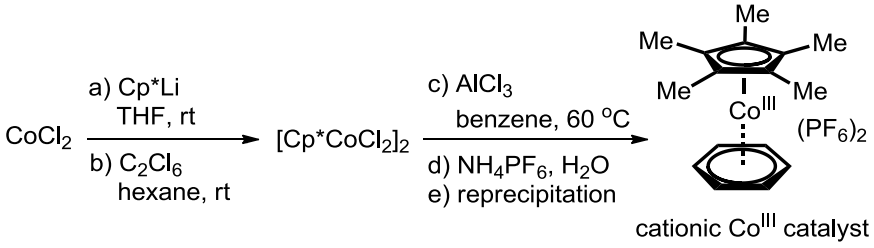
Scheme 2.1 Cationic high-valent cobalt(III) complexes

This was the first utility on high-valent cobalt(III)-catalyzed C-H bond functionalization reactions. $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex **(a)** showed best catalytic activity among these Co catalysts. The $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex promoted the addition of 2-aryl pyridines to imines, enones, and α,β-unsaturated *N*-acyl pyrroles as ester and amide surrogates in good yields **(Scheme 2.2)**.



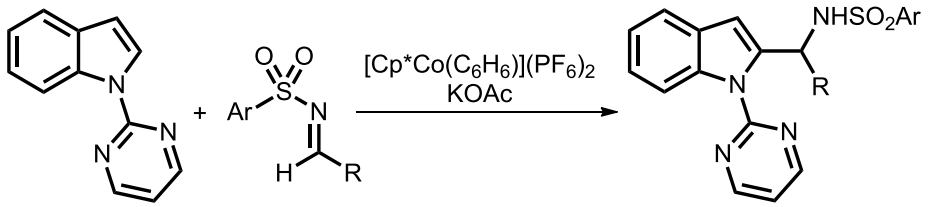
Scheme 2.2 $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex catalysed C-H functionalization

The preparation of $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex was firstly reported by Koelle[4]. From $CoCl_2$, the reaction with Cp*Li, oxidation, and counter ion exchange gave $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex as an air- and moisture-stable solid in 24 % overall yield in gram quantities after purification by re-precipitation **(Scheme 2.3).**



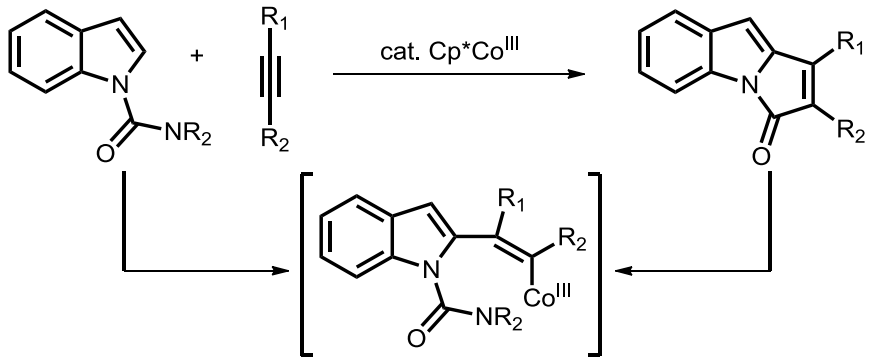
Scheme 2.3 Preparation of $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex

In the same year, Dr. Yoshino[3] utilized the $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex for promoting the C2-selective addition of indoles to imines. The Co^{III} catalyst completely changed the regioselectivity in comparison with simple Lewis acid-catalyzed Friedel–Crafts C3-selective addition **(Scheme 2.4)**.



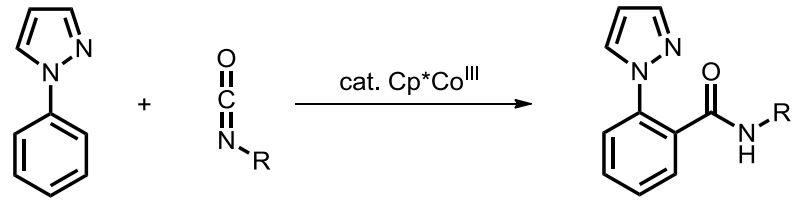
Scheme 2.4 Cp^*Co^{III}-catalyzed C2-selective addition of indoles to imines

In 2014, Mr. Ikemoto in Kanai/Matsunaga group[5] reported one-pot synthesis of pyrroloindolone via a $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$-catalyzed redox-neutral directed C–H alkenylation/annulation sequence. Cp^*Co^{III} showed unique catalytic reactivity in comparison with related Cp^*Rh^{III} catalysts **(Scheme 2.5)**.



Scheme 2.5 Cp^*Co^{III}-catalyzed redox-neutral directed C–H alkenylation/annulation

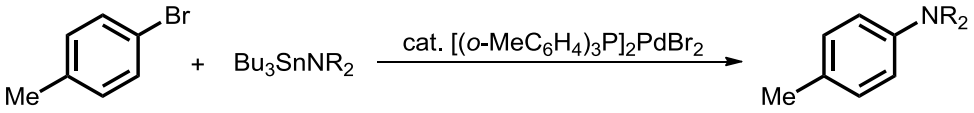
In 2015, Ellman group[6] reported $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ catalyzed C–H bond amidation with isocyanates. This transformation demonstrated a broad isocyanate scope and good functional-group compatibility and has been performed on gram scale **(Scheme 2.6)**.



Scheme 2.6 Cp*Co^{III}-catalyzed C–H bond amidation with isocyanates

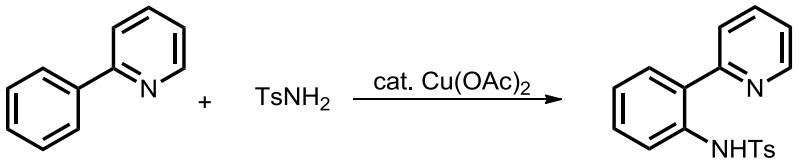
2.1.2 Precedents of transition metals-catalyzed amidation or amination reactions

In 1994, Hartwig group[7] and Buchwald group[8] reported palladium-catalyzed formation of carbon-nitrogen bonds from the hetero cross-coupling of aryl halides and tin amides **(Scheme 2.7)**.



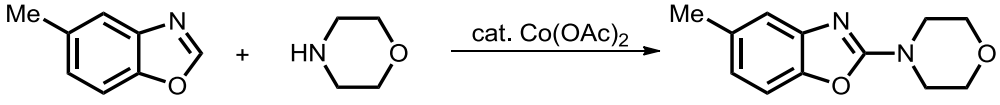
Scheme 2.7 Palladium-catalyzed amination reaction

In 2006, Yu group[9] reported using 2-phenylpryidine as substrate reacted $TsNH_2$, catalyzed by $Cu(OAc)_2$ and use of O_2 as a stoichiometric oxidant **(Scheme 2.8)**.



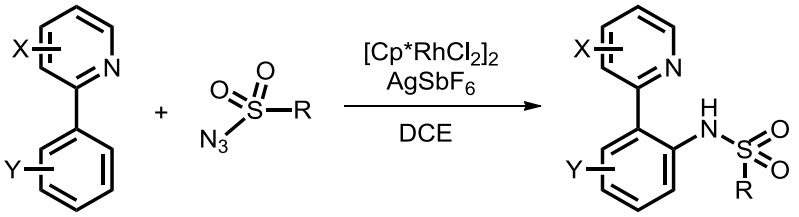
Scheme 2.8 Copper-catalyzed amidation reaction

In 2010, Chang group[10] reported cobalt-catalyzed direct amination of azoles with ammonia, and primary or secondary amines under mild reaction conditions **(Scheme 2.9)**.



Scheme 2.9 Cobalt-catalyzed amination reaction

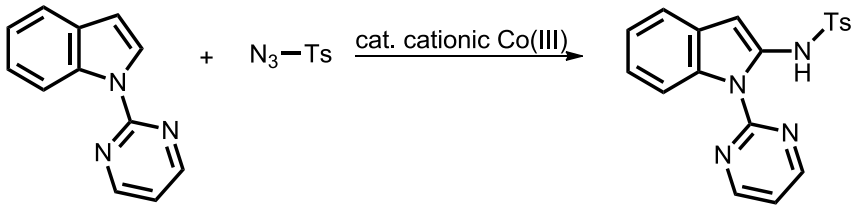
In 2012, Chang and coworkers[13a] reported Cp*Rh^{III}-catalyzed direct amination/ amidation reactions using sulfonyl, aryl, and alkyl azides as amino sources.[11-16] The reactions using a variety of substrates proceeded smoothly in good yields, releasing N_2 gas as a sole by-product **(Scheme 2.10)**. [13-15]



Scheme 2.10 Cp*Rh^{III}-catalyzed amidation reactions with sulfonyl azides

2.1.3 My research purposes

For cationic [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ complex, Ellman and our group reported it showed a good catalytic reactivity for the addition of 2-phenylpyridines and indoles to imines, alkynes, and isocyanate. Chang group's results in **Scheme 2.10** led me to evaluate Co(III) catalytic activity of a cationic [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ complex for the same reaction, using indoles moiety as substrates **(Scheme 2.11)**.



Scheme 2.11 Cationic Co(III)-catalyzed amidation reactions of indole

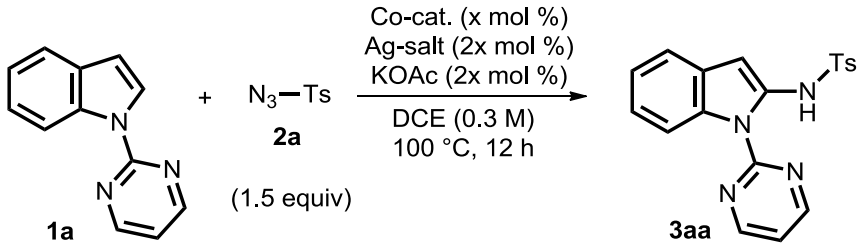
On the other hand, the synthetic procedure of the [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ complex, utilized by Dr. Yoshino and Mr. Ikemoto, was rather lengthy and the use of Glove box was required. Furthermore, the catalytic activity of the [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ complex was also moderate in many reactions (unpublished). Thus, further studies to find out new readily available, yet more reactive Co(III)-complexes were required. In the following sections. I will describe how I developed readily available Cp*Co^{III} complexes for C-H bond functionalization and expanded the scopes of Cp*Co^{III} catalysis to C-H amidation and other reactions.

2.2 Air-Stable $Cp^*Co(CO)I_2$ complex as a precursor for cationic Cp^*Co^{III} catalysis: application for directed C2-selective C-H amidation of indoles

2.2.1 Cobalt catalyst effects

I initially utilized the $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex for my first model reaction, the reaction of indole **1a** with azide **2a**. The reactivity of the $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex, however, was poor, giving product **3aa** in only 4% yield in the presence of KOAc **(Table 2.1, entry 1)**. Thus, I investigated the reaction in more detail to identify a suitable cobalt-based catalyst. I assumed that the inferior activity of the $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex could be due to the thermal instability of the PF_6^- ion under the present reaction conditions.[17] Trials to exchange the counter ion of the cationic $Cp^*Co^{III}(C_6H_6)$ complex were not successful due to problems in the purification step. As an alternative method to generate catalytically active cationic Cp^*Co^{III} species *in situ*, I determined that a $Cp^*Co(CO)I_2$ complex in combination with a suitable Ag-salt was effective. **Entry 2** used $AgPF_6$ as an activator to activate $Cp^*Co(CO)I_2$ to generate Cp*Co(III), but only 14% yield of **3aa** was obtained. Commercially available Co^{III} salts such as $Co(acac)_3$ and $Co(NH_3)_6Cl_3$ did not promote the reaction **(entries 3-4)**. No reaction occurred when using other Co-catalysts, such as $Co_2(CO)_8$ or CoI_2 with $AgSbF_6$ **(entries 5-6)**.

Table 2.1 Cobalt catalyst effects



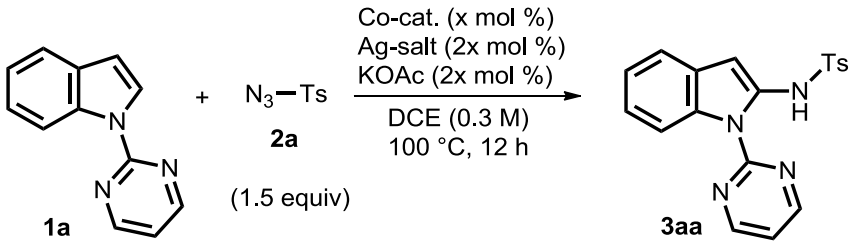
Entry	Co cat (mol%)	Ag salt (mol%)	KOAc (mol%)	Yield (%)[a]
1	$[Cp^*Co(C_6H_6)](PF_6)_2$ (5)	none	10	4
2	$[Cp^*Co(CO)I_2]$ (2.5)	$AgPF_6$ (5)	5	14
3	$Co(acac)_3$ (5)	none	10	0
4	$Co(NH_3)_6Cl_3$ (5)	none	10	0
5	$Co_2(CO)_8$ (2.5)	none	10	0
6	CoI_2 (5)	$AgSbF_6$ (10)	10	0

[a] NMR yield.

2.2.2 Ag-salt and base effects

Among the Ag-salts screened **(Table 2.2, entries 1-3)**, $AgSbF_6$ was best, and 2.5 mol % of $Cp^*Co(CO)I_2$ with 5 mol % of $AgSbF_6$ gave **3aa** in 81% yield **(entry 1)**. A cationic Cp^*Co^{III} species generated with $AgPF_6$ had much lower reactivity than that generated with other Ag-salts **(Table 2.1, entry 2 vs Table 2.2 entries 1-2)**, supporting our assumption that the PF_6^- ion was not appropriate. Trials to generate an efficient catalyst with AgOAc in the absence of KOAc failed, resulting in poor reactivity **(entry 3)**. The reaction in the absence of either KOAc or $AgSbF_6$ also gave a low yield **(entry 4**: 33%, **entry 5**: 0%**)**, indicating that both $AgSbF_6$ and KOAc were essential to generate the catalytically active species *in situ*. Finally, performing the reaction with 1.5 equiv of **1a** led to the best yield of **3aa (**92% isolated yield based on **2**, **entry 6)**. The reaction proceeded nicely with reduced catalyst loading **(entry 7**: 1.25 mol %**)**, and a good catalyst turnover number was observed (TON = 68).

Table 2.2 Ag-salt and base effects



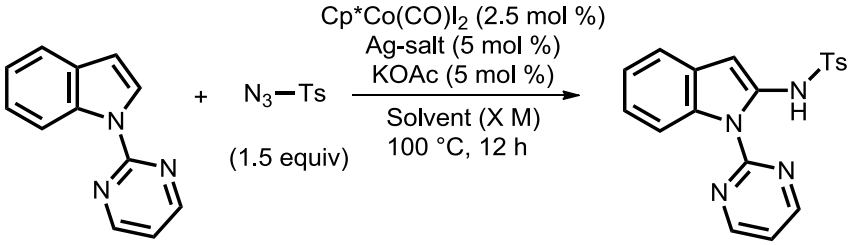
Entry	Co cat (mol%)	Ag salt (mol%)	KOAc (mol%)	Yield (%)[a]
1	$[Cp^*Co(CO)I_2]$ (2.5)	$AgSbF_6$ (5)	5	81
2	$[Cp^*Co(CO)I_2]$ (2.5)	$AgNTf_2$ (5)	5	79
3	$[Cp^*Co(CO)I_2]$ (2.5)	AgOAc (5)	0	trace
4	$[Cp^*Co(CO)I_2]$ (2.5)	$AgSbF_6$ (5)	0	33
5	$[Cp^*Co(CO)I_2]$ (2.5)	none	5	0
6[b]	$[Cp^*Co(CO)I_2]$ (2.5)	$AgSbF_6$ (5)	5	92[c]
7[b,d]	$[Cp^*Co(CO)I_2]$ (1.25)	$AgSbF_6$ (2.5)	2.5	86

[a] NMR yield. [b] Indole derivative is 1.5 eq. [c] Isolated yield. [d] The reaction was run in DCE (0.5 M).

2.2.3 Solvent and concentration effects

Different solvents were checked, and 1,4-dioxane gave the target product in only 44% yield **(Table 2.3, entry 1)**. PhCl and Toluene afforded similar results, 81% and 79%, respectively, but the yield was no improved than DCE **(entries 2-3)**. Increasing or decreasing the concentration resulted in no improvement **(entries 4-7)**.

Table 2.3 Solvent and concentration effects



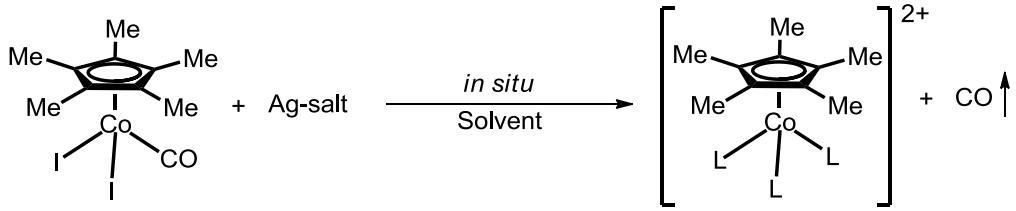
Entry	Concentration (M)	Solvent	Yield (%)[a]
1	0.3	1,4-dioxane	44
2	0.3	PhCl	81
3	0.3	Toluene	79
4	0.1	DCE	32
5	0.2	DCE	34
6	0.5	DCE	78
7	0.8	DCE	64

[a] NMR yield.

2.2.4 Preparation of Cp*Co(CO)I_2 complex

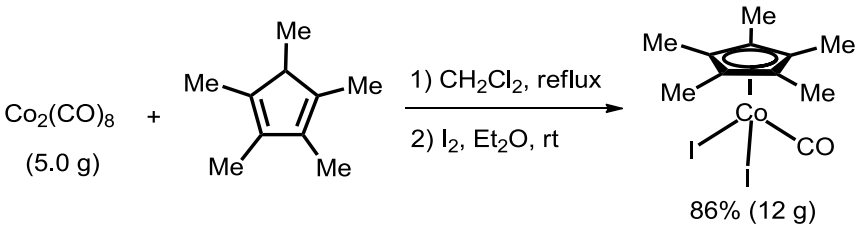
The results in previous section clearly indicated that the Cp*Co(CO)I_2 complex was useful for generating an active cationic Co(III) species *in situ* by mixing with Ag salts as reported by White and coworkers[18] in 1979 **(Scheme 2.12)**. Results of optimization studies indicated that the selection of counter ion was critical in catalytic activity, and the use of *in situ* generated Co(III)-catalyst with SbF_6 anions was important to achieve good catalytic activity. I assumed that the inferior activity of the [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ complex could be due to the thermal instability of the PF_6^- ion under the present reaction conditions. The stablity of PF_6^- ion in Cp*Co^{III}(ligand)$_n$ complexes depended on ligands and for example, rapid solvolysis of PF_6^- ion in a [Cp*Co^{III}(acetone)$_3$](PF_6)$_2$ complex was reported, by White[18]. With my improved system using the air-stable Cp*Co(CO)I_2

complex, now variety of counter ion was selected easily simply by changing commercially available Ag-salts. The modular approach clearly expanded the utility of the Co(III)-catalysis. Furthermore, the synthetic procedure of $Cp^*Co(CO)I_2$ complex is quite sample, and this catalyst-precursor is stable under the air circumstance.



Scheme 2.12 Transformation of $Cp^*Co(CO)I_2$ complex

For the gram-scale preparation of the $Cp^*Co(CO)I_2$ complex, I slightly modified the reported original synthetic procedure[19], and synthesized air-stable and readily available in just one-pot (two steps) from commercially available $Co_2(CO)_8$ and pentamethylcyclopentadiene with 86% yield in >10 gram scale **(Scheme 2.13)**.



Scheme 2.13 Preparation of $Cp^*Co(CO)I_2$ complex

2.2.5 Substrate scope

The substrate scope of indole derivatives with 4-methylbenzenesulfonyl azide **(2a)** is summarized in **Table 2.4** Both electron-donating and electron-withdrawing substituents on indoles were compatible, and various 4-, 5-, or 6-substituted indoles showed good reactivity. Not only other aryl-sulfonyl azides, but also alkyl-sulfonyl azides **2c-2d** reacted smoothly under Cp^*Co^{III} catalysis, and the products were obtained in 86-98% yield **(Table 2.5)**.

Table 2.4 The scope of indole derivatives with 4-methylbenzenesulfonyl azide **(2a)**

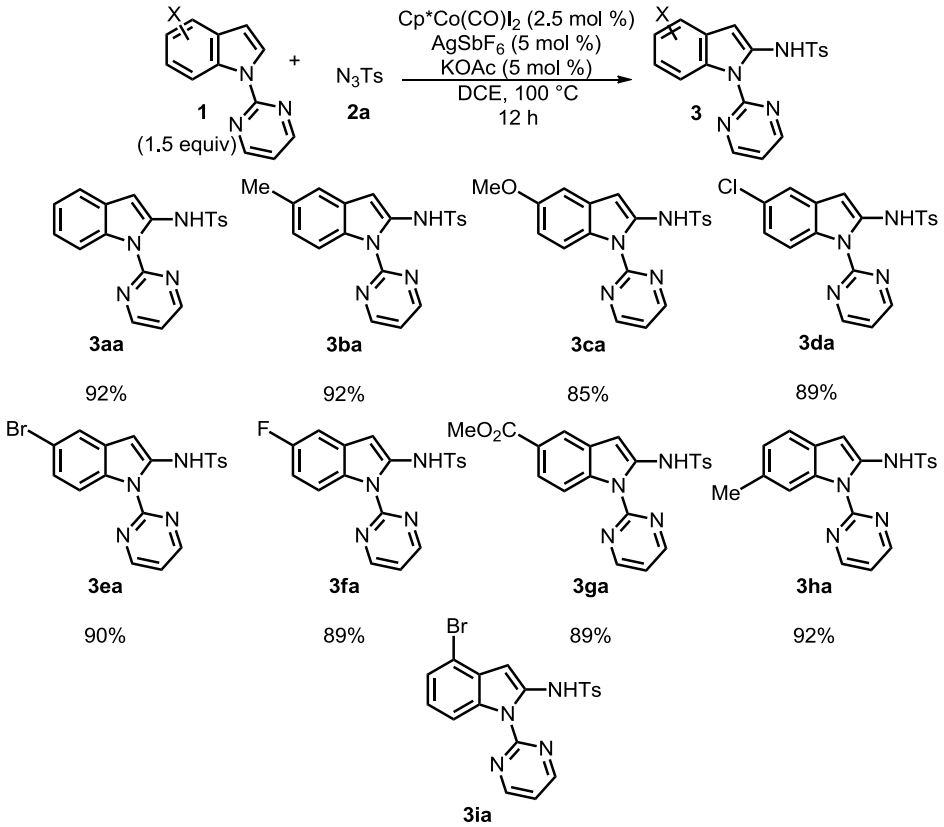
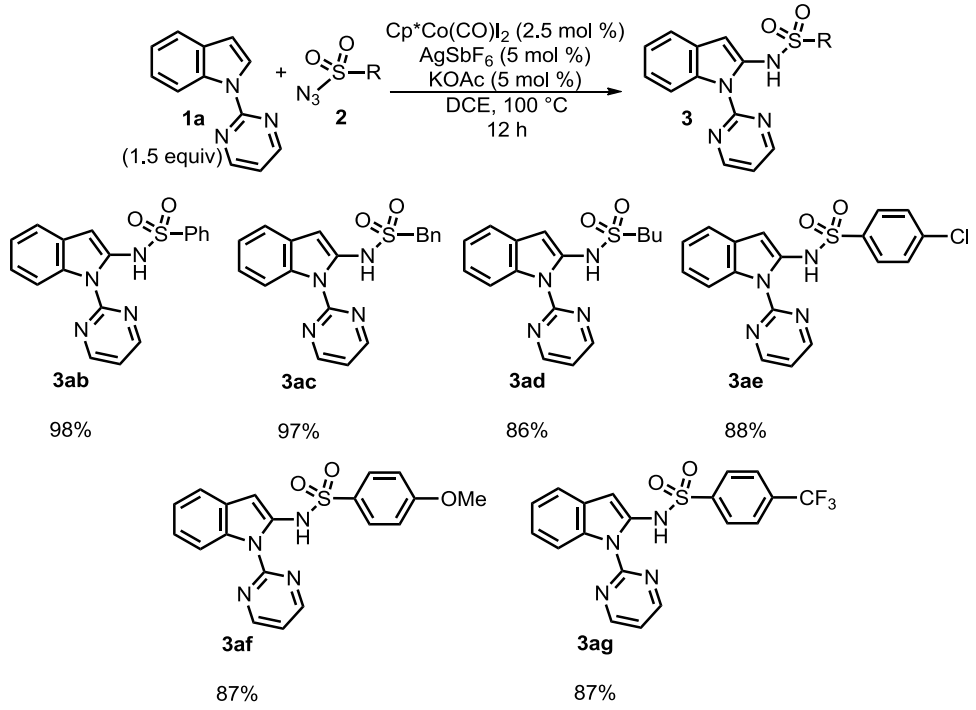


Table 2.5 The scope of indole moiety (**1a)** with azides



2.2.6 Proposed mechanism

A plausible catalytic cycle of the reaction is shown in **Figure 2.1**. As an initiation step, halogen abstraction from Cp*Co(CO)I_2 with $AgSbF_6$, dissociation of CO, and ligand exchange to acetate (or substrate) generates the postulated active species **I**. After coordination of the pyrimidyl group of indole **1** (**II**), regioselective C-H metalation occurs at the C2-position via either S_EAr or a concerted metalation-deprotonation mechanism[20] to afford cobaltacyclic complex **III**. Coordination of azide **2** to cobalt (**IV**) and further migratory insertion generate Co^{III} amido species **V** with the release of N_2. Protonation of **V** with AcOH then gives product **3** and regenerates active species **I**.

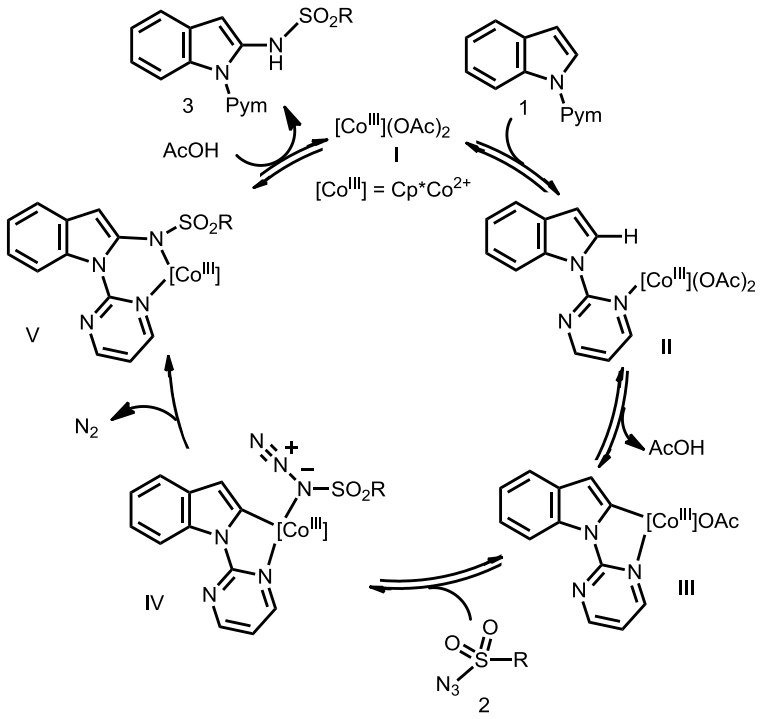
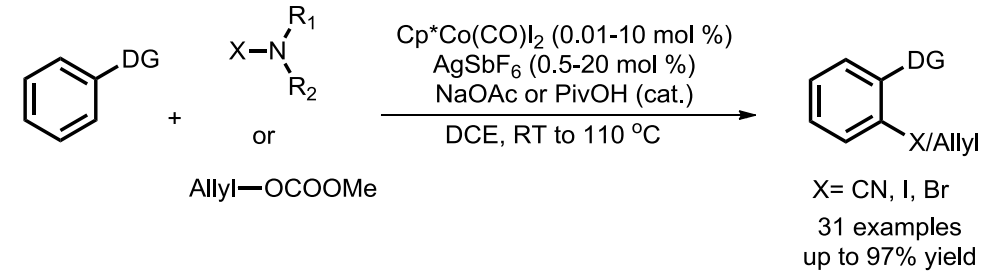


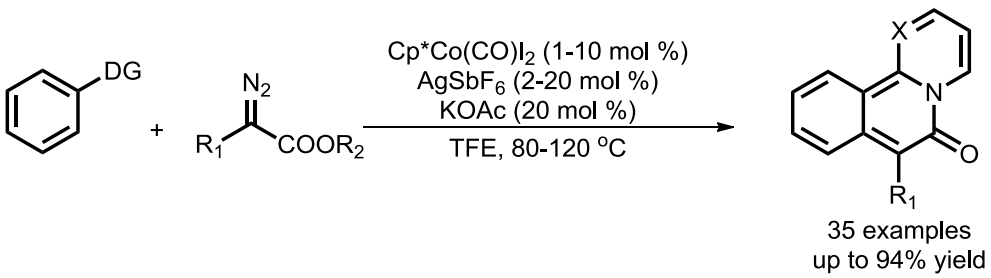
Figure 2.1 Proposed Mechanism

2.3 Applications of Cp*Co(CO)I_2 complex

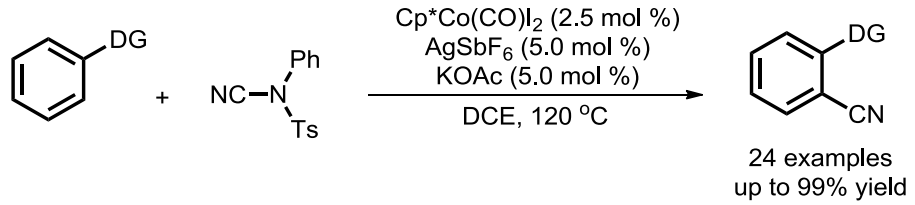
After I reported the utility of the air-stable and readily available Cp*Co(CO)I_2 complex in combination with Ag-salt for directed C-H bond functionalization, many other groups[21-28] started to follow my work to expand the scope of Cp*Co catalysis **(Scheme 2.14)**.

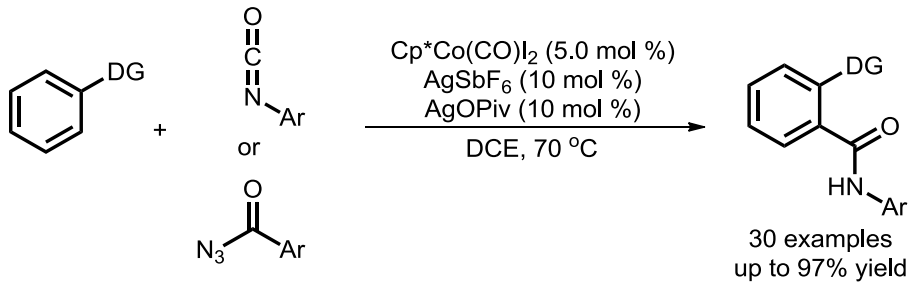
Glorius group's works:



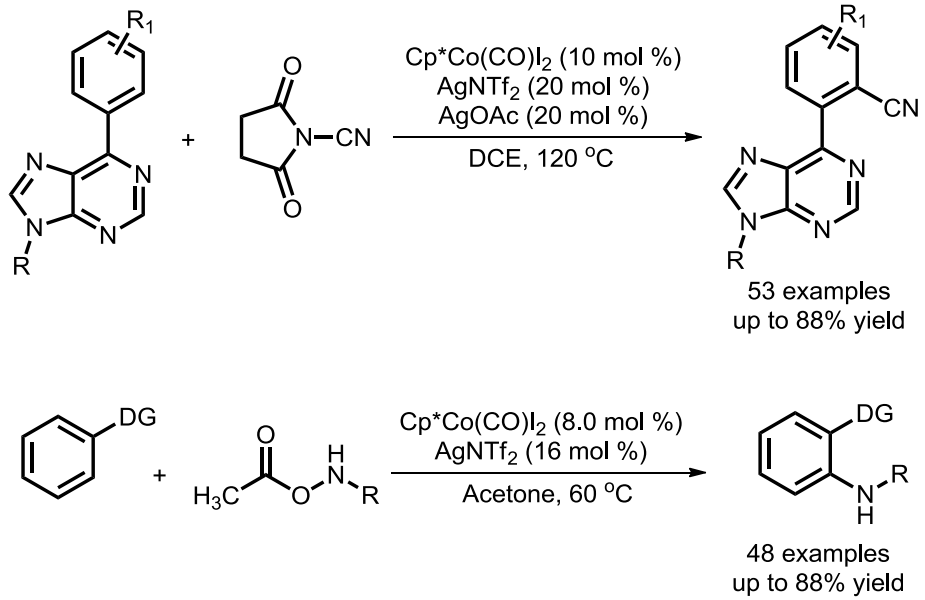


Ackermann group's works:

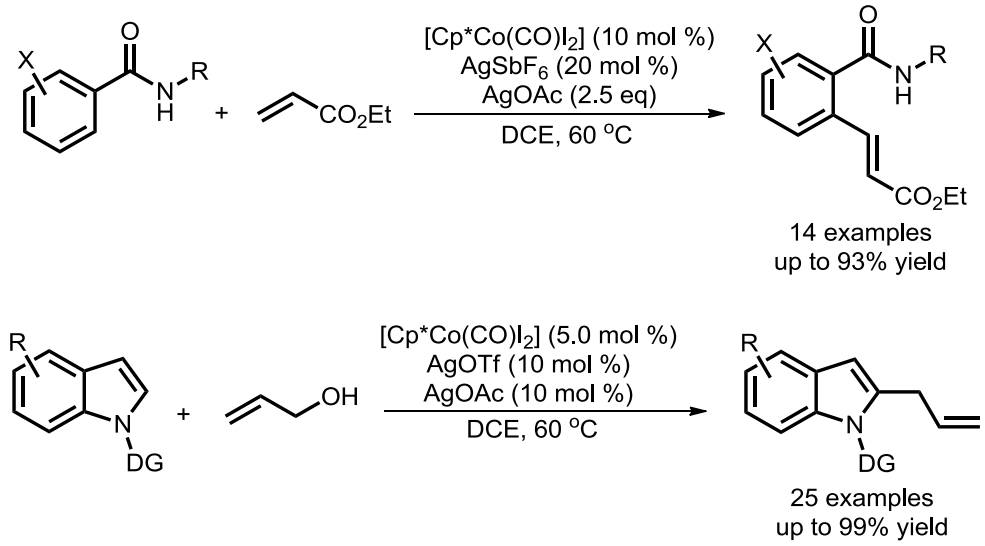




Chang group's works:



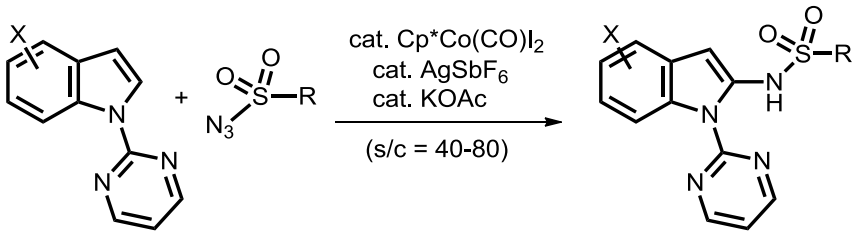
Our group's works (Mr. Suzuki):



Scheme 2.14 Cp*Co^{III}-catalyzed C-H bond functionalization

2.4 Summary

I demonstrated the utility of a readily available Cp*Co(CO)I_2 complex as the precursor for cationic Cp*Co^{III} active species. C2-selective directed C-H amidation of indoles was efficiently promoted by *in situ*-generated Cp*Co^{III} catalysis, while previously developed preformed [Cp*Co^{III}(C_6H_6)](PF_6)$_2$ complex was not effective. A Cp*Co(CO)I_2/$AgSbF_6$/KOAc combined system gave products in 85-98% yield, and catalyst loading was successfully reduced to 1.25 mol % (TON up to 68, based on Co) **(Scheme 2.8)**.[29] Stimulated by my work, further studies to expand the scope of the Cp*Co^{III} catalysis are actively ongoing by many research groups.



B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Adv. Synth. Catal*., **2014**, *356*, 1491.

Scheme 2.8 Summary of C2 selective amidation reaction

2.5 Reference

[1] See: Chapter 1

[2] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207.

[3] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142.

[4] a) U. Kolle, B. Fuss, Chem. Ber.**1984**, *117*, 743; b) U. Kolle, B. Fuss, M. V. Rajasekharan, B. L. Ramakrishna, J. H. Ammeter, M. C. Bohm, *J. Am. Chem. Soc.* **1984**, *106*, 4152.

[5] H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai. *J. Am. Chem. Soc*. **2014**, *136*, 5424.

[6] J. R. Hummel, J. A. Ellman. *Org. Lett.* **2015**, *17*, 2400.

[7] F. Paul, J. Patt, J. F. Hartwig, *J. Am. Chem. Soc.* **1994**, *116*, 5969.

[8] A. S. Guram, S. L. Buchwald, *J. Am. Chem. Soc*. **1994**, *116*, 7901.

[9] X. Chen, X. S. Hao, C. E. Goodhue, J. Q. Yu, *J. Am. Chem. Soc*. **2006**, *128*, 6790.

[10] J. Y. Kim, S. H. Cho, J. Joseph, S. Chang, *Angew. Chem., Int. Ed*. **2010**, *49*, 9899.

[11] Reviews on transition metal-catalyzed N-atom transfer reactions of azides: a) T. Katsuki, *Chem. Lett*. **2005**, *34*, 1304; b) T. G. Driver, *Org. Biomol. Chem*. **2010**, *8*, 3831; c) S. H. Kim, S. H. Park, J. H. Choi, S. Chang, *Chem. Asian J*. **2011**, *6*, 2618.

[12] Reviews on transition metal-catalyzed C-H amination/ amidation based on different strategies: a) J. Du Bois, *Org. Process Res. Dev*. **2011**, *15*, 758; b) A. Armstrong, J. C. Collins, *Angew. Chem. Int. Ed.* **2010**, *49*, 2282; c) F. Collet, R. H. Dodd, P. Dauban, *Chem. Commun*. **2009**, 5061; d) H. M. L. Davies, J. R. Manning, *Nature*. **2008**, *451*, 417; e) A. R. Dick, M. S. Sanford, *Tetrahedron*. **2006**, *62*, 2439; f) H. M. L. Davies, M. S. Long, *Angew. Chem. Int. Ed*. **2005**, *44*, 3518; g) P. Muller, C. Fruit, *Chem. Rev*. **2003**, *103*, 2905.

[13] a) J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc*. **2012**, *134*, 9110; b) J. Ryu, K. Shin, S. H. Park, J. Y. Kim, S. Chang, *Angew. Chem. Int. Ed*. **2012**, *51*, 9904; c) K. Shin, Y. Baek, S. Chang, *Angew. Chem. Int. Ed*. **2013**, *52*, 8031.

[14] Cp*Rh(III)-catalyzed N-atom transfer reactions with azides from other groups, a) J.

Shi, B. Zhou, Y. Yang, Y. Li, *Org. Biomol. Chem*. **2012**, *10*, 8953; b) D. G. Yu, M. Suri, F. Glorius, *J. Am. Chem. Soc*. **2013**, *135*, 8802; c) Y. Lian, J. R. Hummel, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc*. **2013**, *135*, 12548.

[15] For related C-H amination/ amidation reactions with acyl, sulfonyl, and aryl azides under Ir and Ru catalysis, a) J. Ryu, J. Kwak, K. Shin, D. Lee, S. Chang, *J. Am. Chem. Soc*. **2013**, *135*, 12861; b) D. Lee, Y. Kim, S. Chang, *J. Org. Chem*. **2013**, *78*, 11102; c) J. Kim, J. Kim, S. Chang, *Chem. Eur. J*. **2013**, *19*, 7328; d) M. R. Yadav, R. K. Rit, A. K. Sahoo, *Org. Lett*. **2013**, *15*, 1638; e) M. Bhanuchandra, M. R. Yadav, R. K. Rit, M. R. Kuram, A. K. Sahoo, *Chem. Commun*. **2013**, *49*, 5225; f) Q. Z. Zheng, Y. F. Liang, C. Qin, N. Jiao, *Chem. Commun*. **2013**, *49*, 5654.

[16] Other C-H amination/ amidation reactions under Cp*Rh(III) catalysis, see a) K. H. Ng, Z. Zhou, W. Y. Yu, *Org. Lett*. **2012**, *14*, 272; b) C. Grohmann, H. Wang, F. Glorius, *Org. Lett*. **2012**, 14, 656; c) R. J. Tang, C. P. Luo, L. Yang, C. J. Li, *Adv. Synth. Catal*. **2013**, *355*, 869; d) C. Grohmann, H. Wang, F. Glorius, *Org. Lett*. **2013**, *15*, 3014; e) H. Zhao, Y. Shang, W. Su, *Org. Lett*. **2013**, *15*, 5106.

[17] The stablity of PF_6^- ion in $Cp^*Co^{III}(ligand)_n$ complexes depended on ligands. For example, rapid solvolysis of PF_6^- ion in a $[Cp^*Co^{III}(acetone)_3](PF_6)_2$ complex was reported, see: G. Fairhurst, C. White, *J. C. S. Dalton*. **1979**, 1524.

[18] G. Fairhurst, C. White, *J. Chem. Soc. Dalton. Trans*. **1979**, 1524.

[19] a) S.A. Frith, J. L. Spencer, *Inorganic Syntheses.* **1990**, *28*, 273; b) W. Li, L. H. Weng, G. X. Jin. *Inorg. Chem. Commun*. **2004**, *7*, 1174.

[20] Review on concerted metalation-deprotonation mechanism: D. Lapointe, K. Fagnou, *Chem. Lett*. **2010**, *39*, 1118.

[21] D. G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc*. **2014**, *136*, 17722.

[22] D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed*. **2015**, *54*, 4508.

[23] J. Li, L. Ackermann, *Angew. Chem. Int. Ed*. **2015**, *54*, 3635.

[24] J. Li, L. Ackermann, *Angew. Chem. Int. Ed*. **2015**, *54*, in press.

[25] A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660.

[26] P. Patel, S. Chang, *ACS Catal.* **2015**, *5*, 853.

[27] Y. Suzuki, B. Sun, T. Yoshino, M. Kanai, S. Matsunaga, *Tetrahedron*. **2015**, *71*,

4552.

[28] Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed*. **2015**, *54*, in press.

[29] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.*, **2014**, *356*, 1491.

Chapter 3

A Cp^*CoI_2-dimer as a Precursor for Cationic Co(III)-catalysis: Application to C-H Phosphoramidation of Indoles

3.1 Introduction

Since Dr. Yoshino's first report on the utility of a cationic $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex in 2013 **(Figure 3.1)**, many other groups have expended tremendous effort to broaden the scope of Co(III)-catalysis. The development of a readily available, stable, and easy-to-handle catalyst is in high demand to further enhance the application of cationic Cp*Co(III) catalysis. Toward this aim, I previously discussed the synthesis and utility of a $Cp^*Co(CO)I_2$ complex in Chapter 2. The $Cp^*Co(CO)I_2$ complex was useful for generating an active cationic Co(III) species *in situ*. Herein, I described my own efforts to expand the scope of Cp^*Co^{III} catalysis. A readily available $[Cp^*CoI_2]_2$ complex was successfully utilized as the precursor of a cationic Co^{III} active catalyst in a directed C2-selective amidation of indoles.

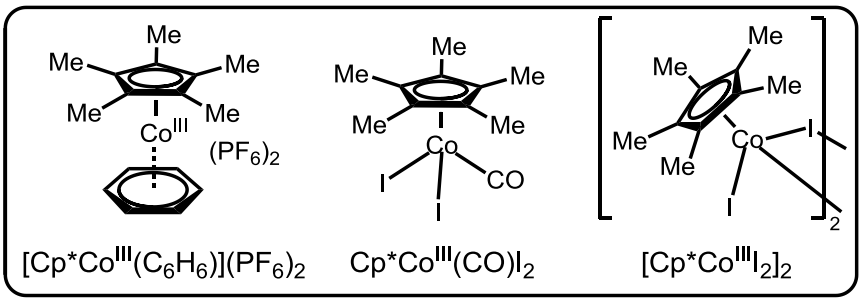


Figure 3.1 Cp*Co(III) catalysts

3.1.1 Phosphoramidates

Phosphoramidates are important structural units in natural products, amino acid analogues, pharmacological agents, and synthetic precursors,[1] such as agrocin 84,[2a] microcin C7,[2b] and phosmidosine antibiotics,[2c] and pro-nucleotides as prodrugs of antiviral and antitumor agents **(Figure 3.2)**.[2d] In addition, phosphoramidates are useful synthetic intermediates for synthesizing various nitrogen-containing heterocycles.[3]

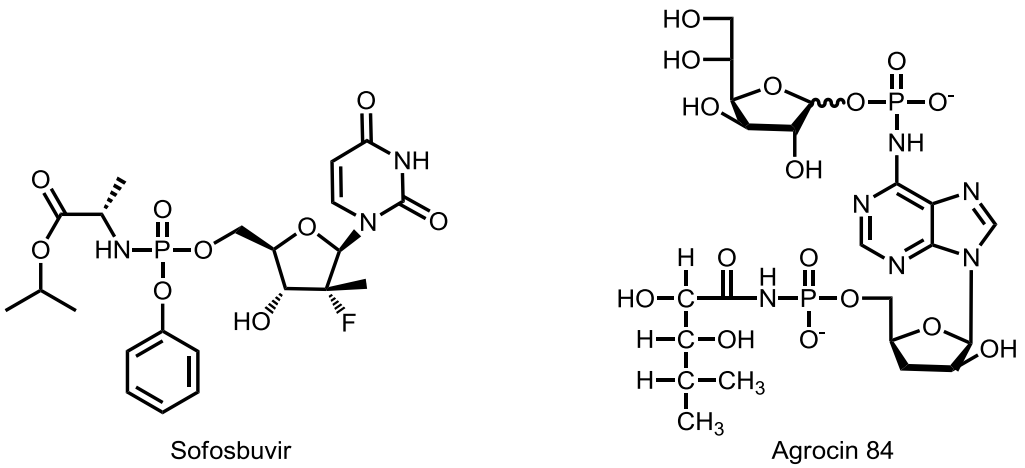
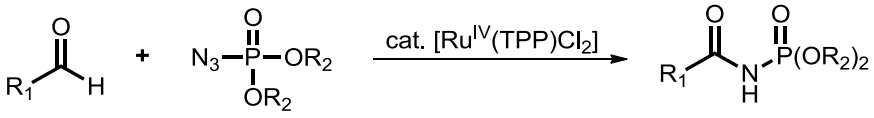


Figure 3.2 Structure of Sofosbuvir and Agrocin 84

3.1.2 Precedents of phosphoramidation reactions

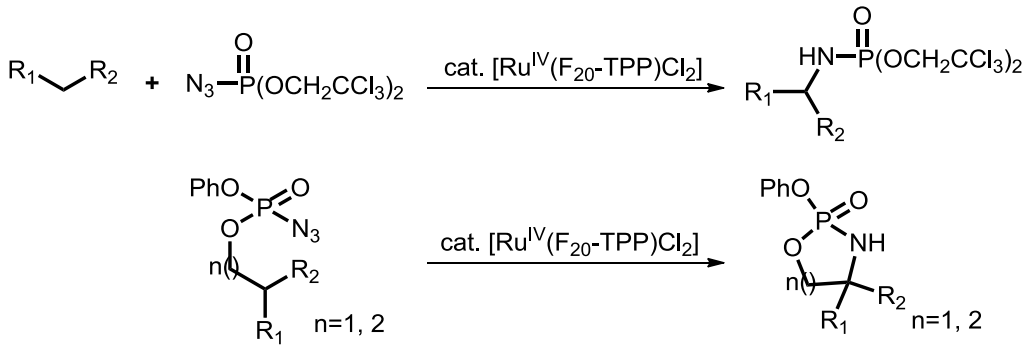
Conventional methods for phosphoramidates rely on P-N bond formation, while the C-H bond phosphoramidation strategy is less studied. Recently, a couple of C-H phosphoramidation reactions with phosphoryl azides were disclosed under transition metal catalysis.

In 2012, Che[4] group reported ruthenium(IV) prophyrin-catalyzed phosphoramidation of aldehydes with phosphoryl azides as a nitrene source, gave N-acylphosphoramidates in good to high yields **(Scheme 3.1)**.



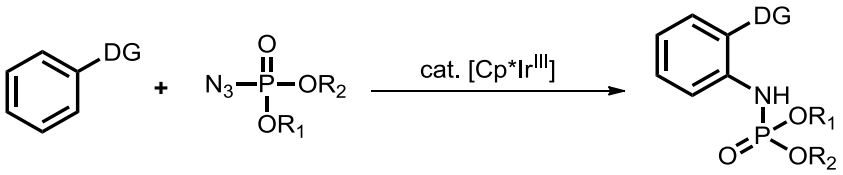
Scheme 3.1 $[Ru^{IV}(TPP)Cl_2]$-catalyzed phosphoramidation reactions

In 2013, Che[5] group reported $[Ru^{IV}(F_{20}\text{-TPP})Cl_2]$ efficiently catalysed inter- and intra-molecular nitrene insertion into sp^3 C–H bonds of hydrocarbons using phosphoryl azides as nitrene sources **(Scheme 3.2)**.



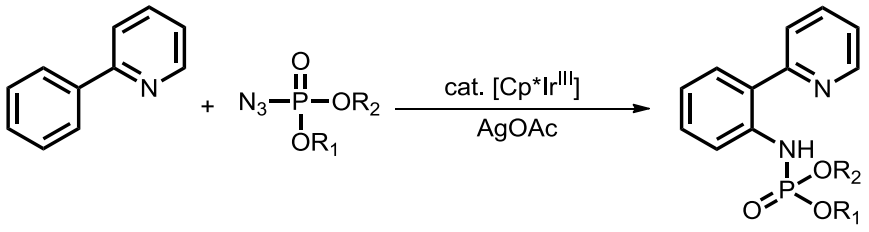
Scheme 3.2 $[Ru^{IV}(F_{20}\text{-TPP})Cl_2]$-catalyzed phosphoramidation reactions

In 2014, Chang[6] group reported Cp*Ir^{III}-catalyzed synthesis of phosphoramidates through directed C-H bond functionalization from several different substrates and phosphoryl azides as nitrene sources **(Scheme 3.3)**. Before this work, they reported Cp*Rh^{III}-catalyzed the direct amination/ amidation reactions using sulfonyl, aryl, and alkyl azides as amino sources.[7]



Scheme 3.3 Cp*Ir^{III}-catalyzed phosphoramidation reactions

In the same year, a similar work was reported by Zhu group,[8] using 2-phenylpyridine as substrate. This work's catalytic system required AgOAc to promote the reaction **(Scheme 3.4)**.

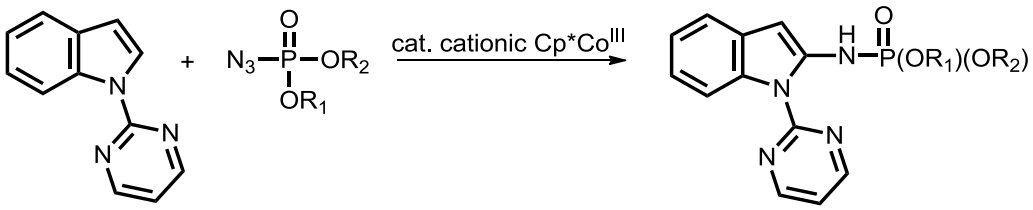


Scheme 3.4 Cp*Ir^{III}-catalyzed phosphoramidation reactions

3.1.3 My target substrate for C-H phosphoramidation

Chang and Zhu's groups reported phosphoramidation reactions with phosphoryl azides catalyzed by noble metal $[Cp^*IrCl_2]_2$ complex combination with Ag salt. In Chapter 2, I talked about $Cp^*Co(CO)I_2$ complex combination with Ag salt to generate active Cp^*Co^{III} species. Cobalt is the same group with iridium, So, air-stable and commercially available Cp^*Co^{III} catalyst could be useful as an alternative to cationic Cp*Ir catalyst for directed C-H bond functionalization.

Herein, I will describe the utility of an air-stable dimeric $[Cp^*CoI_2]_2$ complex, which is readily available in multi-gram quantity. It can promote Cp^*Co^{III}-catalyzed synthesis of phosphoramidates through directed C-H bond functionalization from indoles moiety and phosphoryl azides as nitrene sources **(Scheme 3.5)**.

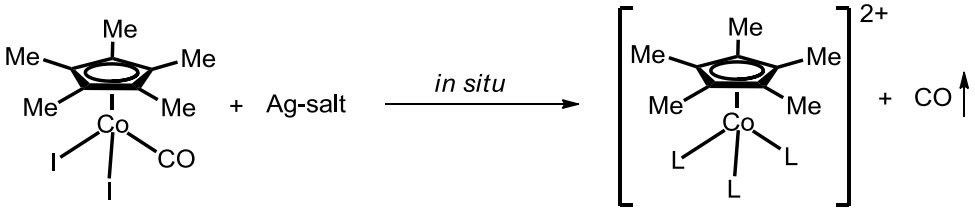


Scheme 3.5 Cationic Cp^*Co^{III}-catalyzed amidation reactions of indole

3.2 A Cp^*CoI_2-dimer as a precursor for cationic Co(III)-catalysis: application to C-H phosphoramidation of indoles

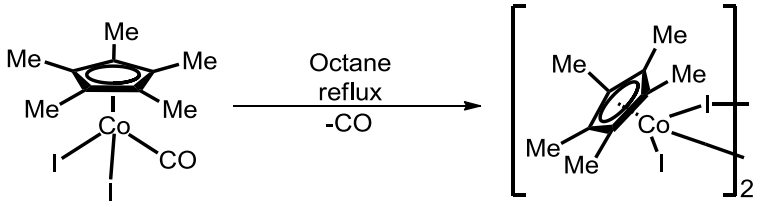
3.2.1 Preparation of $[Cp^*CoI_2]_2$ complex

In Chapter 2, $Cp^*Co(CO)I_2$ complex combined with Ag salt to generate active Cp*Co species *in situ*. $Cp^*Co(CO)I_2$ complex nicely expanded the scope of Co(III)-catalysis. However, there still remained a problem from practical point of view, that is, toxic carbon monoxide was inevitably released during the reaction process, and all reaction vessels had to be handled carefully, especially when conducting the reaction in large scale **(Scheme 3.6)**.



Scheme 3.6 *In situ*-generation of active Cp*Co species with release of CO

Thus, further studies are needed to avoid the safety issues in future industrial applications of the cobalt(III) catalyst. So, I synthesized an air-stable $[Cp^*CoI_2]_2$ dimer complex[9] with release of CO **(Scheme 3.7)**. Because dimeric $[Cp^*CoI_2]_2$ was synthesized by thermal decarbonylation of $Cp^*Co(CO)I_2$ in a gram scale, it was necessary to carefully perform the decarbonylation process. Once dimeric $[Cp^*CoI_2]_2$ was obtained, however, $[Cp^*CoI_2]_2$ itself was air-stable and easy-to-handle. So, I decided to evaluated its utility.

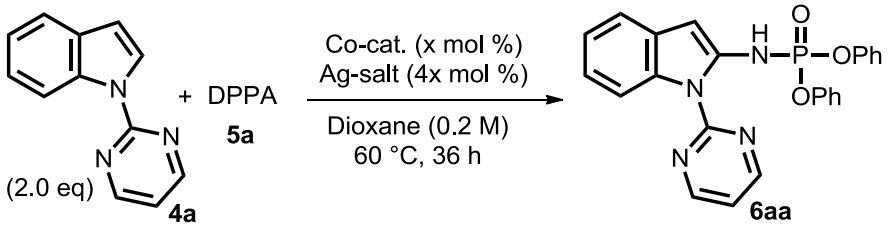


Scheme 3.7 Preparation of $[Cp^*CoI_2]_2$ complex

3.2.2 Cobalt catalyst effects

Initial optimization studies on cobalt complex effects using indole **4a** and azide **5a** are summarized in **Table 3.1**. The original cationic Cp*Co-arene complex, developed by Dr. Yoshino, did not afford any product **(entry 1)**. *In situ* generation of an active cationic Cp*Co(III) species was effective, and the combination of Cp*Co(CO)I_2 and $AgSbF_6$ gave the desired product **6aa**, albeit in moderate yield **(entry 2**, 34%**)**. The yield was improved by changing the catalyst precursor to a dimeric iodide complex $[Cp^*CoI_2]_2$ **(**50%, **entry 3)**. Neither other Co(III)-salts nor *in situ*-generated cationic Co(II)-species promoted the reaction **(entries 4-6)**, suggesting that the use of cationic Co(III) species was essential to promote the reaction.

Table 3.1 Cobalt catalyst effects



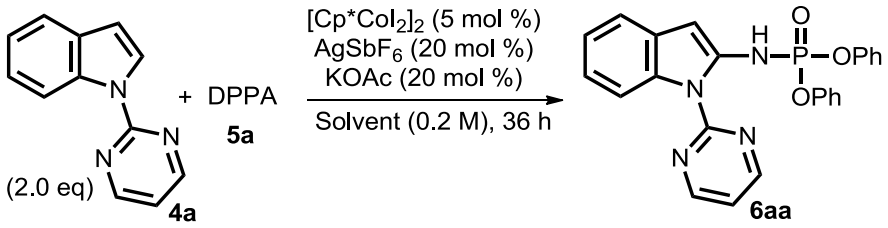
Entry	Co cat (mol%)	Ag salt (mol%)	Yield (%)[a]
1	$[Cp^*Co(C_6H_6)](PF_6)_2$ (5)	none	0
2	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	34
3	$[Cp^*CoI_2]_2$ (5)	$AgSbF_6$ (20)	50
4	$Co(NH_3)_6Cl_3$ (10)	none	0
5	$Co(acac)_3$ (10)	none	0
6	CoI_2 (10)	$AgSbF_6$ (20)	0

[a] NMR yield.

3.2.3 Solvent and temperature effects

I checked different solvents under 60 ^oC and 80 ^oC **(Table 3.2)**, using the $[Cp^*CoI_2]_2$ and $AgSbF_6$. [Note: In this screening, I added KOAc as a base, because KOAc sometimes improved the reaction**]**. As indicated by the results in **entry 1** vs **entry 2**, higher temperature resulted in lower yield, possibly because instability of DPPA at 80 ^oC. Other solvents screened also had no positive effects.

Table 3.2 Solvent and temperature effects



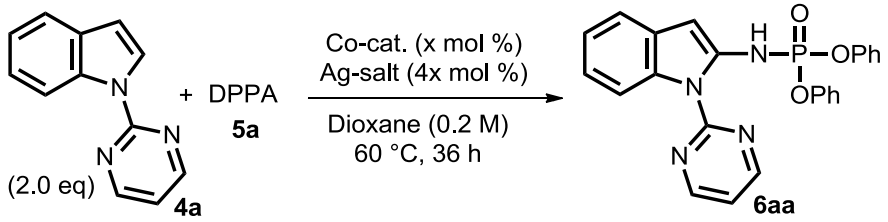
Entry	Solvent	Temp. (°C)	Yield (%)[a]
1	1,4-dioxane	60	45
2	1,4-dioxane	80	35
3	DCM	60	40
4	Toluene	80	27
5	THF	60	14

[a] NMR yield.

3.2.4 Control experiments

Other silver salts **(Table 3.3, entries 1-2)** did not improve the yield. While high temperature decreased the yield, probably due to the thermal instability of **5a (entries 3-4)**. The reaction was completely C2-selective, and no regioisomeric product was detected under the optimized reaction conditions. Negative control experiments in **entries 5-6** indicated that both $[Cp^*CoI_2]_2$ complex and $AgSbF_6$ are essential to promote the reaction.

Table 3.3 Control experiments



Entry	Co cat (mol%)	Ag salt (mol%)	Yield (%)[a]
1	$[Cp^*CoI_2]_2$ (5)	$AgPF_6$ (20)	trace
2	$[Cp^*CoI_2]_2$ (5)	$AgBF_4$ (20)	5
3[b]	$[Cp^*CoI_2]_2$ (5)	$AgSbF_6$ (20)	17
4[c]	$[Cp^*CoI_2]_2$ (5)	$AgSbF_6$ (20)	0
5[d]	none	$AgSbF_6$ (20)	0
6[d]	$[Cp^*CoI_2]_2$ (5)	none	trace

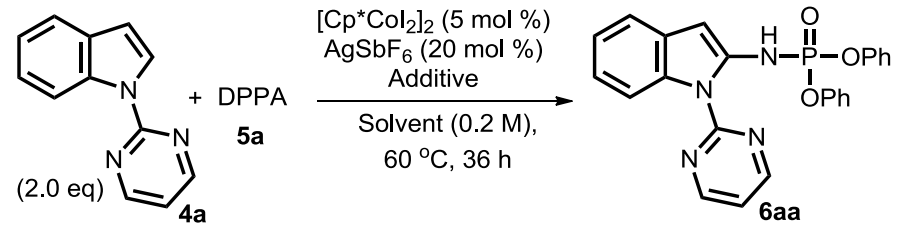
[a] NMR yield. [b] The reaction was run at 80 °C. [c] The reaction was run at 100 °C.

[d] Concentration is 2.0 M

3.2.5 Base and concentration effects

Base and concentration effects are summaried in **Table 3.4**. High concentration led to good yield **(entry 17)**. In contrast to Dr. Yoshino and Mr. Ikemoto's previous studies on indole C-H functionalization, the addition of KOAc was not effective **(entries 1-10)**.

Table 3.4 Base and concentration effects



Entry	Additive (%)	Concentration (M)	Yield (%)[a]
1	KOAc (20)	0.1	24
2	KOAc (30)	0.1	27
3	KOAc (40)	0.1	16
4	KOAc (30)	0.2	45
5	KOAc (40)	0.2	<10
6	KOAc (10)	0.3	54
7	KOAc (20)	0.3	52
8	none	0.3	57
9	KOAc (10)	0.4	53
10	KOAc (20)	0.4	55
11	none	0.4	64
12	none	0.5	56
13	none	0.6	58
14	none	0.8	72
15	none	1.0	79
16	none	1.5	79
17	none	2.0	80[b]

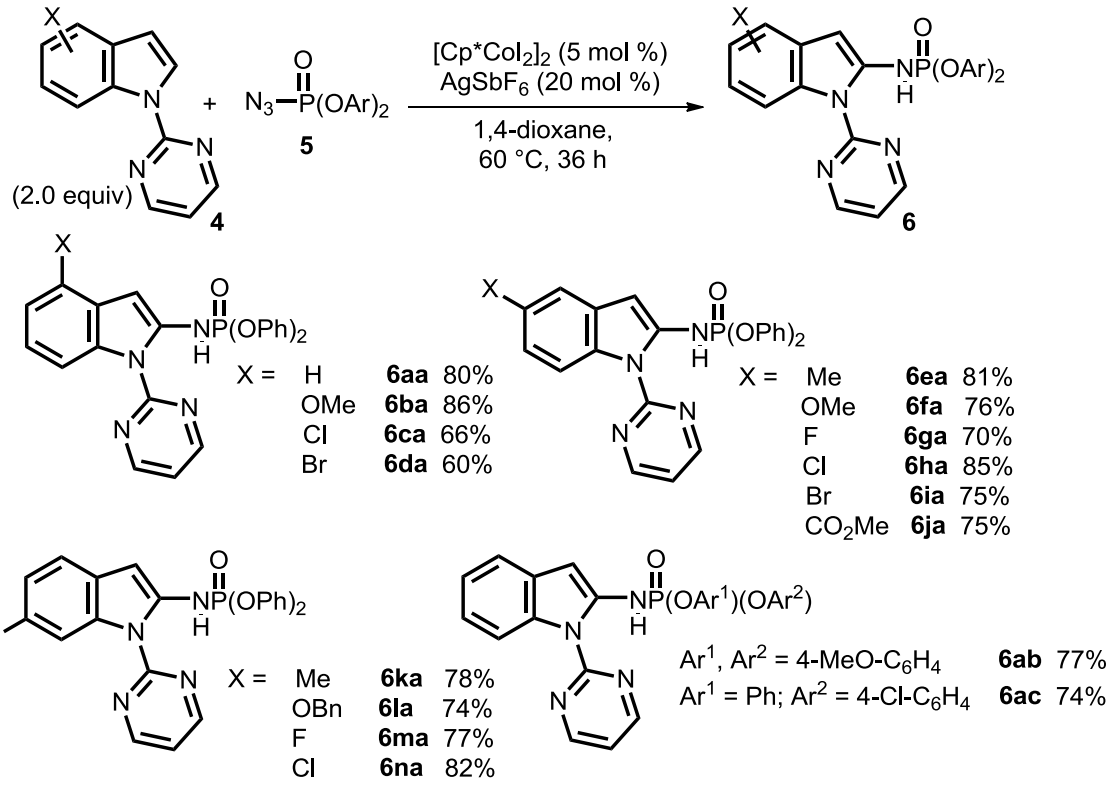
[a] NMR yield. [b] Isolated yield.

3.2.6 Substrate scope

The substrate scope of the phosphoramidation of indoles under the optimized conditions is summarized in **Table 3.5**.[10] Various indoles bearing electron-donating (Me, MeO, and BnO) and electron-withdrawing groups (halogen and CO_2Me) at either the C4-, C5-, or C6-position afforded products **6aa**–**6na** in 60–86% yield. These results clearly indicated good chemoselectivity of the present Cp*Co(III) catalysis. The C2-selectivity should arise from the inner sphere mechanism involving directing

group-assisted C-H bond metalation. Thus, my reaction conditions are complementary to the intra- and intermolecular alkane amidation reaction via an outersphere mechanism under Co- and Ru-porphyrin catalysis.[5] With regard to the scope of the phosphoryl azide, an electron-donating MeO-substituent and an electron-withdrawing Cl-substituent were compatible (**6ab**, 77%; **6ac**, 74%). On the other hand, diethyl phosphoryl azide did not afford desired phosphoramidation product.

Table 3.5 The scope of indoles moiety and phosphoryl azides



3.2.7 Proposed mechanism

A plausible reaction mechanism is depicted in **Figure 3.3**, based on the previously reported Cp*Co(III)-catalyzed C-H bond functionalization reaction of indoles and the mechanistic studies by Chang and coworkers on the Cp*Rh(III)-catalyzed[11] C-H bond amidation reactions. Initial halide abstraction from $[Cp^*CoI_2]_2$ by $AgSbF_6$ in the presence of the pyrimidyl-protected indole **4** would form cationic complex **I**. A C-H bond activation step to afford metalacycle **II** would proceed via either electrophilic aromatic substitution mechanism or concerted metalation-deprotonation (CMD) assisted

by some basic functional groups. Coordination of phosphoryl azide **5** (**III**) followed by C-N bond formation with release of N_2 gave **IV**. Although stepwise C-N bond formation through a Rh(V)-nitrenoid species rather than concerted C-N bond formation was supported in the Cp*Rh^{III}-catalyzed amidation reaction,[10] we cannot yet conclude which mechanism is plausible, either nitrenoid formation or concerted substitution, for the Cp*Co(III) catalysis. Because there is no evidence for the formation of a high valent, possibly unstable, Co(V) intermediate under the present reaction conditions, further studies are required to clarify the reaction pathway. Protonation by the acidic proton released in the C-H bond metalation step **(path A)** or direct deprotonation from a C-H bond of another substrate **4 (path B)** would dissociate the product **6**.

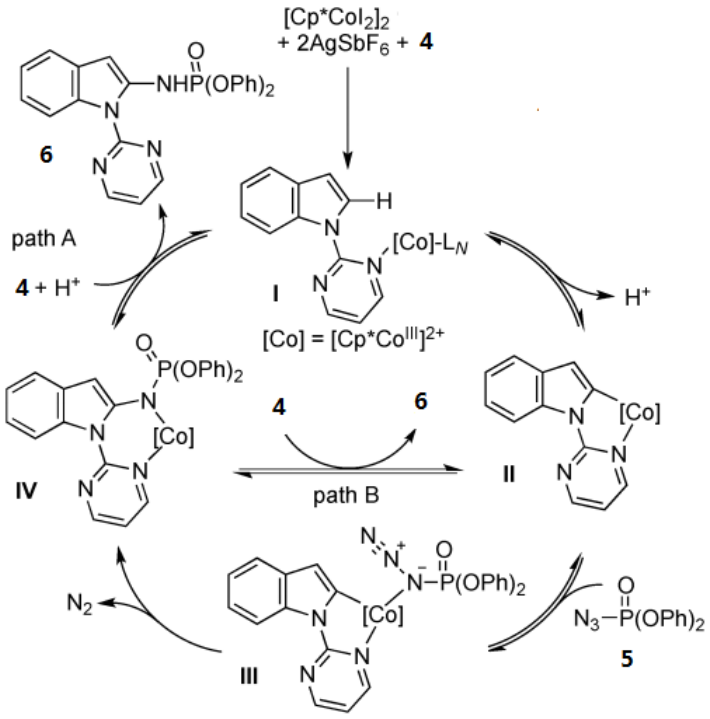
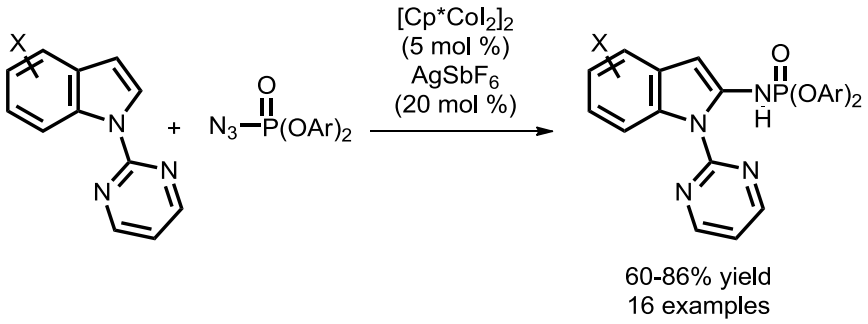


Figure 3.3 Proposed mechanism

3.3 Summary

In conclusion, an improved cationic Cp*Co(III) catalyst generated from $[Cp^*CoI_2]_2$ complex and $AgSbF_6$ exhibited higher catalytic activity than those from other Cp*Co(III)-complexes. Directing group-assisted C-H bond metalation realized high regio- and chemoselectivity under mild conditions, and the C2-selective C-H bond phosphoramidation reaction of 2-pyrimidyl-protected indoles proceeded in 60–86% yield **(Scheme 3.8)**.[12] Studies of the reaction mechanism as well as further applications of Cp*Co(III)-catalysis are actively ongoing.



B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Chem. Commun*., **2015**, *51*, 4659.

Scheme 3.8 Summary of C2 selective amidation reaction

3.4 Reference

[1] W. W. Metcalf, W. A. van der Donk, *Annu. Rev. Biochem.,* **2009**, *78*, 65.

[2] a) A. Kerr, *Plant Disease,* **1980**, *64*, 24; b) S. Duquesne, D. Destoumieux-Garzón, J. Peduzzi, S. Rebuffat, *Nat. Prod. Rep.,* **2007**, *24*, 708; c) D. R. Phillips, M. Uramoto, K. Isono, J. A. McCloskey, *J. Org. Chem.,* **1993**, *58*, 854; d) S. R. Wagner, V. V. Iyer, E. J. McIntee, *Med. Res. Rev.* **2000**, *20*, 417.

[3] For selected examples, see a) T. Minami, M. Ogata, I. Hirao, *Synthesis,* **1982**, 231; b) M. A. Ciufolini, G. O. Spencer, *J. Org. Chem.,* **1989**, *54*, 4739; c) L. D. S. Yadav, C. Awasthi, V. K. Rai, A. Rai, *Tetrahedron Lett.,* **2007**, *48*, 8037; d) L. D. S. Yadav, A. Rai, V. K. Rai, C. Awasthi, *Tetrahedron Lett.,* **2008**, *49*, 687; e) L. D. S. Yadav, V. P. Srivastava, R. Patel, *Tetrahedron Lett.,* **2008**, *49*, 5652.

[4] W. Xiao, C. Y. Zhou, C. M. Che, *Chem. Commun.,* **2012**, *48*, 5871.

[5] W. Xiao, J. Wei, C. Y. Zhou, C. M. Che, *Chem. Commun.,* **2013**, *49*, 4619.

[6] H. Kim, J. Park, J. G. Kim, S. Chang, *Org. Lett.,* **2014**, *16*, 5466.

[7] See: Chapter 2

[8] C. Pan, N. Jin, H. Zhang, J. Han, C. Zhu, *J. Org. Chem.,* **2014**, *79*, 9427.

[9] S.A. Frith, J. L. Spencer, *Inorganic Syntheses*. **1990**, *28*, 273.

[10] Results of unsuccessful substrates: 3-Me-*N*-(pyrimidin-2-yl) indole **4o** gave product **6oa** in only 7% yield. Indole bearing a dimethyl carbamoyl group afforded trace, if any, product. 2-Phenylpyridine and *N*-Me-benzamide, which are suitable substrates under Cp*Ir-catalysis, did not afford products under Cp*Co-catalysis.

[11] S. H. Park, J. Kwak, K. Shin, J. Ryu, Y. Park, S. Chang, *J. Am. Chem. Soc.,* **2014**, *136*, 2492.

[12] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Chem. Commun*., **2015**, *51*, 4659.

Chapter 4

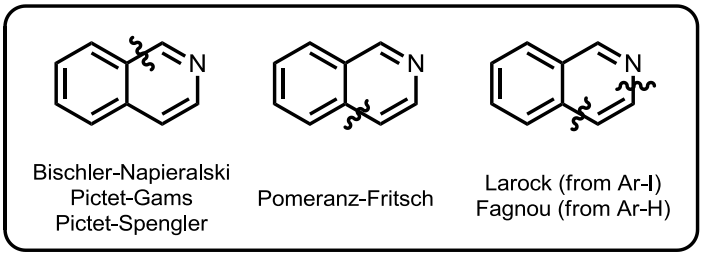
Regioselectivity in Cp*Co^{III} vs Cp*Rh^{III} Catalyzed C-H Activation: Isoquinoline Synthesis from *O*-Acyloximes and Terminal Alkynes

4.1 Introduction

In previous chapters, I described the utility of the air-stable and readily available Cp*Co(CO)I_2 and [Cp*CoI_2]$_2$ complexes[1] in combination with Ag-salt for directed C-H bond functionalization. Glorius, Ackermann, Chang, and coworkers of mine in our group[2] started to follow my work to expand the scope of Cp*Co catalysis. Cyanation, halogenation, allylation and many different types of reactions were reported under the catalysis of Cp*Co^{III} active species, exhibiting higher catalytic activities or unique reactivities. Recently, Mr. Suzuki in Kanai/Matsunaga group reported Cp*Co(III)-catalyzed oxidative C-H alkenylation of benzamides with ethyl acrylate. This catalytic system required addition of an external oxidant. Herein, I described my own efforts to expand the scope of Cp*Co^{III} catalysis. Cp*Co^{III} was successfully utilized in oxidative regioselective formation of isoquinolines with internal oxidant strategy.

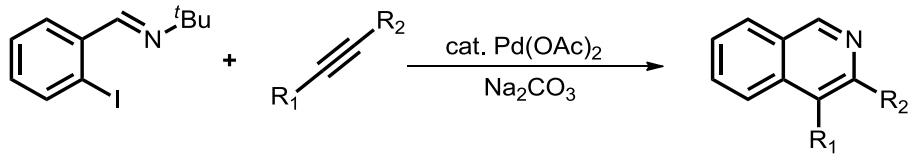
4.1.1 Precedents of isoquinoline formation reactions

Isoquinoline is an important and common structure seen in a series of biologically active alkaloids. There are many approaches reported for the synthesis of isoquinolines **(Scheme 4.1)**.[3]



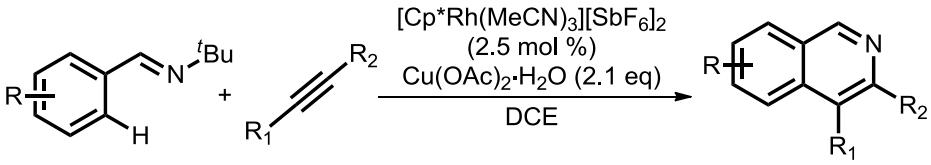
Scheme 4.1 Synthetic strategies for synthesis of isoquinoline

In the last 10 years, metal-catalyzed approaches have begun to attract some interests. Larock group[4] reported synthesis of isoquinoline using couples *o*-iodoaldimines and alkynes in the presence of a palladium catalyst **(Scheme 4.2)**.



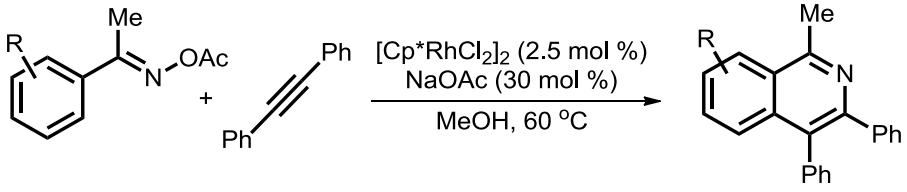
Scheme 4.2 Pd-catalyzed synthesis of isoquinoline

In 2009, Fagnou group[5] reported Cp*Rh^{III}-catalyzed synthesis of isoquinoline via oxidative cross-coupling/cyclization of aryl aldimines and alkynes **(Scheme 4.3)**. This catalytic system required an additional external oxidant, stoichiometric amount of Cu(II)-salt.



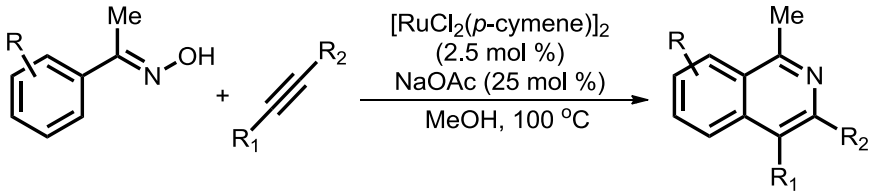
Scheme 4.3 Cp*Rh^{III}-catalyzed synthesis of isoquinoline

In 2010, Chiba group[6] reported a Cp*Rh^{III}-catalyzed annulation reaction of *O*-acyloximes with internal alkynes via internal oxidant strategy **(Scheme 4.4)**. Around the same time, Zhao, Jia, Li, and cowokers[7] reported the reaction with unactivated oximes under the similar conditions**.**



Scheme 4.4 Cp*Rh^{III}-catalyzed synthesis of isoquinoline

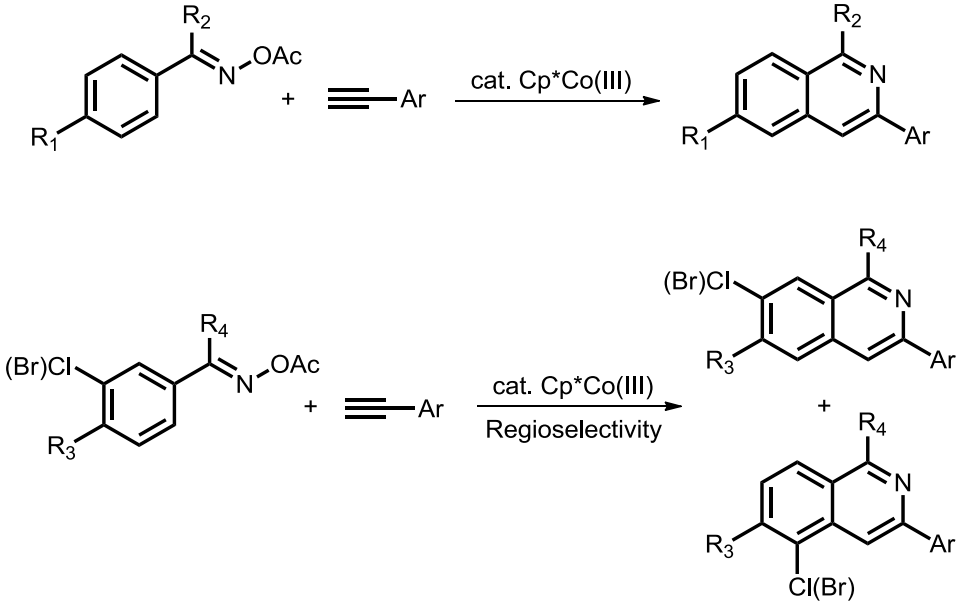
In 2012, Jeganmohan group[8] reported Ru(II)-catalyzed formation of isoquinoline with unactivated oximes **(Scheme 4.5)**.



Scheme 4.5 Ru(II)-catalyzed formation of isoquinoline

4.1.2 My research purposes

In Chiba group's work[6], when using *meta*-bromo substitued substrate, two isomers were obtained, and the ratio was poor, around 2.7:1. Only very limited substrates bearing methyl or alkoxy groups showed sufficient selectivity so far, reacted at less hindered position. Regioselectivity of the C-H activation step to form a metallacycle is also a difficult issue when *meta*-substituted oxime derivatives are used as a substrate. From *meta*-halogen substituted substrates, highly regioselective formation of isoquinolins has not been reported so far. Herein, I will describe Cp*Co^{III}-catalyzed regioselective cyclization reaction of *O*-acyloximes and terminal alkynes **(Scheme 4.6)**. Furthermore, this is the first report on cobalt-catalyzed C-H bond functionalization reactions utilizing the internal oxidizing directing groups.



Scheme 4.6 Cp*Co(III)-catalyzed formation and regioselective formation of isoquinolines

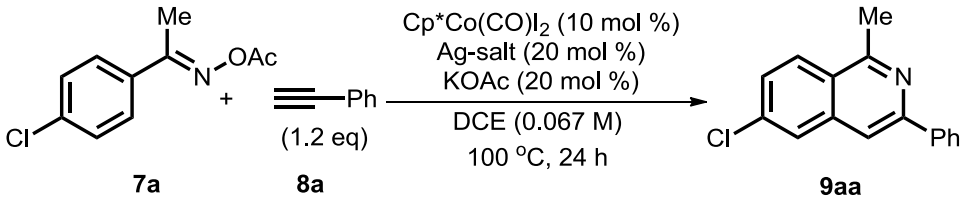
4.2 Regioselectivity in Cp^*Co^{III} vs Cp^*Rh^{III} catalyzed C-H activation: isoquinoline synthesis from *O*-acyloximes and terminal alkynes

4.2.1 *Para*-substitutent *O*-acyloxime for the formation of isoquinolines

4.2.1.1 Ag-salt effects

I initially utilized the $Cp^*Co(CO)I_2$ complex for my first model reaction, the reaction of *para*-Cl substituted *O*-acyloxime **7a** with phenylacetylene **8a**. Among the Ag-salts screened **(Table 4.1, entries 1-5)**, $AgSbF_6$ was the best, and 10 mol % of $Cp^*Co(CO)I_2$ with 20 mol % of $AgSbF_6$ gave **9aa** in 81% yield **(entry 1)**. This reaction was run at 100 ^oC, under low concentration of DCE. Other Ag-salts resulted in no improvement **(Table 4.1)**.

Table 4.1 Ag-salt effects



7a **8a** **9aa**

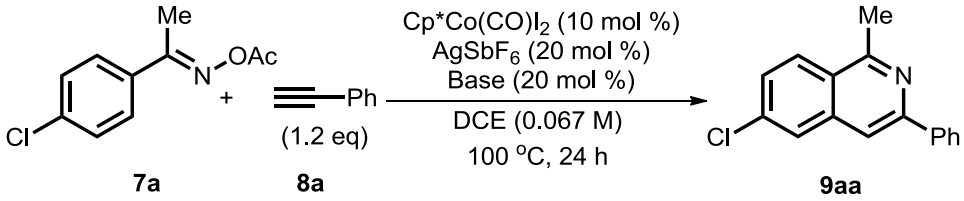
Entry	Ag-salt (mol%)	Yield (%)[a]
1	$AgSbF_6$ (20)	81
2	$AgPF_6$ (20)	57
3	$AgBF_4$ (20)	58
4	AgOTf (20)	34
5	$AgNTf_2$ (20)	62

[a] NMR yield.

4.2.1.2 Base effects

Trial to generate an efficient catalyst with $AgSbF_6$ in the absence of KOAc resulted in 73% yield **(Table 4.2, entry 1)**. **Entry 2** using NaOAc gave similar result compared with that using KOAc **(Table 4.2, entry 2 vs Table 4.1 entry 1).** CsOPiv as a base only afforded 50% yield **(entry 3).** In **entry 4** and **5,** CsOAc and K_2CO_3 afforded 72% and 75% yield, respectively, but the yield was not improved.

Table 4.2 Base effects



7a **8a** **9aa**

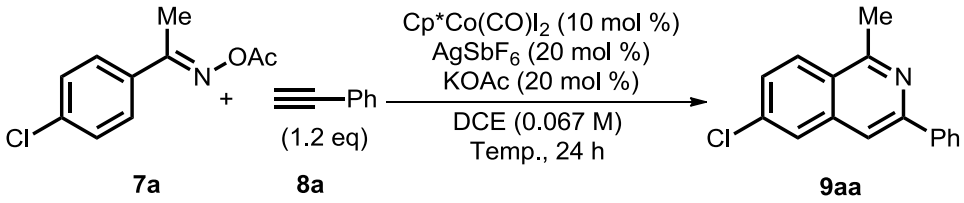
Entry	Base (mol%)	Yield (%)[a]
1	none	73
2	NaOAc (20)	80
3	CsOPiv (20)	50
4	CsOAc (20)	72
5	K_2CO_3 (20)	75

[a] NMR yield.

4.2.1.3 Temperature effects

When the reaction was run at 80 °C, product was obtained in only 54% yield **(Table 4.3, entry 1)**. When increasing the temperature to 120 °C, product was afforded in 92 % NMR yield, and 86% isolated yield after purification by column chromatography **(entry 2).**

Table 4.3 Temperature effects



7a **8a** **9aa**

Entry	Temp. (°C)	Yield (%)[a]
1	80	54
2	120	92(86)[b]

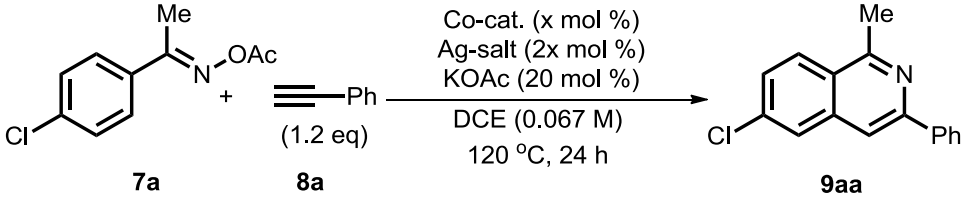
[a] NMR yield. [b] Isolated yield.

4.2.1.4 Cobalt catalyst effects: negative control experiments

I checked the catalytic activity of other cobalt-salts. When the $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex was utilized for the reaction, the $[Cp^*Co^{III}(C_6H_6)](PF_6)_2$ complex gave product **9aa** in only 64% yield under otherwise identical reaction conditions **(Table 4.4, entry**

1). I also investigated the reaction in more detail to confirm that the use of *in situ* generated cationic Cp*Co(III) was the best. Commercially available Co^{III} salts such as $Co(acac)_3$ and $Co(NH_3)_6Cl_3$ did not promote the reaction **(entries 2-3)**. No reaction occurred when using other Co-catalysts, such as $Co(OAc)_2$ or CoI_2 with $AgSbF_6$ **(entries 4-5)**.

Table 4.4 Cobalt catalyst effects



7a **8a** **9aa**

Entry	Co cat (mol%)	Ag-salt (mol%)	Yield (%)[a]
1	$[Cp^*Co(C_6H_6)](PF_6)_2$ (10)	none	64
2	$Co(acac)_3$ (10)	none	0
3	$Co(NH_3)_6Cl_3$ (10)	none	0
4	$Co(OAc)_2$ (10)	none	0
5	CoI_2 (10)	$AgSbF_6$ (20)	0

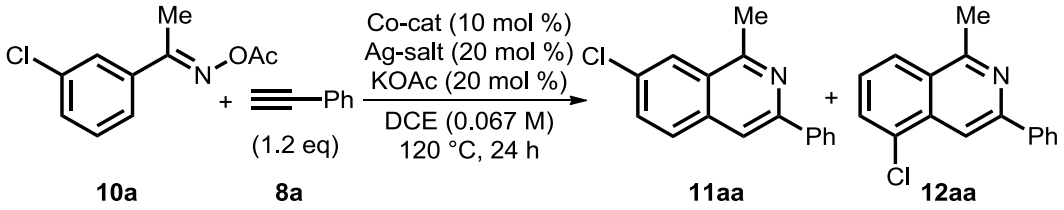
[a] NMR yield.

4.2.2 *meta*-Cl, Br substitutent *O*-acyloxime for the regioselective formation of isoquinolines

4.2.2.1 Cobalt catalyst effects

I set out to investigate the reaction conditions using *meta*-Cl substituted *O*-acyloxime **10a** with phenylacetylene **8a** **(Table 4.5)**. A cationic benzene complex $[Cp^*Co(C_6H_6)][PF_6]_2$ combined with KOAc in DCE at 120 °C gave a desired annulated product **11aa** and **12aa** in 46% yield and high regioselectivity **(entry 1)**. The less hindered C-H bond was selectively functionalized under Cp^*Co^{III} catalysis. *In situ* generation of an active catalyst using $Cp^*Co(CO)I_2$ and cationic $AgSbF_6$ showed high reactivity, afforded the best result (82% isolated yield, 17/1 selectivity, **entry 2**). Control experiments using other commercially available Co^{III} salts such as $Co(acac)_3$ and $Co(NH_3)_6Cl_3$ did not promote the reaction **(entries 3-4)**. No reaction occurred when using other Co-catalysts, such as $Co(OAc)_2$ or CoI_2 with $AgSbF_6$ **(entries 5-6)**.

Table 4.5 Cobalt catalyst effects



10a **8a** **11aa** **12aa**

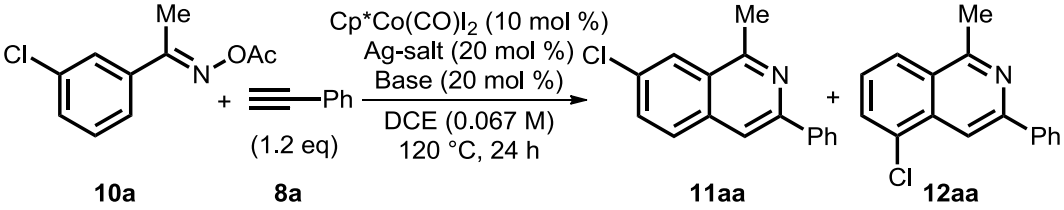
Entry	Co cat (mol%)	Ag-salt (mol%)	Yield (%)[a]
1	$[Cp^*Co(C_6H_6)](PF_6)_2$ (10)	none	46(14/1)
2	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	82(17/1)[b]
3	$Co(acac)_3$ (10)	none	0
4	$Co(NH_3)_6Cl_3$ (10)	none	0
5	$Co(OAc)_2$ (10)	none	0
6	CoI_2 (10)	$AgSbF_6$ (20)	trace

[a] NMR yield; Regioselectivity was determined by NMR. [b] Isolated yield.

4.2.2.2 Ag-salt and base effects

Among the Ag-salts screened, other Ag-salts were slightly worse than $AgSbF_6$ **(Table 4.5, entry 2 vs Table 4.6, entries 1-3),** but also afforded good regioselectivity. Other bases than KOAc were generally less effective, and diminished yields were obtained **(entries 4–6)**.

Table 4.6 Ag-salt and base effects



10a **8a** **11aa** **12aa**

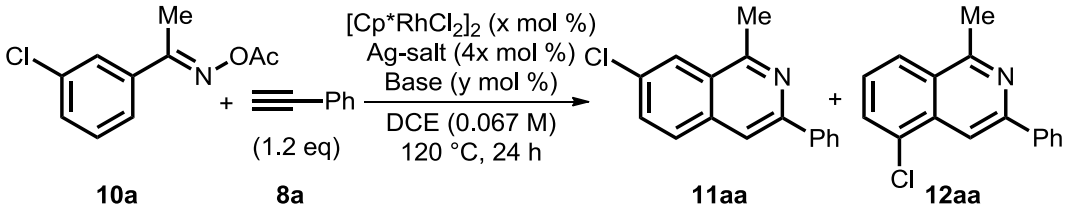
Entry	Ag-salt (mol%)	Base (mol%)	Yield (%)[a]
1	$AgPF_6$ (20)	KOAc (20)	73(17/1)
2	$AgBF_4$ (20)	KOAc (20)	65(19/1)
3	$AgNTf_2$ (20)	KOAc (20)	70(16/1)
4	$AgSbF_6$ (20)	K_2CO_3 (20)	71(13/1)
5	$AgSbF_6$ (20)	CsOAc (20)	63(19/1)
6	$AgSbF_6$ (20)	CsOPiv (20)	64(17/1)

[a] NMR yield; Regioselectivity was determined by NMR.

4.2.2.3 Conditions reported by Cp*Rh(III) catalysis

I also checked the catalytic activity of Cp^*Rh^{III} catalysts in several conditions to investigate the difference between Co and Rh. The reported reaction conditions for internal alkynes using acetate bases in MeOH[9] at 60–80 °C resulted in no reaction **(Table 4.7, entries 1-3)**. Although similar conditions to the cobalt catalysis using $AgSbF_6$ and carboxylate or carbonate bases in DCE at 120 °C afforded the annulated products, yields were poor 9-28% and almost no regioselectivity in the C-H activation was observed in all cases **(entries 4-7)**.

Table 4.7 Conditions reported by Cp*Rh(III) catalysis



10a **8a** **11aa** **12aa**

Entry	Ag-salt (mol%)	Base (mol%)	Yield (%)[a]
1[b,c]	none	NaOAc (30)	trace
2[b,c]	$AgSbF_6$ (10)	CsOAc (30)	trace
3[b,d]	none	CsOAc (30)	trace
4	$AgSbF_6$ (20)	KOAc (20)	11(1/1.3)
5	$AgSbF_6$ (20)	CsOAc (20)	28(1/1.3)
6	$AgSbF_6$ (20)	K_2CO_3 (20)	9(1/1.6)
7	$AgSbF_6$ (20)	CsOPiv (20)	13(1/1.3)

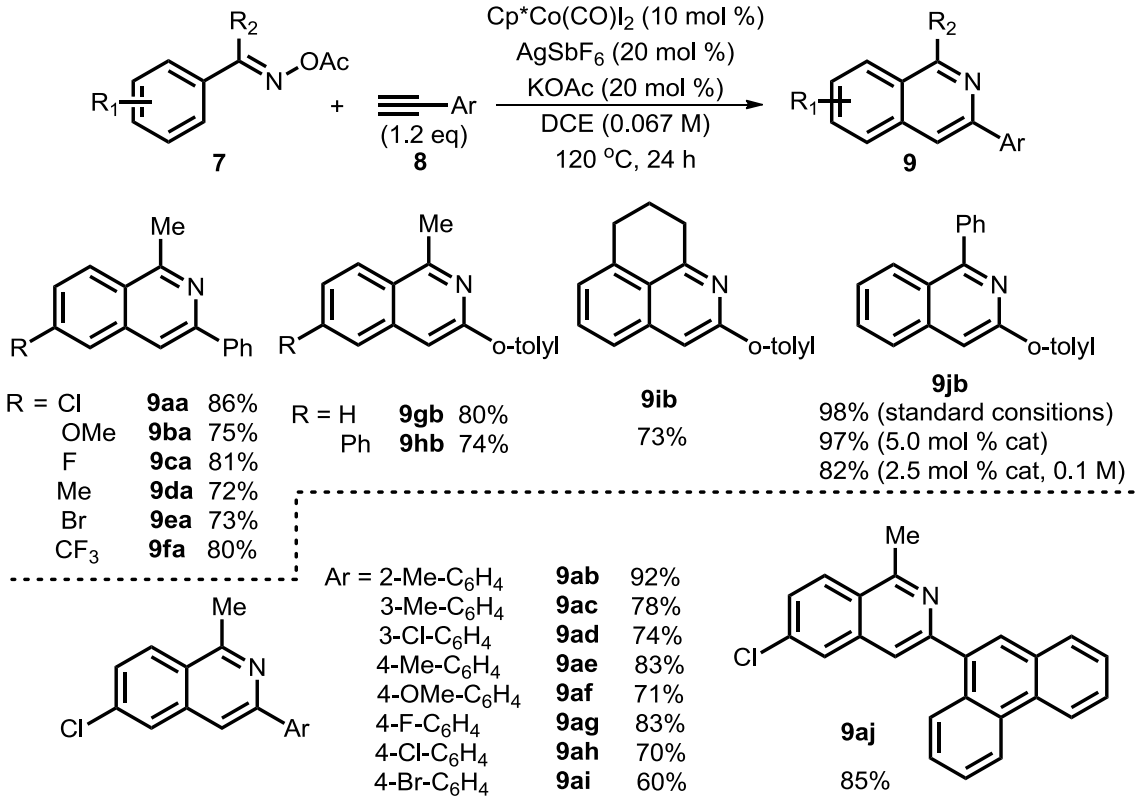
[a] NMR yield; Regioselectivity was determined by NMR. [b] Solvent was MeOH (0.2 M); $[Cp^*RhCl_2]_2$ was 2.5 mol %. [c] The reaction was run at 60 °C. [d] The reaction was run at 80 °C.

4.2.3 Substrate scope

The scope of *para*-substituted *O*-acyloximes **7** and terminal alkynes **8** is summarized in **Table 4.8**. Various substituents at the *para*-position were compatible **(9aa-9fa, 9gb, 9hb)**, and a cyclic *O*-acyloxime **7i** gave a good yield **(9ib)**. A benzophenone-type *O*-acyloxime **7j** is also a good substrate under the current conditions to afford **9jb** in 98% yield. I also tried decreasing the catalyst loading with **7j** and **8b** as model substrates. The reaction smoothly proceeded with 5.0 mol % of the cobalt catalyst, and

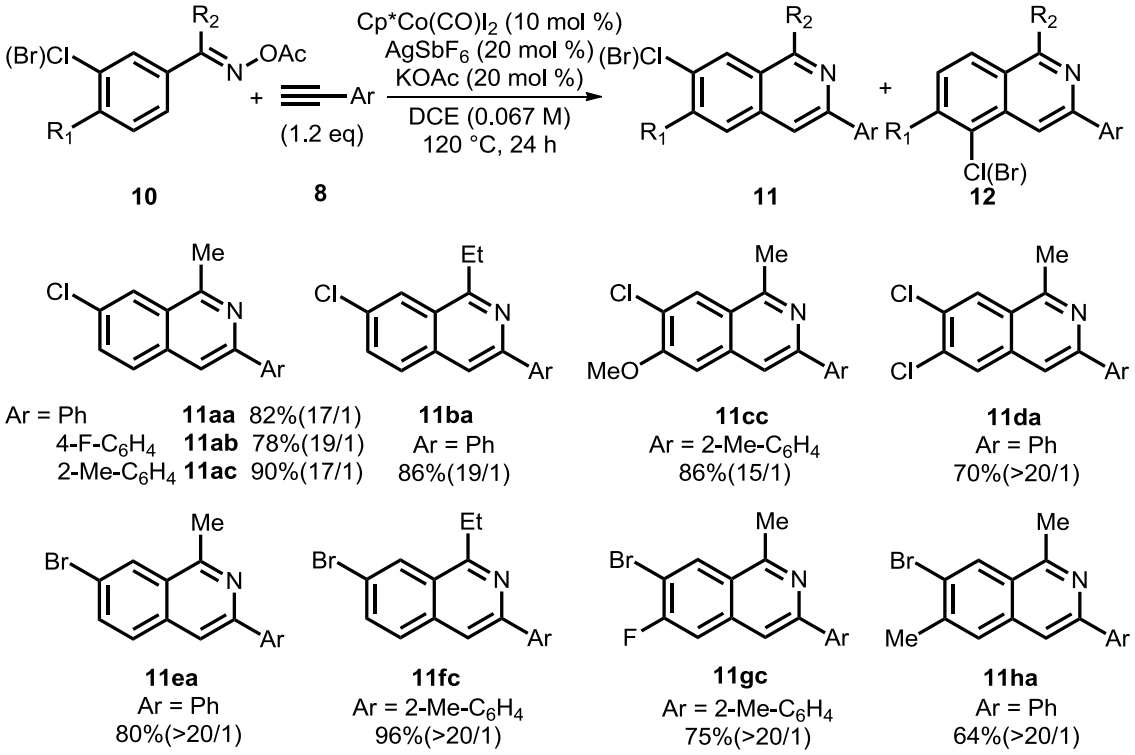
the yield is retained. Decreasing the catalyst loading to 2.5 mol % led to a diminished reactivity, but an acceptable yield (82%) was obtained by slightly increasing the concentration to 0.1 M. Reactions with *O*-acyloxime **7a** and several *para*-, *meta*- and *ortho*-substituted phenylacetylenes proceeded in 60-92% yields **(9ab-9ai)**. 9-ethynylphenanthrene **8j** afforded the product **9aj** in 85%.

Table 4.8 The scope of *para*-substituted *O*-acyloxime with terminal alkyne

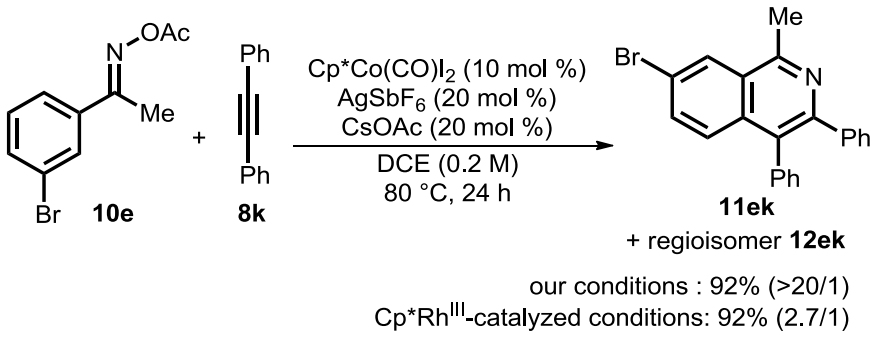


The scope of *meta*-Cl or Br substituted *O*-acyloximes **10** and terminal alkynes **8** is summarized in **Table 4.9**. *O*-Acyloximes bearing chloro or bromo substituents at the *meta*-position generally showed high regioselectivity, and the less hindered C-H bonds were functionalized **(11aa-11ac, 11ea)**. Another substituent at the *para*-position did not affect the selectivity and reactivity **(11cc, 11da, 11gc, 11ha)**. Not only the acetophenone-derived substrates, but also propiophenone derived *O*-acyloximes afforded the desired product with excellent regioselectivity **(11ba, 11fc)**.

Table 4.9 The scope of *meta*-Cl, Br substituted *O*-acyloxime with terminal alkyne



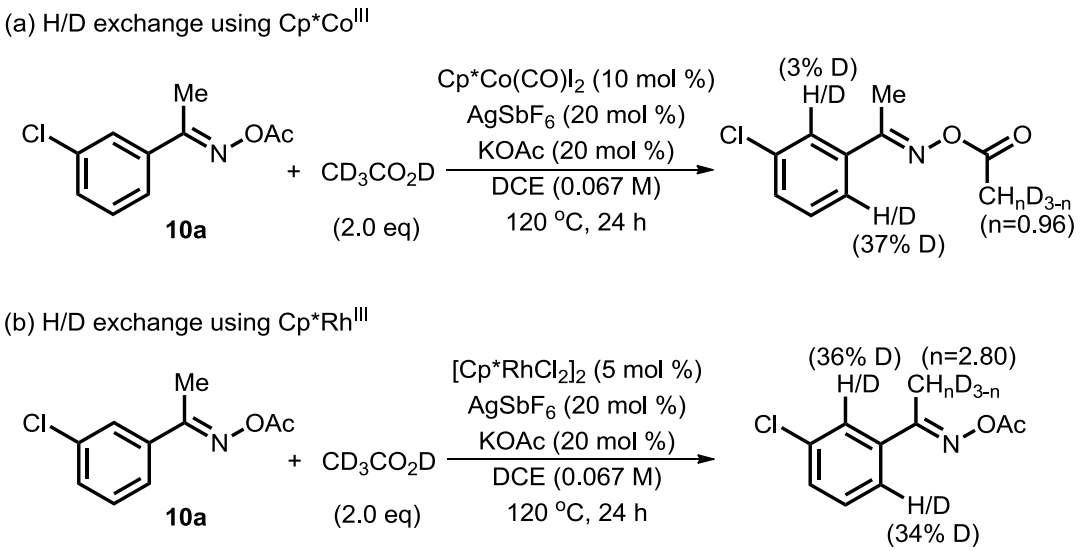
To demonstrate the generality of the regioselectivity of the Cp*Co^{III} catalysis, I also carried out the reaction using **10e** and internal alkyne **8k**. Under the optimized conditions shown in **Scheme 4.7**, polysubstituted isoquinoline **11ek** was isolated in 92% yield and with >20/1 regioselectivity. This selectivity is noteworthy because low selectivity (2.7/1) was reported under Cp*Rh^{III}-catalyzed conditions.[6]



Scheme 4.7 Regioselective reaction using **10e** and internal alkyne **8k**

4.2.4 H/D exchange experiments

To gain insight into the reaction mechanism and the origin of high regioselectivity, I performed several experimental mechanistic studies. When *O*-acyloxime **10a** and CD_3CO_2D was subjected to the optimized reaction conditions using Cp*Co(CO)I_2, selective deuterium incorporation was observed at the less hindered position **(Scheme 4.8a)**. On the other hand, Cp*Rh^{III} catalyst promoted non-selective H/D exchange under the same conditions **(Scheme 4.8b)**. This high selectivity of the Cp*Co^{III} catalyst would reflect the smaller ionic radius of cobalt compared with rhodium.



Scheme 4.8 H/D exchange experiments

4.2.5 Proposed mechanism

Possible reaction pathways to form isoquinoline are summarized in **Figure 4.1**. Coordination of *O*-acyloxime **10a** to the Co^{III} center and acetate-assisted C-H activation gives 5-membered metallacycle **A**, which undergoes insertion to alkynes to afford vinyl cobalt species **B**, subsequent alkyne insertion leads to the formation of common intermediate **C**. Pathway (a) consists of reductive elimination of the C-N bond to form *N*-acetoxyisoquinolinium cation **D**, then isoquinoline was formed along with regeneration of the Co(III) catalyst. In pathway (b), a concerted C-N bond formation and N-O bond cleavage process provides isoquinoline and regenerates the Co(III) catalyst.

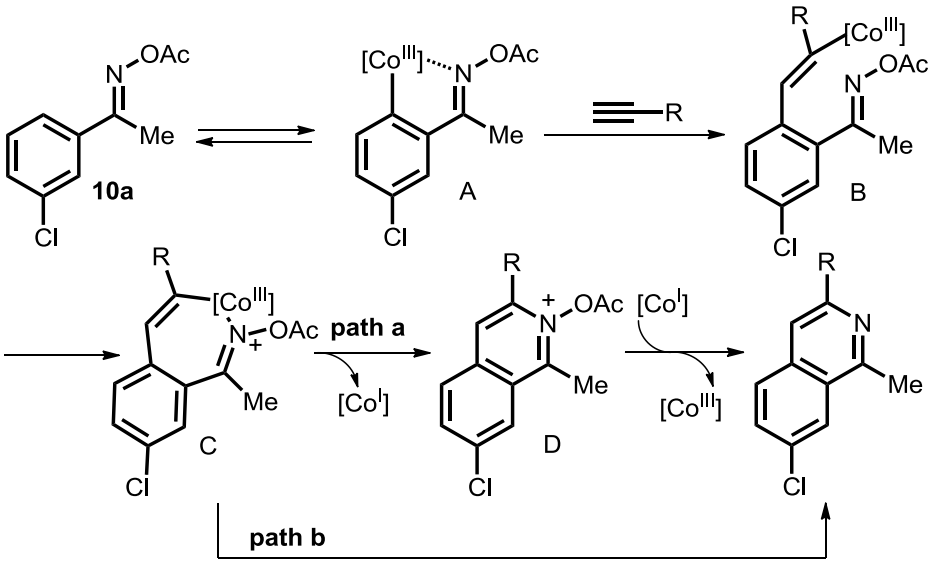
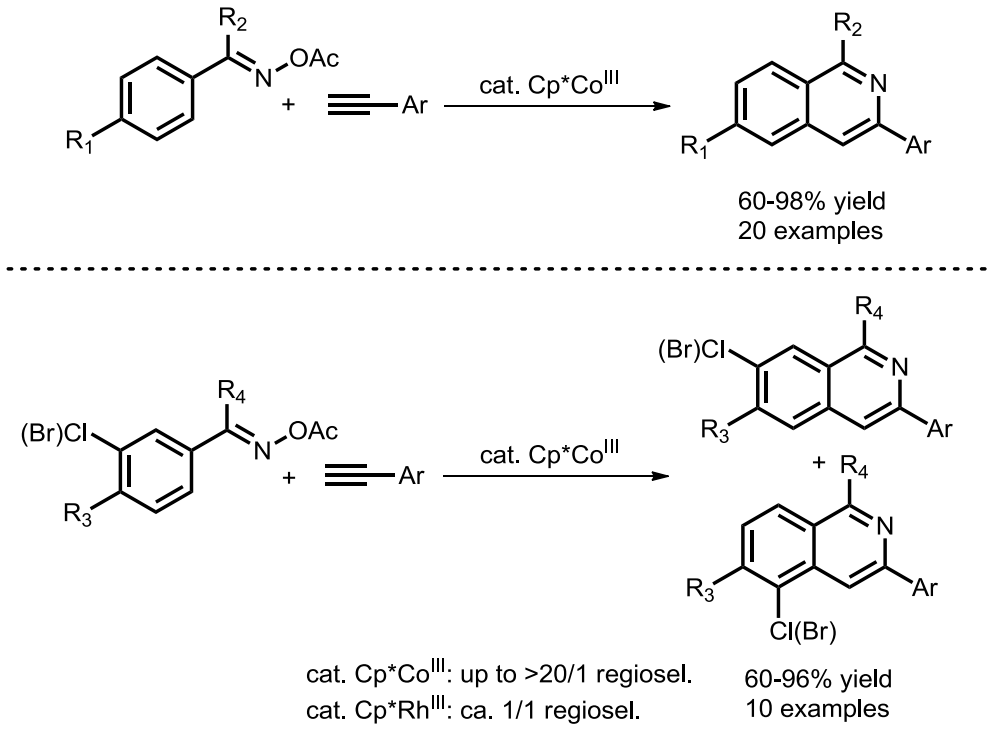


Figure 4.1 Proposed mechanism

4.3 Summary

In summary, I demonstrated the utility of the Cp^*Co^{III} catalyst for the isoquinline synthesis from *O*-acyloximes and terminal alkynes via regioselective C-H bond activation **(Scheme 4.9)**.[10] The Cp^*Co^{III} catalyst showed higher regioselectivity than Cp^*Rh^{III} catalysts probably due to the smaller ionic radius of cobalt. An oxidizing directing group bearing an N-O bond was first utilized as an internal oxidant in cobalt-catalyzed oxidative C-H bond functionalization reactions. The use of *O*-acyloxime directing group is expected to further broaden the scope of the recently emerging high-valent cobalt-catalyzed C-H bond functionalization reactions.



B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Manuscript in preparation*.

Scheme 4.9 Regioselective formation of isoquinolins

4.4 Reference

[1] a) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Adv. Synth. Catal*., **2014**, *356*, 1491. b) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Chem. Commun*., **2015**, *51*, 4659.

[2] See: Chapter 2

[3] For Bischler-Napieralski examples, see: a) X. Xu, S. Guo, Q. Dang, J. Chen, X. J Bai. *Comb. Chem*.**2007**, *9*, 773; b) T. Ishikawa, K. Shimooka, T. Narioka, S. Noguchi, T. Saito, A. Ishikawa, E. Yamazaki, T. Harayama, H. Seki, K. J. Yamaguchi. *Org. Chem*. **2000**, *65*, 9143; c) A. Bischler, B. Napieralski. *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 1903. For Pomeranz-Fritsch examples, see: d) E. V. Brown. *J. Org. Chem*. **1977**, *42*, 3208; e) W. Herz, S. Tocker. *J. Am. Chem. Soc*. **1955**, *77*, 6355; f) P. Fritsch. *Ber. Dtsch. Chem. Ges*. **1893**, *26*, 419; g) C. Pomeranz. *Monatsh. Chem*. **1893**, *14*, 116. For Pictet-Spengler examples, see: h) S. W. Youn. *J. Org. Chem*. **2006**, *71*, 2521; i) A. Pictet, T. Spengler, *Chem. Ber*. **1911**, *44*, 2030.

[4] a) K. R. Roesch, H. Zhang, R. C. Larock. *J. Org. Chem*. **2001**, *66*, 8042; b) K. R. Roesch, R. C. Larock. *Org. Lett.***1999**, *1*, 553; c) K. R. Roesch, R. C. Larock. *J. Org. Chem*. **1998**, *63*, 5306.

[5] N. Guimond, K. Fagnou. *J. Am. Chem. Soc*. **2009**, *131*, 12050.

[6] P. C. Too, Y. F. Wang, S. Chiba. *Org. Lett.* **2010**, *12*, 5688.

[7] X. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia, X. Li, *Adv. Synth. Catal.* **2011**, *353*, 719.

[8] R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032.

[9] A review on isoquinoline synthesis via C-H functionalization reactions: R. He, Z. T. Huang, Q. Y. Zheng, C. Wang. *Tetrahedron Lett.* **2014**, *55*, 5705.

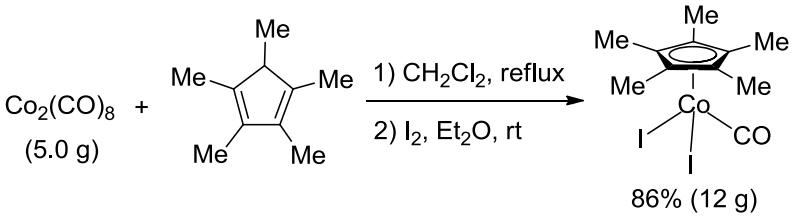
[10] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Manuscript in preparation*.

Experimental Section

1. Air-Stable $Cp^*Co(CO)I_2$ Complex as a Precursor for Cationic Cp^*Co^{III} Catalysis: Application for Directed C2-Selective C-H Amidation of Indoles

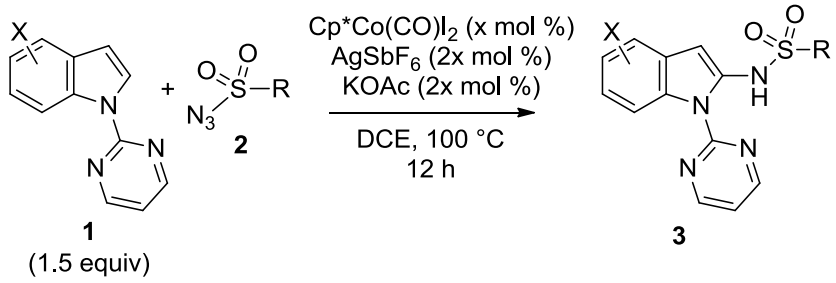
General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-ECX500 spectrometers, operating at 500 MHz for ^1H NMR and 125 MHz for ^{13}C NMR or JNM-ECS400 spectrometers, operating at 400 MHz for ^1H NMR and 100 MHz for ^{13}C NMR. All spectra were obtained at ambient temperature. The chemical shifts (δ) were recorded in parts per million (ppm). The coupling constants (*J*) were shown in Hertz (Hz). Chemical shifts in $CDCl_3$ were reported the residual $CHCl_3$ (7.24 ppm for ^1H NMR, 77.0 ppm for ^{13}C NMR). ESI mass spectra for HRMS were measured on a JEOL JMS-T100LC AccuTOF spectrometer. 1,2-Dichloroethane (DCE) was distilled from CaH_2, purged with argon for over 30 min and stored over activated molecular sieves 4A under argon atmosphere. $Co_2(CO)_8$ was purchased from Aldrich and used without purification. 1-(Pyrimidin-2-yl)-1H-indole derivatives **1** were prepared by following the same procedure as described in the literature.[1,2] All azide derivatives **2** were prepared by following the same procedure as described in the literature.[3]

Preparation of Cp*Co(CO)I_2 catalyst: [4,5]



To a well-dried 2-necked 500-mL flask were successively added $Co_2(CO)_8$ (5.0 g, 14.6 mmol), degassed CH_2Cl_2 (100 mL) and pentamethylcyclopentadiene (5.55 mL, 35.4 mmol). The mixture was refluxed under argon stream for 6 h and then cooled to room temperature. The solvent was removed in vacuo. The residue was dissolved in degassed Et_2O (50 mL) and then iodine (9.0 g, 35.5 mmol) in degassed Et_2O (50 mL) was added dropwisely at room temperature with stirring. [Caution: During the addition, the mixture was refluxed due to the exothermic reaction and CO gas evolution was observed.] After the mixture was stirred at room temperature for 1 h, the solvent was evaporated. Resulting residue was purified by silica gel column chromatography (hexane then CH_2Cl_2/hexane=4/1) to afford deep purple crystalline solid (12.0 g, 86% yield based on Co); known metal complex;[S4] IR (KBr) ν 2080 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.21 (s, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 100.9, 11.4.

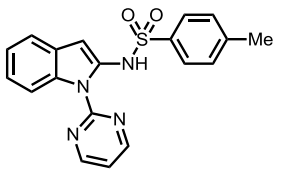
General Procedure of Co-catalyzed C-H Amidation of Indoles:



To a dried screw-capped vial were added indole **1** (0.30 mmol), azide **2** (0.20 mmol), Cp*Co(CO)I_2 (2.4 mg, 5 μmol), $AgSbF_6$ (3.4 mg, 10 μmol), KOAc (1.0 mg, 10 μmol), and 1,2-dichloroethane (0.60 mL) under Ar atmosphere. The vial was capped, and the mixture was heated at 100 °C for 12 h with stirring. The resulting mixture was cooled to room temperature, and directly purified by silica gel column chromatography

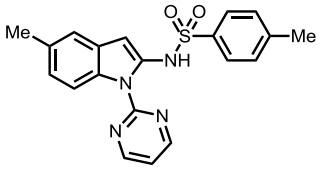
(hexane:ethyl acetate = 2:1 for all compounds) to give product **3**.

4-Methyl-*N*-(1-(pyrimidin-2-yl)-1H-indol-2-yl)benzenesulfonamide (3aa):



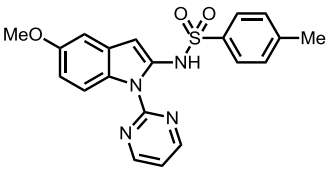
known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.00 (s, 1H), 8.54 (d, *J* = 4.9 Hz, 2H), 8.40-8.36 (m, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.38 (dd, *J* = 5.8, 3.6 Hz, 1H), 7.12-7.06 (m, 2H), 6.99-6.94 (m, 3H), 6.55 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ157.9, 157.5, 143.8, 136.0, 133.5, 133.4, 129.4, 128.5, 127.0, 123.0, 122.9, 119.9, 116.3, 115.7, 97.4, 21.3.

4-Methyl-*N*-(5-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)benzenesulfonamide (3ba):



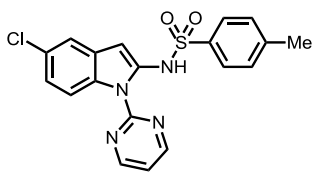
known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.04 (s, 1H), 8.55 (d, *J* = 4.5 Hz, 2H), 8.26 (d, *J*= 8.5 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 2H), 7.18 (s, 1H), 7.02-6.90 (m, 4H), 6.49 (s, 1H), 2.32 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 157.5, 143.8, 136.0, 133.4, 132.4, 131.7, 129.4, 128.7, 127.0, 124.2, 119.9, 116.1, 115.5, 97.3, 21.4, 21.2.

***N*-(5-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)-4-methylbenzenesulfonamide (3ca):**



known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 8.55 (d, *J* = 4.5 Hz, 2H), 8.31 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.02-6.94 (m, 3H), 6.87 (d, *J* = 2.2 Hz, 1H), 6.71 (dd, *J* = 9.2, 2.2 Hz, 1H), 6.48 (s, 1H), 3.75 (s, 3H), 2.19 (3, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 157.5, 156.0, 143.8, 136.0, 134.1, 129.5, 129.4, 128.0, 127.0, 116.8, 116.1, 111.2, 102.6, 97.0, 55.5, 21.4.

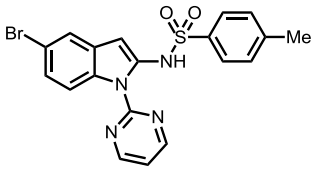
***N*-(5-chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)-4-methylbenzenesulfonamide (3da):**



known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.17 (s, 1H), 8.59 (d, *J* = 4.5 Hz, 2H), 8.33 (d, *J* = 8.5 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 2H), 7.32 (s, 1H), 7.05-7.01

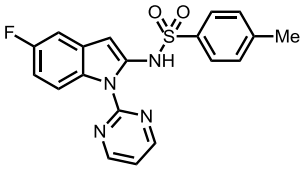
(m, 4H), 6.44 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.6, 144.0, 135.9, 134.9, 131.7, 129.8, 129.5, 128.5, 127.0, 122.7, 119.2, 117.1, 116.6, 95.7, 21.4.

***N*-(5-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)-4-methylbenzenesulfonamide (3ea):**



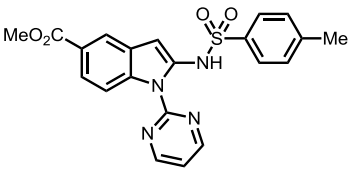
known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.21 (s, 1H), 8.69 (d, *J* = 4.5 Hz, 2H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 1.8 Hz, 1H), 7.17 (d, *J* = 8.5, 1.8 Hz, 1H), 7.05 (t, *J* = 4.5 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 2H), 6.52 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 157.7, 144.1, 135.9, 134.8, 132.1, 130.4, 129.5, 127.1, 125.4, 122.2, 117.4, 116.7, 116.3, 95.6, 21.4.

***N*-(5-fluoro-1-(pyrimidin-2-yl)-1H-indol-2-yl)-4-methylbenzenesulfonamide (3fa):**



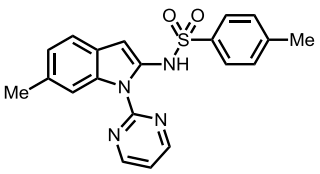
known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.20 (s, 1H), 8.60 (d, *J* = 4.5 Hz, 2H), 8.38 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.04-7.02 (m, 4H), 6.84-6.78 (m, 1H), 6.48 (s, 1H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2 (d, *J* = 238.2 Hz), 157.9, 157.6, 144.0, 136.0, 135.1, 129.7, 129.6, 129.5, 127.1, 117.0 (d, *J* = 9.2 Hz), 110.1 (d, *J* = 24.4 Hz), 105.3 (d, *J* = 24.4 Hz), 96.2 (d, *J* = 3.6 Hz), 21.4.

2-(4-methylphenylsulfonamido)-1-(pyrimidin-2-yl)-1H-indole-5-carboxylate (3ga):



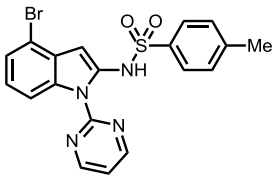
known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.70 (d, *J* = 4.9 Hz, 2H), 8.50 (d, *J* = 9.2 Hz, 1H), 8.16 (d, *J* = 1.8 Hz, 1H), 7.86 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.15 (t, *J* = 4.9 Hz, 1H), 7.07 (d, *J* = 8.5 Hz, 2H), 6.64 (s, 1H), 3.91 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 157.8, 144.1, 136.1, 135.9, 134.8, 129.5, 128.3, 127.1, 124.9, 124.2, 121.9, 117.0, 115.5, 97.2, 52.0, 21.4.

4-Methyl-*N*-(6-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)benzenesulfonamide (3ha):



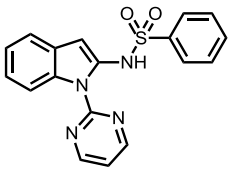
known compound;[S2] colorless solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.85 (s, 1H), 8.64 (d, *J* = 4.9 Hz, 2H), 8.25 (s, 1H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 1H), 7.09 -7.00 (m, 4H), 6.60 (s, 1H), 2.43 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 157.6, 143.7, 136.0, 133.9, 132.9, 132.6, 129.4, 126.9, 126.1, 124.4, 119.6, 116.2, 115.7, 98.4, 22.0, 21.4.

***N*-(4-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)-4-methylbenzenesulfonamide (3ia):**



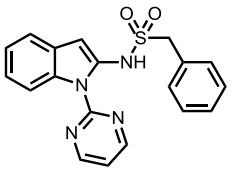
colorless solid; IR (KBr) ν 2954, 1580, 1424, 1335, 1167, 1093, 972, 892, 792, 705, 620 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.14 (s, 1H), 8.69 (d, *J* = 4.0 Hz, 2H), 8.43 (d, *J* = 9.2 Hz, 1H), 7.64 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 4.0 Hz, 1H), 7.10 (d, *J* = 8.2 Hz, 2H), 7.02 (dd, *J* = 9.2, 8.2 Hz, 1H), 6.67 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 157.7, 144.0, 135.9, 134.3, 133.6, 129.5, 129.3, 127.1, 126.0, 123.6, 116.8, 114.9, 113.6, 96.6, 21.5; HRMS (ESI): *m/z* calculated for $C_{19}H_{15}BrN_4NaO_2S^+$ [M+Na$^+$] : 464.9991, found: 464.9997.

***N*-(1-(pyrimidin-2-yl)-1H-indol-2-yl)benzenesulfonamide (3ab):**



colorless solid; IR (KBr) ν 3050, 2855, 1590, 1464, 1346, 1169, 1092, 959, 751, 652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.99 (s, 1H), 8.59 (d, *J* = 4.6 Hz, 2H), 8.41-8.36 (m, 1H), 7.66-7.60 (m, 2H), 7.45-7.38 (m, 1H), 7.34 -7.31 (m, 1H), 7.22-7.15 (m, 2H), 7.14-7.09 (m, 2H), 7.01 (t, *J* = 4.6 Hz, 1H), 6.60 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 157.7, 139.0, 133.6, 133.2, 133.0, 128.8, 128.4, 126.9, 123.1, 123.0, 120.0, 116.3, 115.7, 98.1; HRMS (ESI): *m/z* calculated for $C_{18}H_{14}N_4NaO_2S^+$ [M+Na$^+$] : 373.0730, found: 373.0727.

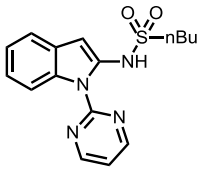
1-Phenyl-*N*-(1-(pyrimidin-2-yl)-1H-indol-2-yl)methanesulfonamide (3ac):



colorless solid;; IR (KBr) ν 3052, 2975, 1565, 1426, 1341, 1258, 1130, 957, 794, 634 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.01 (s,

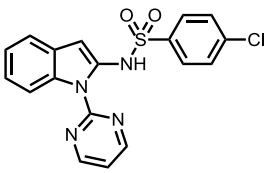
*1*H), 8.66-8.64 (m, 1H), 8.43 (d, *J* = 4.6 Hz, 2H), 7.51-7.48 (m, 1H), 7.23-7.20 (m, 2H), 7.03-7.00 (m, 3H), 6.99-6.93 (m, 3H), 6.69 (s, 1H), 4.35 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.3, 134.3, 133.3, 130.4, 128.9, 128.4, 128.38, 128.32, 123.4, 122.9, 119.8, 116.4, 116.3, 94.9, 55.9; HRMS (ESI): *m*/*z* calculated for $C_{19}H_{16}N_4NaO_2S^+$ [M+Na^+] : 387.0886, found: 387.0883.

_N_-(1-(pyrimidin-2-yl)-1H-indol-2-yl)butane-1-sulfonamide (3ad):



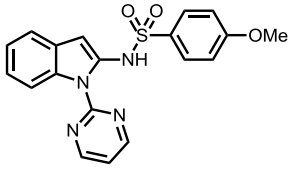
colorless solid; IR (KBr) ν 2939, 2876, 1584, 1424, 1333, 1240, 1146, 957, 797, 638 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, *1*H), 8.74 (d, *J* = 5.2 Hz, 2H), 8.65 -8.63 (m, 1H), 7.49-7.47 (m, 1H), 7.25-7.21 (m, 2H), 7.16-7.14 (m, 1H), 6.60 (s, 1H), 3.16-3.13 (t, *J* = 6.4 Hz, 2H), 1.73-1.67 (m, 2H), 1.35-1.30 (m, 2H), 0.79 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 157.8, 134.3, 133.4, 128.8, 123.3, 122.8, 119.7, 116.5, 116.1, 96.4, 50.5, 25.4, 21.3, 13.4; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{18}N_4NaO_2S^+$ [M+Na^+] : 353.1043, found: 353.1037.

4-chloro-_N_-(1-(pyrimidin-2-yl)-1H-indol-2-yl)benzenesulfonamide (3ae):



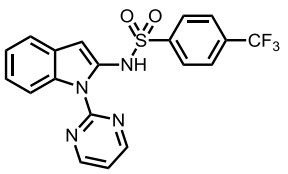
colorless solid; IR (KBr) ν 3086, 2867, 1568, 1337, 1179, 1092, 1014, 886, 751, 611 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.07 (s, 1H), 8.69 (d, *J* = 4.8 Hz, 2H), 8.51-8.47 (m, 1H), 7.64 (d, *J* = 8.6 Hz, 2H), 7.53-7.49 (m, 1H), 7.27-7.21 (m, 4H), 7.12 (t, *J* = 4.8 Hz, 1H), 6.67 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 157.7, 139.5, 137.5, 133.6, 132.8, 129.1, 128.4, 128.3, 123.3, 123.2, 120.1, 116.5, 115.8, 98.3; HRMS (ESI): *m*/*z* calculated for $C_{18}H_{13}ClN_4NaO_2S^+$ [M+Na^+] : 407.0340, found: 407.0340.

4-Methoxy-_N_-(1-(pyrimidin-2-yl)-1H-indol-2-yl)benzenesulfonamide (3af):



known compound;[S2] yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.58 (d, *J* = 4.1 Hz, 2H), 8.41-8.38 (m, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.40 (dd, *J* = 5.7, 3.4 Hz, 1H), 7.16-7.09 (m, 2H), 7.00 (t, *J* = 4.1 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 2H), 6.55 (s, 1H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.0, 158.0, 157.6, 133.6, 133.5, 130.5, 129.1, 128.5, 123.0, 122.9, 119.9, 116.3, 115.8, 114.0, 97.6, 55.5.

***N*-(1-(pyrimidin-2-yl)-1H-indol-2-yl)-4-(trifluoromethyl)benzenesulfonamide (3ag):**

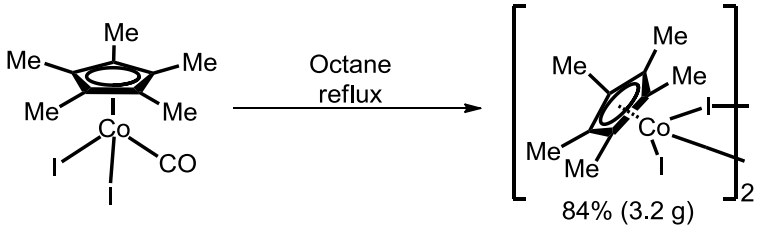


yellow solid; IR (KBr) ν 3050, 1588, 1458, 1322, 1173, 1136, 1017, 961, 744, 637 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 11.11 (s, 1H), 8.66 (d, *J* = 4.6 Hz, 2H), 8.49-8.47 (m, 1H), 7.83 (d, *J* = 8.1 Hz, 2H), 7.57-7.50 (m, 3H), 7.26-7.21 (m, 2H), 7.10 (t, *J* = 4.6 Hz, 1H), 6.71 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ157.8, 157.7, 142.5, 134.5 (q, *J* = 33.4 Hz), 133.6, 132.4, 128.2, 127.5, 126.0 (q, *J* = 3.6 Hz), 123.4, 123.2, 123.0 (q, *J* = 273.0 Hz), 120.2, 116.5, 115.9, 98.6; HRMS (ESI): *m*/*z* calculated for $C_{19}H_{13}F_3N_4NaO_2S^+$ [M+Na^+] : 441.0604, found: 441.0596.

2. A Cp*CoI_2-dimer as a Precursor for Cationic Co(III)-catalysis: Application to C-H Phosphoramidation of Indoles

General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-ECX500 spectrometers, operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR or JNM-ECS400 spectrometers, operating at 400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR and 158 MHz for ^{31}P NMR. All spectra were obtained at ambient temperature. The chemical shifts (δ) were recorded in parts per million (ppm). The coupling constants (*J*) were shown in Hertz (Hz). Chemical shifts in $CDCl_3$ were reported the residual $CHCl_3$ (7.24 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). ESI mass spectra for HRMS were measured on a JEOL JMS-T100LC AccuTOF spectrometer. 1,4-dioxane(Super Dehydrated) was purchased from Wako Ltd. and used without purification. 1-(Pyrimidin-2-yl)-1H-indole derivatives **4** were prepared by following the same procedure as described in the literature.[6,7] DPPA **5a** was purchased from Tokyo Chemical Industry Co., Ltd. and used without purification. Bis(4-methoxyphenyl)phosphoroazidate and 4-Chlorophenyl phenyl phosphorazidate were prepared by following the same procedure as described in the literature.[8,9]

Preparation of $[Cp^*CoI_2]_2$ catalyst [10]**:**

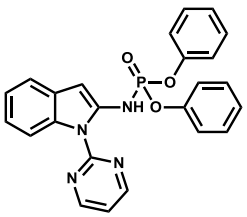


To a round-bottomed flask was charged with *n*-octane (50 mL) and $Cp^*Co(CO)I_2$ (4.0 g). The mixture was heated to reflux under argon for 12 h. After cooling to room temperature, the solid precipitate was collected in a sintered- glass filtration funnel, washed with pentane, and dried under high vacuum to afford $[Cp^*CoI_2]_2$ (3.2 g, 84%) as a black powder. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.76 (s, 30H).

General Procedure of Co-catalyzed C-H Amidation of Indoles:

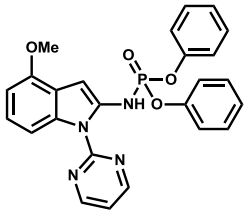
To a dried screw-capped vial were added indole **4** (0.80 mmol), phosphoryl azide **5** (0.40 mmol), $[Cp^*CoI_2]_2$ (17.6 mg, 20 μmol), $AgSbF_6$ (27.2 mg, 80 μmol), and 1,4-dioxane (0.20 mL) under Ar atmosphere. The vial was capped, and the mixture was heated at 60 °C for 36 h with stirring. The resulting mixture was cooled to room temperature, and directly purified by silica gel column chromatography (hexane:ethyl acetate = 1:1 for all compounds) to give product **6**.

Diphenyl (1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6aa):



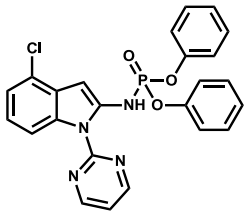
colorless solid; IR (KBr) ν 3052, 2917, 1615, 1423, 1283, 1185, 951, 781, 687 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (d, J = 12.1 Hz, 1H), 8.55 -8.49 (m, 3H), 7.43 -7.39 (m, 1H), 7.22 -7.16 (m, 8H), 7.16 -7.09 (m, 2H), 7.09 -7.02 (m, 2H), 6.92 (t, J = 4.9 Hz, 1H), 6.45 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.5, 150.2 (d, J = 6.3 Hz), 136.4 (d, J = 7.2 Hz), 133.0, 129.7, 129.3, 125.4, 123.0, 121.8, 120.4 (d, J = 5.4 Hz), 119.0, 116.2, 115.9, 91.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.01; HRMS (ESI): m/z calculated for $C_{24}H_{19}N_4NaO_3P^+$ [M+Na^+] : 465.1087, found: 465.1089.

Diphenyl (4-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ba):



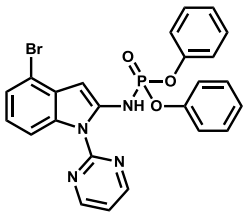
colorless solid; IR (KBr) ν 3067, 2955, 1568, 1367, 1270, 1194, 1014, 963, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.17 (d, *J* = 12.1 Hz, 1H), 8.58 (d, *J* = 4.9 Hz, 2H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.26 -7.19 (m, 8H), 7.12 -7.07 (m, 3H), 6.97 (t, *J* = 4.9 Hz, 1H), 6.67 (d, *J* = 7.6 Hz, 1H), 6.62 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 157.5, 151.7, 150.2 (d, *J* = 6.3 Hz), 134.9 (d, *J* = 6.3 Hz), 134.0, 129.7, 125.3 (d, *J* = 1.8 Hz), 122.5, 120.5 (d, *J* = 5.4 Hz), 119.3, 116.3, 109.1, 103.7, 89.3, 55.4; ^{31}P NMR (158 MHz, $CDCl_3$) δ -8.80; HRMS (ESI): *m/z* calculated for $C_{25}H_{21}N_4NaO_4P^+$ [M+Na^+] : 495.1193, found: 495.1183.

Diphenyl (4-chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ca):



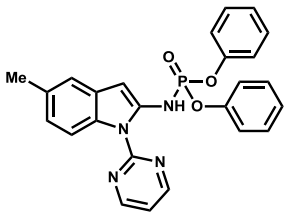
colorless solid; IR (KBr) ν 3081, 2909, 1567, 1428, 1279, 1193, 1024, 954, 765 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.47 (d, *J* = 12.1 Hz, 1H), 8.67 (d, *J* = 4.6 Hz, 2H), 8.54 (d, *J* = 8.6 Hz, 1H), 7.37 -7.29 (m, 8H), 7.28 -7.23 (m, 1H), 7.21 -7.16 (m, 2H), 7.15 -7.09 (m, 2H), 6.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.6, 150.2 (d, *J* = 7.2 Hz), 137.3 (d, *J* = 7.2 Hz), 133.5, 129.8, 128.1, 125.5, 124.1, 122.9, 122.3, 120.4 (d, *J* = 4.8 Hz), 116.7, 114.5, 89.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.45; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}ClN_4NaO_3P^+$ [M+Na^+] : 499.0697, found: 499.0689.

Diphenyl (4-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6da):



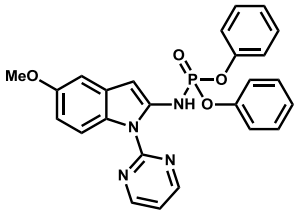
colorless solid; IR (KBr) ν 3039, 2914, 1567, 1447, 1280, 1192, 1020, 902, 757 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (d, *J* = 12.1 Hz, 1H), 8.57 (d, *J* = 4.9 Hz, 2H), 8.49 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 8.1 Hz, 1H), 7.25 -7.17 (m, 8H), 7.11 -7.05 (m, 2H), 7.02 (t, *J* = 4.9 Hz, 1H), 6.97 (dd, *J* = 8.5, 8.1 Hz, 1H), 6.50 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 157.6, 150.2 (d, *J* = 7.2 Hz), 137.3 (d, *J* = 7.2 Hz), 133.1, 129.9, 129.8, 125.9, 125.5, 122.6, 120.4 (d, *J* = 4.5 Hz), 116.7, 115.1, 112.7, 91.7; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.51; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}BrN_4NaO_3P^+$ [M+Na^+] : 543.0192, found: 543.0198.

Diphenyl (5-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ea):



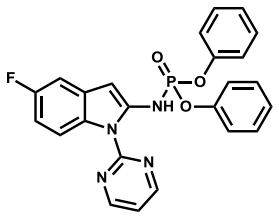
colorless solid; IR (KBr) ν 3041, 2915, 1561, 1480, 1274, 1012, 957, 788, 615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (d, *J* = 12.6 Hz, 1H), 8.51 (d, *J* = 4.9 Hz, 2H), 8.41 (d, *J* = 8.5 Hz, 1H), 7.23 -7.14 (m, 9H), 7.09 -7.02 (m, 2H), 6.96 -6.89 (m, 2H), 6.37 (s, 1H), 2.36 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 157.4, 150.2 (d, *J* = 7.2 Hz), 136.5 (d, *J* = 7.2 Hz), 132.5, 131.1, 129.7, 129.5, 125.4, 123.0, 120.4 (d, *J* = 4.5 Hz), 119.1, 116.0, 115.7, 91.7, 21.3; ^{31}P NMR (158 MHz, $CDCl_3$) δ -8.98; HRMS (ESI): *m/z* calculated for $C_{25}H_{21}N_4NaO_3P^+$ [M+Na^+] : 479.1243, found: 479.1237.

Diphenyl (5-methoxy-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6fa):



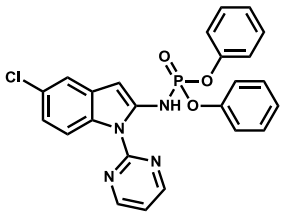
yellow solid; IR (KBr) ν 3062, 2995, 1582, 1424, 1212, 1089, 936, 779, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (d, *J* = 12.1 Hz, 1H), 8.52 (d, *J* = 4.9 Hz, 2H), 8.45 (d, *J* = 9.0 Hz, 1H), 7.23 -7.15 (m, 8H), 7.09 -7.04 (m, 2H), 6.94 -6.89 (m, 2H), 6.73 -6.70 (m, 1H), 6.39 (s, 1H), 3.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.4, 156.1, 150.2 (d, *J* = 6.3 Hz), 137.2 (d, *J* = 7.2 Hz), 130.3, 129.7, 127.5, 125.4, 120.4 (d, *J* = 4.5 Hz), 117.0, 116.0, 109.7, 102.2, 91.8, 55.5; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.05; HRMS (ESI): *m/z* calculated for $C_{25}H_{21}N_4NaO_4P^+$ [M+Na^+] : 495.1193, found: 495.1197.

Diphenyl (5-fluoro-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ga):



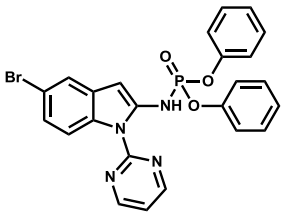
yellow solid; IR (KBr) ν 3063, 2923, 1597, 1495, 1285, 1200, 1024, 905, 767 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (d, *J* = 12.1 Hz, 1H), 8.56 (d, *J* = 4.9 Hz, 2H), 8.51 (dd, *J* = 9.2, 4.5 Hz, 1H), 7.25 -7.16 (m, 8H), 7.10 -7.04 (m, 3H), 6.99 (t, *J* = 4.9 Hz, 1H), 6.82 (ddd, *J* = 9.2, 9.2, 2.7 Hz, 1H), 6.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (d, *J* = 237.4 Hz), 158.2, 157.5, 150.1 (d, *J* = 6.3 Hz), 138.0 (d, *J* = 7.2 Hz), 130.4 (d, *J* = 9.9 Hz), 129.8, 129.2, 125.4 (d, *J* = 1.8 Hz), 120.4 (d, *J* = 4.5 Hz), 117.1 (d, *J* = 9.0 Hz), 116.4, 109.0 (d, *J* = 24.3 Hz), 104.6 (d, *J* = 24.3 Hz), 91.6 (d, *J* = 3.6 Hz); ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.31; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}FN_4NaO_3P^+$ [M+Na^+] : 483.0993, found: 483.0987.

Diphenyl (5-chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ha):



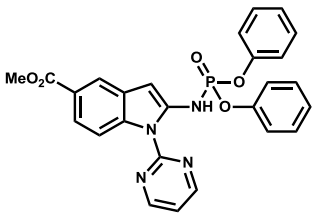
colorless solid; IR (KBr) ν 3062, 2927, 1565, 1498, 1256, 1071, 983, 764, 652 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.42 (d, *J* = 12.1 Hz, 1H), 8.55 (d, *J* = 4.6 Hz, 2H), 8.47 (d, *J* = 8.6 Hz, 1H), 7.36 (d, *J* = 2.3 Hz, 1H), 7.24 -7.16 (m, 8H), 7.10 -7.03 (m, 3H), 6.99 (t, *J* = 4.6 Hz, 1H), 6.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 157.6, 150.1 (d, *J* = 6.0 Hz), 137.8 (d, *J* = 7.2 Hz), 131.3, 130.7, 129.8, 128.5, 125.5, 121.7, 120.4 (d, *J* = 4.8 Hz), 118.4, 117.2, 116.5, 91.1; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.36; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}ClN_4NaO_3P^+$ [M+Na^+] : 499.0697, found: 499.0710.

Diphenyl (5-bromo-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ia):



colorless solid; IR (KBr) ν 3042, 2924, 1582, 1492, 1276, 1163, 954, 771, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (d, *J* = 12.1 Hz, 1H), 8.55 (d, *J* = 4.9 Hz, 2H), 8.41 (d, *J* = 9.0 Hz, 1H), 7.51 (s, 1H), 7.25 -7.15 (m, 9H), 7.10 -7.04 (m, 2H), 6.99 (t, *J* = 4.9 Hz, 1H), 6.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 157.5, 150.1 (d, *J* = 6.3 Hz), 137.7 (d, *J* = 7.2 Hz), 131.6, 131.1, 129.8, 125.5 (d, *J* = 1.8 Hz), 124.4, 121.4, 120.3 (d, *J* = 4.5 Hz), 117.6, 116.5, 116.3, 90.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.39; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}BrN_4NaO_3P^+$ [M+Na^+] : 543.0192, found: 543.0199.

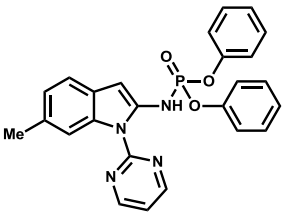
Methyl 2-((diphenoxyphosphoryl)amino)-1-(pyrimidin-2-yl)-1H-indole-5-carboxylate (6ja):



colorless solid; IR (KBr) ν 3057, 2953, 1704, 1564, 1491, 1292, 970, 767, 652cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (d, *J* = 12.1 Hz, 1H), 8.60 -8.53 (m, 3H), 8.13 (d, *J* = 1.8 Hz, 1H), 7.81 (dd, *J* = 9.0, 1.8 Hz, 1H), 7.25 -7.16 (m, 8H), 7.09 -7.05 (m, 2H), 7.03 (t, *J* = 4.9 Hz, 1H), 6.50 (s, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 158.1, 157.7, 150.1 (d, *J* = 7.2 Hz), 137.6 (d, *J* = 7.2 Hz), 135.7, 129.8, 129.0, 125.5, 124.8, 123.3, 120.9, 120.3 (d, *J* = 4.5 Hz), 116.9, 115.6, 92.0, 51.9; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.36; HRMS (ESI): *m/z*

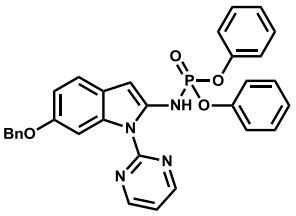
calculated for $C_{26}H_{21}N_4NaO_5P^+$ [M+Na^+] : 523.1142, found: 523.1125.

Diphenyl (6-methyl-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ka):



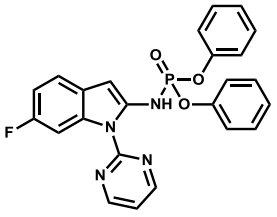
colorless solid; IR (KBr) ν 3063, 2915, 1577, 1428, 1284, 1185, 954, 813, 691 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.17 (d, *J* = 12.6 Hz, 1H), 8.55 (d, *J* = 4.9 Hz, 2H), 8.35 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.22 -7.14 (m, 8H), 7.08 -7.03 (m, 2H), 7.00 -6.97 (m, 1H), 6.94 (t, *J* = 4.9 Hz, 1H), 6.41 (s, 1H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.5, 150.2 (d, *J* = 7.2 Hz), 135.7 (d, *J* = 7.2 Hz), 133.3, 131.7, 129.7, 126.9, 125.3, 124.3, 120.5 (d, *J* = 4.5 Hz), 118.7, 116.1, 116.0, 92.1, 22.0; ^{31}P NMR (158 MHz, $CDCl_3$) δ -8.80; HRMS (ESI): *m/z* calculated for $C_{25}H_{21}N_4NaO_3P^+$ [M+Na^+] : 479.1243, found: 479.1241.

Diphenyl (6-(benzyloxy)-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate(6la):



yellow solid; IR (KBr) ν 3061, 2905, 1578, 1416, 1281, 1158, 953, 775, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (d, *J* = 14.1 Hz, 1H), 8.52 (d, *J* = 4.6 Hz, 2H), 8.30 (d, *J* = 2.3 Hz, 1H), 7.41 (brd, *J* = 7.5 Hz, 2H), 7.32 -7.27 (m, 3H), 7.25 -7.16 (m, 9H), 7.08 -7.02 (m, 2H), 6.94 (t, *J* = 4.6 Hz, 1H), 6.88 (dd, *J* = 8.6, 2.3 Hz, 1H), 6.38 (s, 1H), 5.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.5, 155.2, 150.2 (d, *J* = 7.2 Hz), 137.5, 135.4 (d, *J* = 6.0 Hz), 133.8, 129.7, 128.5, 127.8, 127.6, 125.3, 123.3, 120.4 (d, *J* = 4.8 Hz), 119.2, 116.1, 111.5, 103.3, 92.1, 70.8; ^{31}P NMR (158 MHz, $CDCl_3$) δ -8.83; HRMS (ESI): *m/z* calculated for $C_{31}H_{25}N_4NaO_4P^+$[M+Na^+] : 571.1506, found: 571.1531.

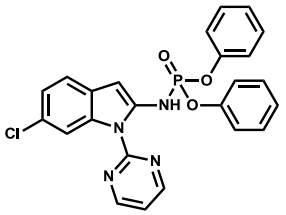
Diphenyl (6-fluoro-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ma):



colorless solid; IR (KBr) ν 3065, 2911, 1577, 1496, 1283, 1197, 969, 809, 687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.22 (d, *J* = 12.1 Hz, 1H), 8.56 (d, *J* = 4.9 Hz, 2H), 8.35 (dd, *J* = 11.2, 2.2 Hz, 1H), 7.33 -7.28 (m, 1H), 7.24 -7.16 (m, 8H), 7.09 -7.04 (m, 2H), 6.99 (t, *J* = 4.9 Hz, 1H), 6.94 -6.88 (m, 1H), 6.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (d, *J* = 234.7 Hz), 158.2, 157.6,

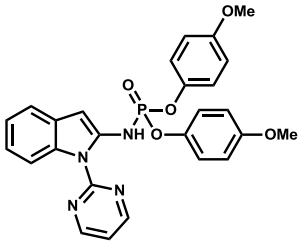
150.2 (d, *J* = 6.3 Hz), 136.7 (d, *J* = 3.6 Hz), 136.6 (d, *J* = 3.6 Hz), 132.9 (d, *J* = 12.6 Hz), 129.7, 125.4, 120.4 (d, *J* = 4.5 Hz), 119.2 (d, *J* = 9.9 Hz), 116.5, 110.8 (d, *J* = 23.4 Hz), 103.8 (d, *J* = 29.7 Hz), 91.7; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.11; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}FN_4NaO_3P^+$[M+Na^+] : 483.0993, found: 483.0976.

Diphenyl (6-chloro-1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6na):



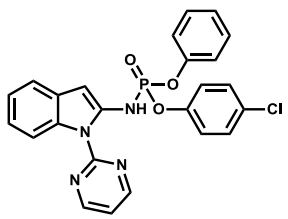
colorless solid; IR (KBr) ν 3054, 2919, 1577, 1496, 1281, 1194, 953, 770, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.31 (d, *J* = 12.1 Hz, 1H), 8.61 (d, *J* = 1.8 Hz, 1H), 8.57 (d, *J* = 4.9 Hz, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 7.24 -7.16 (m, 8H), 7.14 -7.11 (m, 1H), 7.10 -7.05 (m, 2H), 7.01 (t, *J* = 4.9 Hz, 1H), 6.41 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 157.6, 150.1 (d, *J* = 7.2 Hz), 137.1 (d, *J* = 7.2 Hz), 133.2, 129.8, 127.8, 127.3, 125.4, 123.4, 120.4 (d, *J* = 4.5 Hz), 119.5, 116.6, 116.3, 91.6; ^{31}P NMR (158 MHz, $CDCl_3$) δ -9.22; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}ClN_4NaO_3P^+$[M+$Na^+$] : 499.0697, found: 499.0694.

Bis(4-methoxyphenyl) (1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ab):



colorless solid; IR (KBr) ν 3080, 2935, 1600, 1457, 1285, 1184, 955, 828, 743 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (d, *J* = 12.1 Hz, 1H), 8.56 -8.52 (m, 3H), 7.42 (dd, *J* = 6.3, 1.8 Hz, 1H), 7.17 -7.07 (m, 6H), 6.95 (t, *J* = 4.9 Hz, 1H), 6.72 -6.67 (m, 4H), 6.43 (s, 1H), 3.64 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 157.5, 156.9, 143.7 (d, *J* = 6.3 Hz), 136.6 (d, *J* = 6.3 Hz), 133.0, 129.3, 123.0, 121.8, 121.3 (d, *J* = 4.5 Hz), 119.0, 116.2, 115.9, 114.6, 91.9, 55.5; ^{31}P NMR (158 MHz, $CDCl_3$) δ -7.80; HRMS (ESI): *m/z* calculated for $C_{26}H_{23}N_4NaO_5P^+$ [M+Na^+] : 525.1298, found: 525.1319.

4-chlorophenyl phenyl (1-(pyrimidin-2-yl)-1H-indol-2-yl)phosphoramidate (6ac):



yellow oil; IR (neat) ν 3057, 1583, 1485, 1427, 1352, 1190, 944, 747 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.32 (d, *J* = 12.1 Hz, 1H), 8.59 -8.45 (m, 3H), 7.45 -7.36 (m, 1H), 7.25 -7.01 (m,

11H)，6.90 (td, J = 4.9, 1.3 Hz, 1H), 6.41 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.3, 157.4, 150.0 (d, J = 7.2 Hz), 148.6 (d, J = 7.2 Hz), 136.1 (d, J = 7.2 Hz), 133.0, 130.7, 129.7, 129.7, 129.1, 125.5, 123.1, 122.0, 121.8 (d, J = 3.6 Hz), 120.3 (d, J = 4.8 Hz), 119.0, 116.2, 116.0, 92.1; ^{31}P NMR (158 MHz, $CDCl_3$) δ -8.87; HRMS (ESI): *m/z* calculated for $C_{24}H_{18}ClN_4NaO_3P^+$ [M+Na^+] : 499.0697, found: 499.0686.

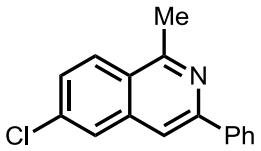
3. Regioselectivity in Cp*Co^{III} vs Cp*Rh^{III} Catalyzed C-H Activation: Isoquinoline Synthesis from *O*-Acyloximes and Terminal Alkynes

General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on JEOL JNM-ECX500 spectrometers, operating at 500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR or JNM-ECS400 spectrometers, operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. All spectra were obtained at ambient temperature. The chemical shifts (δ) were recorded in parts per million (ppm). The coupling constants (*J*) were shown in Hertz (Hz). Chemical shifts in $CDCl_3$ were reported the residual $CHCl_3$ (7.24 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR). ESI mass spectra for HRMS were measured on a JEOL JMS-T100LC AccuTOF spectrometer. Anhydrous 1,2-dichloroethane(DCE) was purchased from Aldrich and stored over molecular sieves under argon. Cp*Co(CO)I_2 was prepared by following the same procedure as described in the literature.[11] (E)-acetophenone *O*-acetyl oxime derivatives **7** and **10** were prepared by following the same procedure as described in the literature.[12] Terminal alkynes(Aldrich or TCI) **8** were used without purification.

General Procedure of Co-catalyzed Oxidative C-H bond Functionalization:

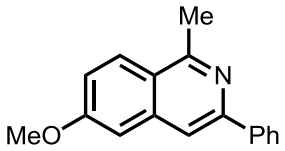
To a dried screw-capped vial was added (E)-acetophenone O-acetyl oxime **7 or 10** (0.15 mmol), alkyne **8** (0.18 mmol), Cp*Co(CO)I_2 (7.2 mg, 15 μmol), $AgSbF_6$ (10.2 mg, 30 μmol), KOAc (3.0 mg, 30 μmol), and 1,2-dichloroethane (2.25 mL) under Ar atmosphere. The vial was capped, and the mixture was heated at 120 °C for 24 h with stirring. The resulting mixture was cooled to room temperature, and directly purified by silica gel column chromatography (hexane:ethyl acetate = 20:1 for all compounds) to give product **9 or 11(12)**.

6-chloro-1-methyl-3-phenylisoquinoline (9aa):



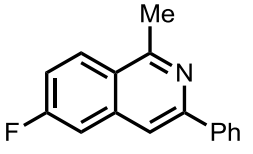
yellow solid; IR (KBr) ν 3036, 2925, 1725, 1615, 1566, 1384, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12-8.07 (m, 2H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.81-7.76 (m, 2H), 7.51-7.43 (m, 3H), 7.42-7.36 (m, 1H), 2.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ158.6, 151.2, 139.4, 137.7, 136.1, 128.8, 128.6, 127.6, 127.4, 127.0, 126.3, 124.8, 114.2, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{12}ClNNa^+$ [M+Na^+] : 276.0550, found: 276.0535.

6-methoxy-1-methyl-3-phenylisoquinoline (9ba):



yellow solid; IR (KBr) ν 3054, 2961, 1615, 1497, 1371, 1235, 1147 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12-8.07 (m, 2H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.81 (s, 1H), 7.50-7.44 (m, 2H), 7.40-7.35 (m, 1H), 7.17 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 3.94 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ160.6, 157.9, 150.7, 140.0, 138.8, 128.7, 128.2, 127.4, 127.0, 122.2, 119.4, 114.8, 105.2, 55.4, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{15}NNaO^+$ [M+Na^+] : 272.1046, found: 272.1045.

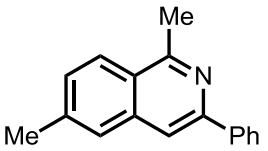
6-fluoro-1-methyl-3-phenylisoquinoline (9ca):



yellow oil; IR (neat) ν 3062, 1628, 1573, 1503, 1419, 1227, 1135 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14-8.08 (m, 3H), 7.84 (s, 1H), 7.51-7.46 (m, 2H), 7.44-7.37 (m, 2H), 7.32-7.26 (m, 1H), 3.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.1 (d, *J* = 249.2 Hz), 158.5, 151.0,

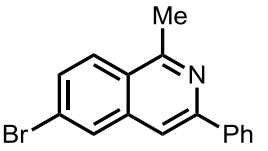
139.4, 138.5, 128.7, 128.7 (d, J = 9.5 Hz), 128.6, 127.0, 123.8, 116.9 (d, J = 25.0 Hz), 114.8 (d, J = 6.0 Hz), 110.7 (d, J = 20.3 Hz), 22.8; HRMS (ESI): m/z calculated for $C_{16}H_{12}FNNa^+$ [M+Na^+] : 260.0846, found: 260.0847.

1,6-dimethyl-3-phenylisoquinoline (9da):



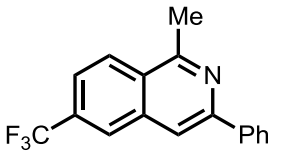
yellow solid; IR (KBr) ν 3062, 2918, 1628, 1495, 1441, 1216 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, J = 8.6 Hz, 2H), 8.00 (d, J = 8.6 Hz, 1H), 7.82 (s, 1H), 7.60 (s, 1H), 7.49-7.46 (m, 2H), 7.40-7.35 (m, 2H), 2.99 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.2, 150.1, 140.2, 140.0, 137.1, 129.0, 128.7, 128.2, 126.9, 126.6, 125.5, 125.0, 114.8, 22.6, 21.8; HRMS (ESI): m/z calculated for $C_{17}H_{15}NNa^+$ [M+Na^+] : 256.1097, found: 256.1104.

6-bromo-1-methyl-3-phenylisoquinoline (9ea):



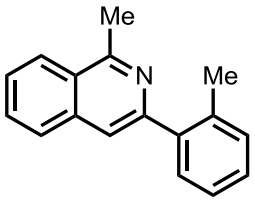
yellow solid; IR (KBr) ν 2922, 1736, 1610, 1565, 1382, 1360, 1769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 2H), 7.99 (s, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.79 (s, 1H), 7.60 (dd, J = 8.6, 1.7 Hz, 1H), 7.50-7.47 (m, 2H), 7.40 (t, J = 7.5 Hz, 1H), 2.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 151.1, 139.4, 138.0, 130.1, 129.6, 128.8, 128.7, 127.4, 127.0, 124.9, 124.7, 114.0, 22.6; HRMS (ESI): m/z calculated for $C_{16}H_{12}BrNNa^+$ [M+Na^+] : 320.0045, found: 320.0031.

1-methyl-3-phenyl-6-(trifluoromethyl)isoquinoline (9fa):



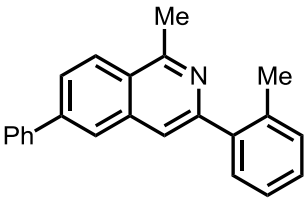
yellow solid; IR (KBr) ν 3074, 2925, 1733, 1595, 1444, 1339, 1182 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.22 (d, J = 8.6 Hz, 1H), 8.16-8.11 (m, 3H), 7.97 (s, 1H), 7.70 (dd, J = 8.6, 1.8 Hz, 1H), 7.53-7.47 (m, 2H), 7.44-7.39 (m, 1H), 3.05 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 151.4, 139.1, 136.0, 131.7 (q, J = 33.2 Hz), 128.8, 128.8, 127.3, 127.0, 126.9, 125.3 (q, J = 4.8 Hz), 123.8 (q, J = 271.8 Hz), 122.3 (q, J = 2.4 Hz), 115.4, 22.7; HRMS (ESI): m/z calculated for $C_{17}H_{12}F_3NNa^+$ [M+Na^+] : 310.0814, found: 310.0812.

1-methyl-3-(o-tolyl)isoquinoline (9gb):



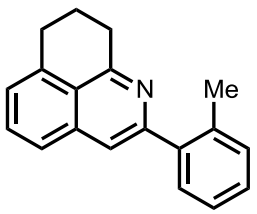
yellow oil; IR (neat) ν 3055, 2921, 1621, 1567, 1497, 1445, 1330, 1145 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.69-7.66 (m, 1H), 7.62-7.57 (m, 2H), 7.50-7.45 (m, 1H), 7.33-7.25 (m, 3H), 3.01 (s, 3H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.9, 152.6, 140.8, 136.3, 136.1, 130.7, 129.9, 127.9, 127.4, 126.8, 126.0, 125.8, 125.6, 118.7, 22.5, 20.5; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{15}NNa^+$ [M+Na^+] : 256.1097, found: 256.1104.

1-methyl-6-phenyl-3-(o-tolyl)isoquinoline (9hb):



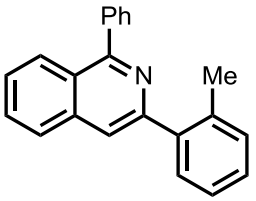
yellow solid; IR (KBr) ν 3023, 2945, 1737, 1621, 1445, 1358, 1068 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.2 Hz, 1H), 8.00 (d, *J* = 1.2 Hz, 1H), 7.85 (dd, *J* = 9.2, 1.2 Hz, 1H), 7.76-7.71 (m, 2H), 7.62 (s, 1H), 7.53-7.48 (m, 3H), 7.44-7.40 (m, 1H), 7.32-7.26 (m, 3H), 3.03 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 153.0, 142.6, 140.8, 140.2, 136.7, 136.1, 130.7, 129.9, 129.0, 128.1, 128.0, 127.5, 126.5, 126.2, 125.9, 125.1, 118.9, 22.5, 20.5; HRMS (ESI): *m*/*z* calculated for $C_{23}H_{19}NNa^+$ [M+Na^+] : 332.1410, found: 332.1398.

2-(o-tolyl)-8,9-dihydro-7H-benzo[de]quinoline (9ib):



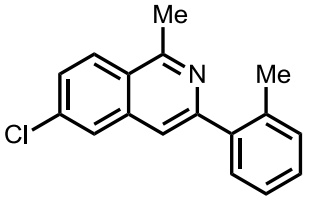
yellow solid; IR (KBr) ν 3049, 2952, 1615, 1577, 1448, 1326, 1158 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.56-7.49 (m, 2H), 7.46-7.42 (m, 1H), 7.29 (d, *J* = 6.9 Hz, 1H), 7.27-7.20 (m, 3H), 3.28 (t, *J* = 6.3 Hz, 2H), 3.12 (t, *J* = 5.7 Hz, 2H), 2.37 (s, 3H), 2.21 (tt, *J* = 6.3, 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.6, 152.6, 141.0, 138.7, 136.5, 136.1, 130.6, 130.0, 130.0, 127.8, 125.8, 124.7, 124.5, 123.8, 118.4, 34.4, 30.5, 23.3, 20.5; HRMS (ESI): *m*/*z* calculated for $C_{19}H_{17}NNa^+$ [M+Na^+] : 282.1253, found: 282.1260.

1-phenyl-3-(o-tolyl)isoquinoline (9gb):



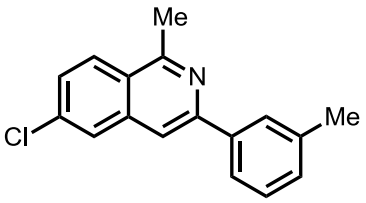
yellow solid; IR (KBr) ν 3054, 2973, 1618, 1558, 1383, 1335 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.6 Hz, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.79-7.73 (m, 3H), 7.71-7.68 (m, 1H), 7.59-7.45 (m, 5H), 7.33-7.26 (m, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 153.0, 140.6, 139.7, 137.4, 136.3, 130.7, 130.1, 130.0, 128.5, 128.3, 128.0, 127.5, 127.2, 127.0, 125.8, 125.2, 119.4, 20.7; HRMS (ESI): *m*/*z* calculated for $C_{22}H_{17}NNa^+$ [M+Na^+] : 318.1253, found: 318.1263.

6-chloro-1-methyl-3-(o-tolyl)isoquinoline (9ab):



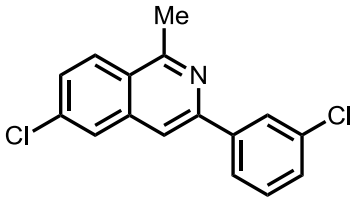
yellow solid; IR (KBr) ν 3062, 2925, 1612, 1492, 1358, 1180, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 9.2 Hz, 1H), 7.79 (d, *J* = 2.3 Hz, 1H), 7.51 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.48 (s, 1H), 7.47-7.43 (m, 1H), 7.32-7.25 (m, 3H), 2.98 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 153.8, 140.3, 137.3, 136.2, 136.1, 130.8, 129.9, 128.2, 127.7, 127.4, 126.1, 125.9, 124.2, 117.8, 22.5, 20.4; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{14}ClNNa^+$ [M+Na^+] : 290.0707, found: 290.0707.

6-chloro-1-methyl-3-(m-tolyl)isoquinoline (9ac):



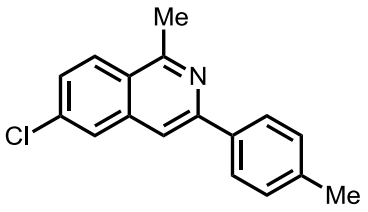
yellow solid; IR (KBr) ν 3069, 2919, 1725, 1614, 1566, 1383, 1083 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 9.2 Hz, 1H), 7.94 (s, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.81-7.77 (m, 2H), 7.46 (dd, *J* = 9.2, 2.3 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 2.99 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 151.3, 139.3, 138.4, 137.7, 136.1, 129.4, 128.7, 127.7, 127.5, 127.4, 126.2, 124.7, 124.1, 114.2, 22.6, 21.6; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{14}ClNNa^+$ [M+Na^+] : 290.0707, found: 290.0707.

6-chloro-3-(3-chlorophenyl)-1-methylisoquinoline (9ad):



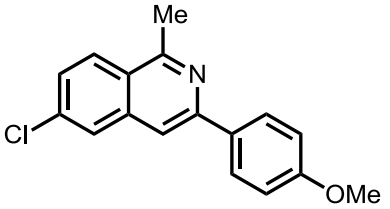
yellow solid; IR (KBr) ν 3067, 2925, 1615, 1569, 1433, 1390, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.03 (d, *J* = 8.6 Hz, 1H), 7.96 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 1.8 Hz, 1H), 7.78 (s, 1H), 7.49 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 149.6, 141.2, 137.5, 136.4, 134.8, 129.9, 128.6, 128.0, 127.4, 127.2, 126.3, 125.0, 125.0, 114.5, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{11}Cl_2NNa^+$ [M+Na^+] : 310.0161, found: 310.0165.

6-chloro-1-methyl-3-(p-tolyl)isoquinoline (9ae):



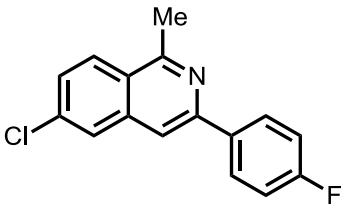
yellow solid; IR (KBr) ν 2918, 1720, 1614, 1568, 1439, 1178, 1085 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07-7.79 (m, 3H), 7.83-7.74 (m, 2H), 7.44 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 2.98 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 151.1, 138.6, 137.7, 136.5, 136.0, 129.5, 127.4, 126.8, 126.2, 124.6, 113.7, 22.6, 21.3; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{14}ClNNa^+$ [M+Na^+] : 290.0707, found: 290.0707.

6-chloro-3-(4-methoxyphenyl)-1-methylisoquinoline (9af):



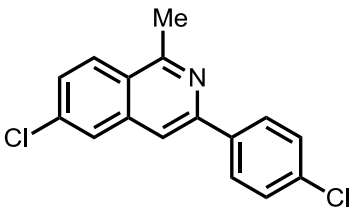
colorless solid; IR (KBr) ν 3066, 2961, 1606, 1509, 1395, 1245, 1172 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.07-8.03 (m, 2H), 8.00 (d, *J* = 9.2 Hz, 1H), 7.77 (d, *J* = 1.8 Hz, 1H), 7.71 (s, 1H), 7.43 (dd, *J* = 9.2, 1.8 Hz, 1H), 7.03-6.98 (m, 2H), 3.86 (s, 3H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 158.4, 150.9, 137.8, 136.1, 132.0, 128.2, 127.4, 127.2, 126.1, 124.4, 114.2, 113.1, 55.4, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{14}ClNNaO^+$ [M+Na^+] : 306.0656, found: 306.0673.

6-chloro-3-(4-fluorophenyl)-1-methylisoquinoline (9ag):



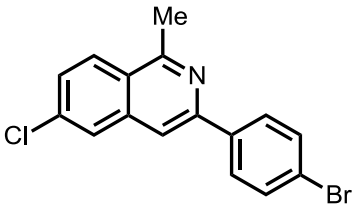
yellow solid; IR (KBr) ν 3046, 2926, 1615, 1509, 1387, 1224, 1085 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.10-8.05 (m, 2H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 1.8 Hz, 1H), 7.73 (s, 1H), 7.46 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.18-7.13 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, *J* = 245.6 Hz), 158.7, 150.1, 137.7, 136.3, 135.5 (d, *J* = 3.6 Hz), 128.7 (d, *J* = 8.4 Hz), 127.7, 127.4, 126.2, 124.7, 115.6 (d, *J* = 21.5 Hz), 113.8, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{11}ClFNNa^+$ [M+Na^+] : 294.0456, found: 294.0470.

6-chloro-3-(4-chlorophenyl)-1-methylisoquinoline (9ah):



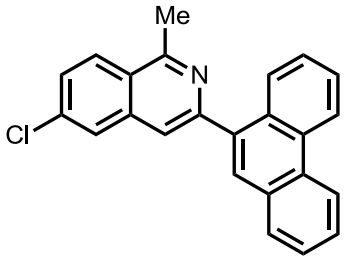
yellow solid; IR (KBr) ν 2921, 1614, 1566, 1492, 1384, 1087 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 8.07-7.97 (m, 3H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.76 (s, 1H), 7.50-7.39 (m, 3H), 2.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 149.8, 137.8, 137.6, 136.3, 134.7, 128.9, 128.2, 127.9, 127.4, 126.3, 124.8, 114.1, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{11}Cl_2NNa^+$ [M+Na^+] : 310.0161, found: 310.0155.

3-(4-bromophenyl)-6-chloro-1-methylisoquinoline (9ai):



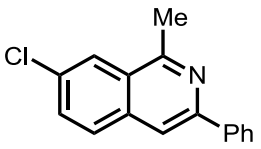
yellow solid; IR (KBr) ν 3061, 2952, 1616, 1489, 1415, 1175, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.5 Hz, 1H), 8.00-7.95 (m, 2H), 7.79 (d, *J* = 1.8 Hz, 1H), 7.76 (s, 1H), 7.62-7.55 (m, 2H), 7.48 (dd, *J* = 8.5, 1.8 Hz, 1H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 149.8, 138.2, 137.6, 136.4, 131.8, 128.5, 127.9, 127.4, 126.3, 124.9, 123.0, 114.1, 22.6; HRMS (ESI): *m*/*z* calculated for $C_{16}H_{11}BrClNNa^+$ [M+Na^+] : 353.9656, found: 353.9658.

6-chloro-1-methyl-3-(phenanthren-9-yl)isoquinoline (9aj):



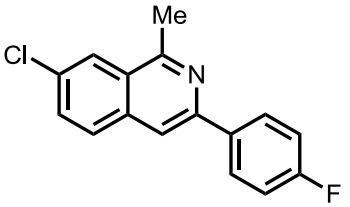
yellow solid; IR (KBr) ν 3062, 1613, 1565, 1390, 1356, 1086 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 8.0 Hz, 1H), 8.72 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 9.2 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.92 (d, *J* = 7.5 Hz, 1H), 7.90 (s, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.74 (s, 1H), 7.70-7.64 (m, 2H), 7.62 (d, *J* = 7.5 Hz, 1H), 7.60-7.56 (m, 1H), 7.56-7.51 (m, 1H), 3.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 153.1, 137.5, 137.2, 136.4, 131.5, 130.9, 130.7, 130.5, 129.0, 128.7, 128.0, 127.5, 127.0, 126.8, 126.8, 126.6, 126.6, 126.2, 124.7, 122.9, 122.6, 119.1, 22.6; HRMS (ESI): *m/z* calculated for $C_{24}H_{16}ClNNa^+$ [M+Na^+] : 376.0863, found: 376.0861.

7-chloro-1-methyl-3-phenylisoquinoline (11aa):



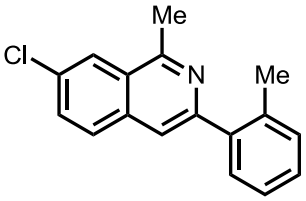
yellow solid; IR (KBr) ν 2920, 1562, 1496, 1439, 1384, 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.13-8.06 (m, 3H), 7.87 (s, 1H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.59 (dd, *J* = 9.0, 2.2 Hz, 1H), 7.51-7.45 (m, 2H), 7.42-7.36 (m, 1H), 2.99 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.7, 150.4, 139.4, 135.1, 132.2, 130.9, 129.2, 128.8, 128.5, 127.1, 126.9, 124.8, 114.7, 22.6; HRMS (ESI): *m/z* calculated for $C_{16}H_{12}ClNNa^+$ [M+Na^+] : 276.0550, found: 276.0543.

7-chloro-3-(4-fluorophenyl)-1-methylisoquinoline (11ab):



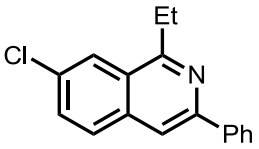
yellow solid; IR (KBr) ν 3052, 2925, 1735, 1566, 1511, 1227, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13-8.04 (m, 3H), 7.80 (s, 1H), 7.75 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.20-7.12 (m, 2H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, *J* = 245.6 Hz), 157.8, 149.4, 135.5 (d, *J* = 2.4 Hz), 135.0, 132.2, 131.0, 129.1, 128.6 (d, *J* = 8.3 Hz), 127.0, 124.7, 115.6 (d, *J* = 21.5 Hz), 114.3, 22.6; HRMS (ESI): *m/z* calculated for $C_{16}H_{11}ClFNNa^+$ [M+Na^+] : 294.0456, found: 294.0470.

7-chloro-1-methyl-3-(o-tolyl)isoquinoline (11ac):



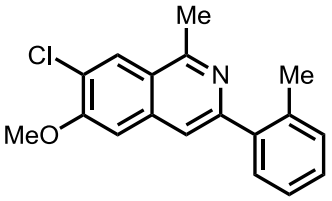
yellow solid; IR (KBr) ν 3016, 2953, 1737, 1561, 1492, 1382, 1090 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 1.7 Hz, 1H), 7.76 (d, *J*= 8.6 Hz, 1H), 7.61 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.55 (s, 1H), 7.47-7.44 (m, 3H), 7.31-7.25 (m, 3H), 2.97 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 153.0, 140.3, 136.1, 134.6, 132.3, 130.9, 130.8, 129.9, 129.0, 128.1, 126.6, 125.9, 124.7, 118.3, 22.4, 20.5; HRMS (ESI): *m/z* calculated for $C_{17}H_{14}ClNNa^+$ [M+Na^+] : 290.0707, found: 290.0706.

7-chloro-1-ethyl-3-phenylisoquinoline (11ba):



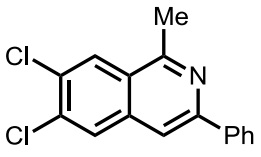
yellow solid; IR (KBr) ν 3051, 2932, 1747, 1566, 1426, 1297, 1089 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17-8.13 (m, 2H), 8.12-8.10 (m, 1H), 7.87 (s, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 7.57 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.51-7.46 (m, 2H), 7.42-7.36 (m, 1H), 3.33 (d, *J* = 7.5 Hz, 2H), 1.52 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 150.1, 139.5, 135.3, 132.1, 130.7, 129.4, 128.7, 128.5, 126.9, 126.4, 124.3, 114.3, 28.3, 13.1; HRMS (ESI): *m/z* calculated for $C_{17}H_{14}ClNNa^+$ [M+Na^+] : 290.0707, found: 290.0707.

7-chloro-6-methoxy-1-methyl-3-(o-tolyl)isoquinoline (11cc):



yellow solid; IR (KBr) ν 2966, 1619, 1563, 1485, 1401, 1247, 1042 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.13 (s, 1H), 7.47-7.42 (m, 2H), 7.31-7.25 (m, 3H), 7.10 (s, 1H), 4.02 (s, 3H), 2.92 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.5, 156.2, 153.5, 140.6, 136.8, 136.1, 130.7, 129.8, 128.0, 127.0, 125.9, 124.3, 121.6, 117.7, 105.9, 56.3, 22.3, 20.4; HRMS (ESI): *m/z* calculated for $C_{18}H_{16}ClNNaO^+$ [M+Na^+] : 320.0813, found: 320.0803.

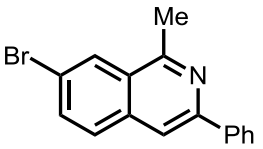
6,7-dichloro-1-methyl-3-phenylisoquinoline (11da):



colorless solid; IR (KBr) ν 3064, 2925, 1725, 1610, 1465, 1384, 1128 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 8.09 (d, *J* = 8.0 Hz, 2H), 7.93 (s, 1H), 7.77 (s, 1H), 7.52-7.45 (m, 2H),

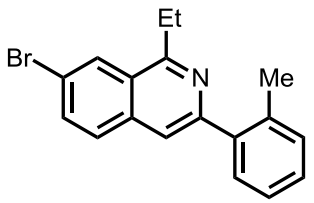
7.43-7.38 (m, 1H), 2.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 151.3, 139.0, 135.9, 134.9, 130.8, 128.8, 128.8, 128.5, 127.1, 127.0, 125.4, 113.5, 22.6; HRMS (ESI): *m/z* calculated for $C_{16}H_{11}Cl_2NNa^+$ [M+Na^+] : 310.0161, found: 310.0155.

7-bromo-1-methyl-3-phenylisoquinoline (11ea):



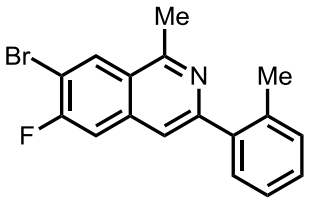
yellow oil; IR (neat) ν 3040, 2905, 1561, 1496, 1414, 1372, 1309, 1080 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 8.13-8.08 (m, 2H), 7.85 (s, 1H), 7.74-7.67 (m, 2H), 7.51-7.45 (m, 2H), 7.42-7.37 (m, 1H), 2.98 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 150.5, 139.4, 135.2, 133.4, 129.3, 128.8, 128.6, 128.1, 127.5, 126.9, 120.3, 114.7, 22.6; HRMS (ESI): *m/z* calculated for $C_{16}H_{12}BrNNa^+$ [M+Na^+] : 320.0045, found: 320.0045.

7-bromo-1-ethyl-3-(o-tolyl)isoquinoline (11fc):



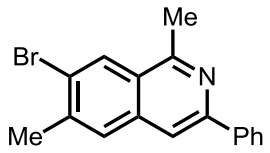
yellow solid; IR (KBr) ν 3042, 2990, 1735, 1566, 1379, 1144, 1083 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.75-7.68 (m, 2H), 7.55 (s, 1H), 7.50-7.47 (m, 1H), 7.33-7.26 (m, 3H), 3.33 (q, *J* = 8.0 Hz, 2H), 2.42 (s, 3H), 1.49-1.44 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.5, 153.2, 140.4, 136.3, 135.2, 133.2, 130.9, 129.9, 129.3, 128.1, 127.6, 126.2, 125.9, 120.4, 118.2, 28.4, 20.6, 13.6; HRMS (ESI): *m/z* calculated for $C_{18}H_{16}BrNNa^+$ [M+Na^+] : 348.0358, found: 348.0351.

7-bromo-6-fluoro-1-methyl-3-(o-tolyl)isoquinoline (11gc):



yellow oil; IR (neat) ν 3061, 2947, 1611, 1559, 1392, 1214, 1121 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, *J* = 6.9 Hz, 1H), 7.51-7.46 (m, 2H), 7.44 (d, *J* = 6.9 Hz, 1H), 7.32-7.25 (m, 3H), 2.96 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2 (d, *J* = 250.4 Hz), 157.0, 154.1, 140.1, 136.9 (d, *J* = 8.4 Hz), 136.1, 131.5, 130.8, 129.8, 128.3, 126.0, 124.0, 118.0 (d, *J* = 4.8 Hz), 111.8 (d, *J* = 21.5 Hz), 110.0 (d, *J* = 23.8 Hz), 22.6, 20.4; HRMS (ESI): *m/z* calculated for $C_{17}H_{13}BrFNNa^+$ [M+Na^+] : 352.0108, found: 352.0115.

7-bromo-1,6-dimethyl-3-phenylisoquinoline (11ha):

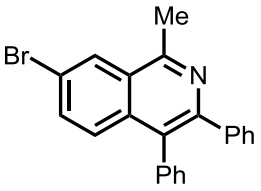


colorless solid; IR (KBr) ν 3057, 1615, 1569, 1475, 1385, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 8.11-8.08 (m, 2H), 7.78 (s, 1H), 7.67 (s, 1H), 7.47 (t, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 2.95 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.3, 150.4, 140.2, 139.6, 135.9, 128.9, 128.7, 128.4, 128.4, 126.9, 126.2, 124.0, 114.2, 23.5, 22.5; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{14}BrNNa^+$ [M+Na^+] : 334.0202, found: 334.0206.

Co-catalyzed Oxidative C-H bond Functionalization with internal alkyne:

To a dried screw-capped vial was added (E)-1-(3-bromophenyl)ethanone *O*-acetyl oxime **10e** (0.10 mmol), 1,2-diphenylethyne **8k** (0.15 mmol), Cp*Co(CO)I_2 (4.8 mg, 10 μmol), $AgSbF_6$ (6.8 mg, 20 μmol), CsOAc (3.8 mg, 20 μmol), and 1,2-dichloroethane (0.5 mL) under Ar atmosphere. The vial was capped, and the mixture was heated at 80 °C for 24 h with stirring. The resulting mixture was cooled to room temperature, and directly purified by silica gel column chromatography to give product **11ek**.

7-bromo-1-methyl-3,4-diphenylisoquinoline (11ek):



colorless solid; IR (KBr) ν 3060, 2954, 1544, 1496, 1380, 1316, 1073 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, *J* = 1.7 Hz, 1H), 7.62 (dd, *J* = 9.2, 1.7 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.37-7.29 (m, 5H), 7.21-7.14 (m, 5H), 3.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 149.8, 140.6, 137.0, 134.6, 133.2, 131.3, 130.2, 129.0, 128.3, 128.2, 127.8, 127.6, 127.4, 127.2, 127.1, 120.5, 22.7; HRMS (ESI): *m/z* calculated for $C_{22}H_{16}BrNNa^+$ [M+Na^+] : 396.0358, found: 396.0374.

H/D-Exchange Experiments

To a dried screw-capped vial was added (E)-1-(3-chlorophenyl)ethanone *O*-acetyl oxime (31.7 mg, 0.15 mmol), CD_3CO_2D (17.5 μL, 0.30 mmol), Cp*Co(CO)I_2 (7.2 mg, 15 μmol), or [Cp*$RhCl_2$]$_2$ (4.8 mg, 7.5 μmol), $AgSbF_6$ (10.2 mg, 30 μmol), KOAc (3.0 mg, 30 μmol), and 1,2-dichloroethane (2.25 mL) under Ar atmosphere. The vial was capped, and the mixture was heated at 120 °C for 24 h with stirring. The resulting mixture was cooled to room temperature, and directly purified by silica gel column

chromatography (hexane:ethyl acetate = 6:1). Deuterium incorporation was evaluated by ^{1}H NMR analysis.

Reference for Experimental Section

[1] L. Ackermann, A. V. Lygin. *Org. Lett.* **2011**, *13*, 3332.

[2] J. Shi, B. Zhou, Y. Yang, Y. Li. *Org. Biomol. Chem*. **2012**, *10*, 8953.

[3] J. Waser, B. Gaspar, H. Nambu, E. M. Carreira. *J. Am. Chem. Soc*. **2006**, *128*, 11693.

[4] S. A. Frith, J. Spencer. *Inorganic Syntheses*. **1990**, *28*, 273.

[5] W. Li, L. Weng, G. Jin. *Inorg. Chem. Commun*. **2004**, *7*, 1174.

[6] L. Ackermann, A. V. Lygin. *Org. Lett.* **2011**, *13*, 3332.

[7] J. Shi, B. Zhou, Y. Yang, Y. Li. *Org. Biomol. Chem.* **2012**, *10*, 8953.

[8] S. H. Kim, D. Y. Jung, S. Chang. *J. Org. Chem*., **2007**, *72*, 9769.

[9] H. Kim, J. Park, J. G. Kim, S. Chang. *Org. Lett.* **2014**, *16*, 5466.

[10] S. A. Frith, J. Spencer. *Inorganic Syntheses*. **1990**, *28*, 273.

[11] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai. *Adv. Synth. Catal.* **2014**, *356*, 1491.

[12] P. C. Too, Y. F. Wang, S. Chiba. *Org. Lett*. **2010**, *12*, 5688.

Publicaition List

1. Bo Sun, Tatsuhiko Yoshino, Shigeki Matsunaga, Motomu Kanai
A Cp*CoI_2-dimer as a Precursor for Cationic Co(III)-catalysis: Application to C-H Phosphoramidation of Indoles
Chem. Commun. **2015**, *51*, 4659.

2. Bo Sun, Tatsuhiko Yoshino, Shigeki Matsunaga, Motomu Kanai
Air-Stable Carbonyl(pentamethylcyclopentadienyl)cobalt Diiodide Complex as a Precursor for Cationic (Pentamethylcyclopentadienyl)cobalt(III) Catalysis: Application for Directed C-2 Selective C-H Amidation of Indoles
Adv. Synth. Catal. **2014**, *356*, 1491.

3. Bo Sun, Tatsuhiko Yoshino, Shigeki Matsunaga, Motomu Kanai
Regioselectivity of Cp*CoIII vs Cp*RhIII Catalyzed C-H Activation: Isoquinoline Synthesis from O-Acyloximes and Terminal Alkynes
Manuscript in preparation.

4. Yudai Suzuki, Bo Sun**,** Ken Sakata, Tatsuhiko Yoshino, Shigeki Matsunaga, Motomu Kanai
Dehydrative Direct C-H Allylation with Allylic Alcohols under Cp*Co(III) Catalysis: Unique Reactivity of Cp*Co(III) over Cp*Rh(III)
Angew. Chem. Int. Ed. **2015**, *in press.*

5. Yudai Suzuki, Bo Sun, Tatsuhiko Yoshino, Shigeki Matsunaga, Motomu Kanai
Cp*Co(III)-catalyzed Oxidative C-H Alkenylation of Benzamides with Ethyl Acrylate
Tetrahedron, **2015**, *71*, 4552.

6. Hirooki Tanabe, Yingjie Xu, Bo Sun, Shigeki Matsunaga, Masakatsu Shibasaki
Direct Catalytic Asymmetric Vinylogous Michael Reaction of α,β -Unsaturated γ-Butyrolactam under Dinuclear Nickel Schiff Base Catalysis
Heterocycles. **2012**, *86*, 611.

Acknowledgement

The work described in this thesis would not have been possible without the help, the cooperation and support of many people, to whom I am deeply indebted.

First and foremost, I would like to express my sincere gratitude to my supervisor Professor Dr. Motomu Kanai for his supreme guidance for my research activities at the University of Tokyo. His enthusiasm and his intelligence toward organic chemistry impress me so much that all these will definitely influence me in the future. As an ambitious and famous organic chemist, he kindly provided me such a precious opportunity. His nice personality and great characters would also impress me forever.

Secondly, I deeply appreciate my second supervisor Professor Dr. Shigeki Matsunaga for his excellent daily supervision and kind care during 3 years of my Ph. D course study. He has a tremendous energy and excitement for new chemistry, and it’s always inspiring to be around him. It's beyond words to describe how much I have learned from him through all of our discussions, from synthesizing a simple compound to exploring new chemistry world.

Thirdly, I gratefully acknowledge other staffs in current organic synthetic lab: Assistant Professor Dr. Kounosuke Oisaki, Assistant Professor Dr. Yohei Shimizu, Dr. Youhei Sohma, Dr. Yoichiro Kuninobu and Dr. Kenzo Yamatsugu for their fruitful suggestions and kind help in many affairs. Mrs. Sayuri Moroo, the secretary in our lab, is acknowledged for her help in daily routines at lab.

I would like to thank Lecture Mrs. Mikiko Kikuchi, supervisor of the International Students Advising Room in the Department of Pharmaceutical Sciences, is also thanked for her enthusiastic help and kind care during my stay in Japan.

I would like to collectively thank all the members in Organic Synthetic Lab for making our laboratory a great working environment. There are also a number of people whom I would like to acknowledge individually: Dr. Shiliang Shi, Dr. Yingjie Xu, Dr. Yao Du, Dr. Luqing Lin, Dr. Qing Xiao, Dr. Tatsuhiko Yoshino, Mr. Yudai Suzuki, for constructive talks referred to experiment; Dr. Jizhi Ni, Mr. Xiaofeng Wei, Mr. Zhen Wang, Dr. Haiyan Zhu, Mr. Jiaan Liu, Mr. Zijia Wang, Mr. Hongliang Li, Mr. Shota Kato, Mr. Keiichi Kaneko, Kiss Kumiko Yamamoto, Mr. Hideya Ikemoto, Mr. Takahiro Shirai, Dr. Harunobu Mitsunuma, Mr. Masahiro Kojima, Dr. Prasanna Kumara Chikkade, Dr. Kyalo Stephen Kanyiva for helps in both life and research.

I particularly thank CSC (China Scholarship Council) and Japanese Government (MEXT) Scholarship for their generous financial supports.

Finally, I would like to express my sincere gratitude to my family for their endless supports and encouragements throughout my overseas study and life.