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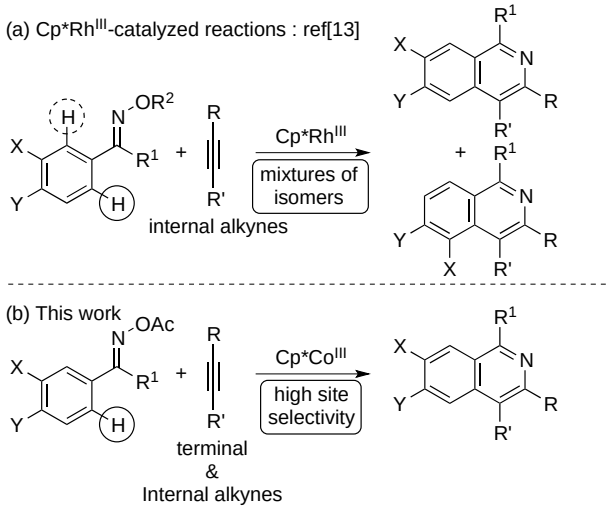
Cp*Co^{III}-Catalyzed Site-Selective C-H Activation of Unsymmetrical *O*-Acyloximes: Multi-substituted Isoquinoline Synthesis from Terminal and Internal Alkynes

Bo Sun,[a] Tatsuhiko Yoshino,[b,c] Motomu Kanai,*[a] and Shigeki Matsunaga*[b,c]

Abstract: *Cp*Co^{III}-catalyzed isoquinoline synthesis via site-selective C-H activation of O-acyloximes is described. C-H activation of various unsymmetrically substituted O-acyloximes selectively occurred at a sterically less hindered site under Cp*Co^{III} catalysis, and reactions with terminal as well as internal alkynes afforded products in up to 98% yield. The Cp*Co^{III} catalyst exhibited high site selectivity (15/1–>20/1), whereas Cp*Rh^{III} catalysts exhibited low selectivity and/or yield when unsymmetrical O-acyloximes and terminal alkynes were used. Deuterium labeling studies indicated a clear difference in the site selectivity of the C-H activation step between the Cp*Co^{III} catalyst and the Cp*Rh^{III} catalyst.*

Transition metal-catalyzed C-H bond functionalization is an atom-[1] and step-economical[2] organic transformation that has emerged over the last two decades.[3] A directing group-assisted C-H bond activation process to form metallacyclic intermediates is frequently used to realize regio- and chemoselective transformation of desired C-H bonds. Among the numerous catalysts explored in this field, Cp*Rh^{III} complexes are prominent catalysts for directing group-assisted functionalization of aromatic C-H bonds due to their high reactivity, generality, and functional group compatibility.[4] The high cost of Cp*Rh^{III} complexes, however, can be an obstacle to future large scale application for producing valuable materials and biologically active compounds. In this context, in 2013 we began to investigate Cp*Co^{III} catalysis as an inexpensive alternative to Cp*Rh^{III} catalysis.[5,6] Since then, we and other groups revealed that several Cp*Co^{III} complexes indeed catalyze various C-H bond functionalization reactions[7] that have already been established with Cp*Rh^{III} catalysts. On the other hand, reports on the unique catalytic activity of Cp*Co^{III} in comparison with Cp*Rh^{III} catalysts are still limited.[8] Our group utilized the high nucleophilicity of alkenyl-Co^{III} species in a one-pot pyrroloindolone synthesis.[8a] Glorius *et al.* also utilized the high Lewis acidity of a cationic Co^{III} to produce 6*H*-pyrido[2,1-*a*]isoquinolin-6-ones.[8b] More recently, our group[8c] and Glorius' group[8d] independently utilized the oxophilic property of Co^{III} in dehydrative C-H allylation with free allylic alcohols. Herein we describe our efforts to further explore the unique catalytic activity of Cp*Co^{III} over Cp*Rh^{III}. Cp*Co^{III} exhibited superior site selectivity in the C-H activation of unsymmetrically substituted *O*-acyloximes, producing multi-substituted isoquinolines from terminal and internal alkynes.

Isoquinoline is an important structural motif found in a series of biologically active natural products and pharmaceuticals.[9] Cyclization reactions of oxime derivatives and alkynes via C-H activation to give isoquinolines without any external oxidants[10,11] have been developed under various transition metal catalyses.[12-14] Among them, Chiba and co-workers reported a Cp*Rh^{III}-catalyzed annulation reaction of *O*-acyloximes with internal alkynes (Scheme 1a).[13a] Zhao, Jia, Li, and co-workers also reported the reaction with oximes under Cp*Rh^{III}-catalysis.[13b] The substrate scope in both cases, however, was limited to internal alkynes.[13,15] Moreover, site selectivity of the C-H activation step to form a metallacycle was also problematic when unsymmetrical *m*-substituted oxime derivatives were used as substrates. Only very limited substrates bearing methyl or alkoxy groups showed sufficient site selectivity in previous transition metal-catalyzed isoquinoline syntheses from oxime derivatives.[13,14] We hypothesized that steric repulsion between the Cp* ligand and substrates would be larger with the Cp*Co^{III} catalyst than with the Cp*Rh^{III} catalyst, because the ionic radius of cobalt is smaller than that of rhodium. Thereby, Cp*Co^{III} would efficiently differentiate the steric difference in unsymmetrical *m*-substituted oxime derivatives.



Scheme 1. Cp*Rh^{III}- and Cp*Co^{III}-catalyzed isoquinoline synthesis; site selectivity with unsymmetrical oxime derivatives and alkynes.

We optimized the reaction conditions using *m*-Cl-substituted *O*-acyloxime **1a** and a terminal alkyne **2a** as model substrates (Table 1). A cationic benzene complex, $[Cp^*Co(C_6H_6)][PF_6]_2$, combined with KOAc at 120 °C afforded the desired annulated product **3aa** and its isomer **4aa** in 46% yield and good selectivity

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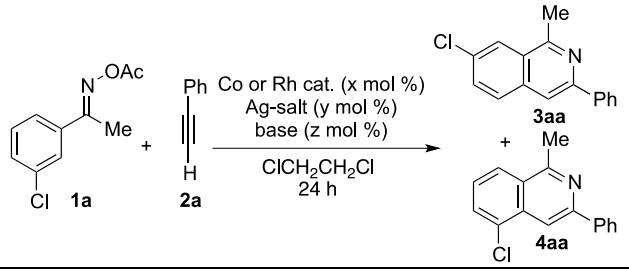
(entry 1, **3aa**:**4aa** = 14/1). The less hindered C-H bond was selectively functionalized under Cp*Co^{III} catalysis. *In situ* generation of an active catalyst using Cp*Co(CO)I_2 and cationic Ag salts showed higher reactivity (entries 2–5), and $AgSbF_6$ afforded the best result (82% isolated yield, 17/1 selectivity, entry 5). Other bases, shown in entries 6-8, were less effective. In the absence of KOAc, the yield of **3aa** decreased (entry 9, 55% yield). We also evaluated the catalytic activity of Cp*Rh^{III} catalysts under several conditions to investigate the difference between Co^{III} and Rh^{III}. The reported reaction conditions for internal alkynes using acetate bases in MeOH[13a,b] at 60–80 °C resulted in no reaction (entries 10, 11). When using $AgSbF_6$ and carboxylate/carbonate bases in 1,2-dichloroethane at 120 °C, the annulated products were obtained in 9–28% yield, but poor site selectivity in C-H activation was observed in all cases (entries 13–16).

The scope of unsymmetrically substituted *O*-acyloximes **1** is summarized in Table 2. *O*-acyloximes bearing halogen substituents at the *m*-position generally exhibited high site-selectivity, and the less hindered C-H bond was functionalized (**3aa**-**3ib**). Another substituent at the *p*-position (Y in **1**) did not affect the selectivity or reactivity (**3ca**, **3db**, **3eb**, **3fa**). Various

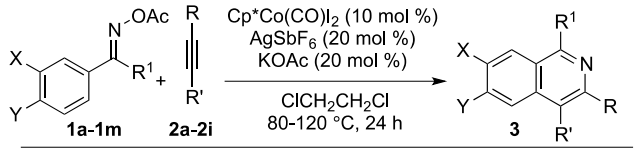
Table 1. Optimization studies and control experiments.[a]



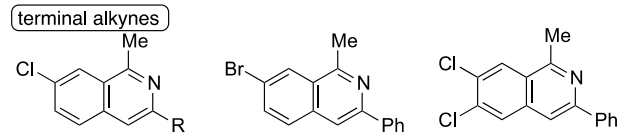
Entry	Catalyst [mol %]	Ag-salt [mol %]	Base [mol %]	*T* [°C]	Yield [%][b]	Ratio of **3**/**4**
1	$[Cp^*Co(C_6H_6)][PF_6]_2$ (10)	None	KOAc (20)	120	46	14/1
2	$Cp^*Co(CO)I_2$ (10)	$AgPF_6$ (20)	KOAc (20)	120	73	17/1
3	$Cp^*Co(CO)I_2$ (10)	$AgBF_4$ (20)	KOAc (20)	120	65	19/1
4	$Cp^*Co(CO)I_2$ (10)	$AgNTf_2$ (20)	KOAc (20)	120	70	16/1
5	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	KOAc (20)	120	82[c]	17/1
6	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	K_2CO_3 (20)	120	71	13/1
7	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	CsOAc (20)	120	63	19/1
8	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	CsOPiv (20)	120	64	17/1
9	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$ (20)	None	120	55	17/1
10[d]	$[Cp^*RhCl_2]_2$ (2.5)	None	NaOAc (30)	60	trace	N.D.
11[d]	$[Cp^*RhCl_2]_2$ (2.5)	None	CsOAc (30)	80	trace	N.D.
12	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$ (20)	KOAc (20)	80	trace	N.D.
13	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$ (20)	KOAc (20)	120	11	1/1.3
14	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$ (20)	K_2CO_3 (20)	120	9	1/1.6
15	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$ (20)	CsOAc (20)	120	28	1/1.3
16	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$ (20)	CsOPiv (20)	120	13	1/1.3

[a] Reactions were run using **1a** (0.15 mmol) and **2a** (0.18 mmol) in $ClCH_2CH_2Cl$ unless otherwise noted. [b] Combined yield of **3aa** and **4aa** determined by ^{1}H NMR analysis with an internal standard. [c] Isolated yield after silica gel column chromatography. [d] The reaction was run in MeOH (conditions reported in ref [13a,13b]).

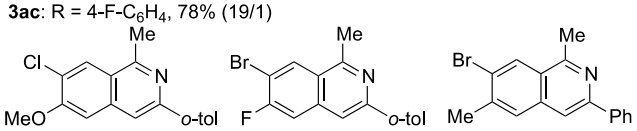
Table 2. Scope of unsymmetrical *O*-acyloximes **1**.[a]



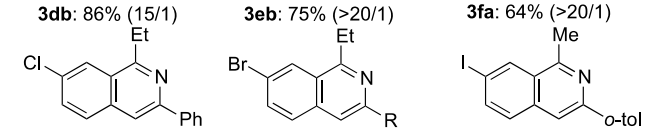
terminal alkynes



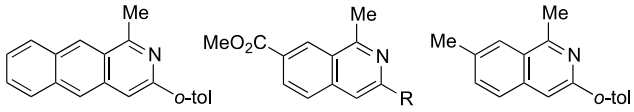
3aa: R = Ph, 82% (17/1) **3ba**: 80% (>20/1) **3ca**: 70% (>20/1)
3ab: R = *o*-tol, 90% (17/1)
3ac: R = 4-F-C_6H_4, 78% (19/1)



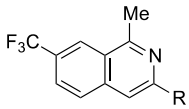
3db: 86% (15/1) **3eb**: 75% (>20/1) **3fa**: 64% (>20/1)



3ga: 86% (19/1) **3hb**: R = *o*-tol, 96% (>20/1) **3ib**: 46% (>20/1)
3hd: R = -CH_2CH_2Ph, 56% (>20/1)[b]

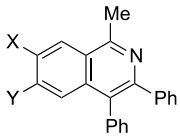


3jb: 79% (>20/1) **3kb**: R = *o*-tol, 91% (>20/1) **3lb**: 75% (>20/1)
3kd: R = -CH_2CH_2Ph, 66% (>20/1)[b]

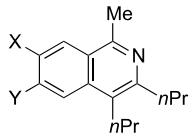


3mb: R = *o*-tol, 93% (>20/1)
3md: R = -CH_2CH_2Ph, 70% (>20/1)[b]
3me: R = *n*Pr, 88% (>20/1)[b]
3mf: R = *n*Pent, 86% (>20/1)[b]
3mg: R = *cyclo*Hex, 68% (>20/1)[b]

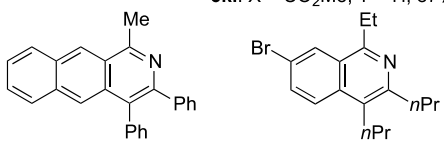
internal alkynes



3ah: X = Cl, Y = H, 94% (>20/1)[b,c]
3bh: X = Br, Y = H, 92% (>20/1)[b,c]
3ch: X = Cl, Y = Cl, 86% (>20/1)[b,d]
3fh: X = Br, Y = Me, 72% (>20/1)[b,c]
3ih: X = I, Y = H, 45% (>20/1)[b,c]
3kh: X = CO_2Me, Y = H, 90% (>20/1)[b,c]
3lh: X = Me, Y = H, 78% (>20/1)[b,d]
3mh: X = CF_3, Y = H, 97% (>20/1)[b,c]



3ai: X = Cl, Y = H, 93% (>20/1)[b,d]
3bi: X = Br, Y = H, 82% (>20/1)[b,d]
3ci: X = Cl, Y = Cl, 83% (>20/1)[b,d]
3di: X = Cl, Y = OMe, 67% (>20/1)[b,d]
3fi: X = Br, Y = Me, 75% (>20/1)[b,d]
3ki: X = CO_2Me, Y = H, 87% (>20/1)[b,d]



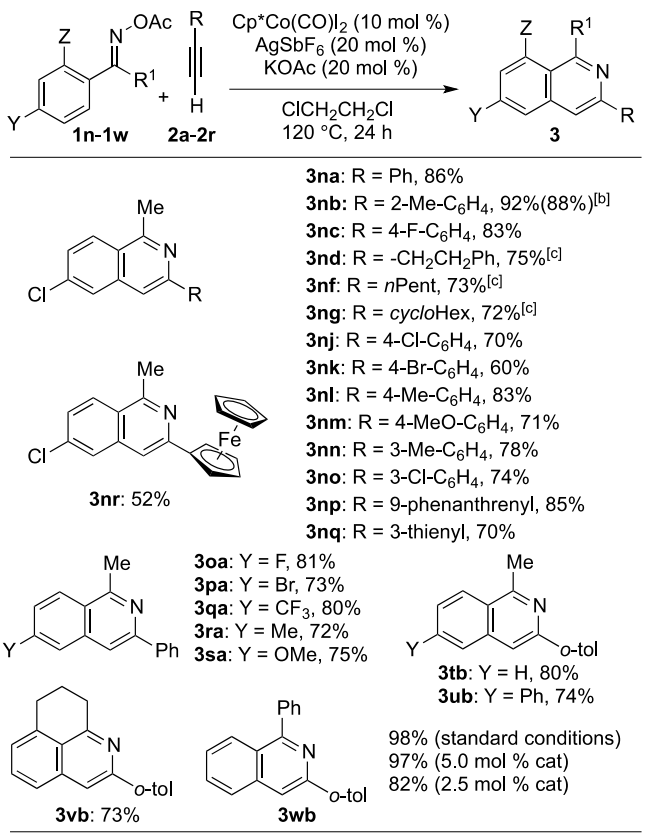
3jh: 89% (>20/1)[b,c] **3hi**: 85% (>20/1)[b,d]

[a] Reactions were run using **1** (0.15 mmol), **2** (0.18 mmol), Cp*Co(CO)I_2 (10 mol %), $AgSbF_6$ (20 mol %), and KOAc (20 mol %) in $ClCH_2CH_2Cl$ at 120 °C for 24 h unless otherwise noted. Indicated yields are combined isolated yield of **3** and its regioisomer **4**. Number in parentheses is ratio of **3**/**4** determined by ^{1}H NMR analysis of the crude mixture. [b] CsOAc (20 mol %) was used instead of KOAc. **1** (0.10 mmol) and **2** (0.15 mmol) were used. [c] Reaction was run at 80°C. [d] Reaction was run at 100°C.

substituents at the *m*-position, such as an ester, methyl, and CF_3 groups were compatible, and high site-selectivity was observed with terminal aryl alkyne **2b**. By slightly modifying the reaction

conditions using CsOAc as a base, terminal alkyl alkynes **2d**-**2g** also afforded products with high site-selectivity (>20:1) and good to moderate yield (**3hd**, **3kd**, **3md**-**3mg**). We evaluated the reactivity of the Cp*Rh^{III} catalyst with several terminal alkynes and unsymmetrical *O*-acyloximes, but the yield and/or site selectivity were much less satisfactory (**3db**/**4db**: 38%, 1/1.7; **3eb**/**4eb**: 62%, 1/1.2; **3hb**/**4hb**: 18%, 1.1/1; **3kb**/**4kb**: 9%, >20/1; **3lb**/**4lb**: 30%, >20/1; **3mb**/**4mb**: trace, n.d.; **3md**/**4md**: 6%, >20:1). In the previous report, Cp*Rh^{III} also resulted in low site-selectivity when using *m*-Br substituted *O*-acyloxime **1b** and internal alkyne **2h** (**3bh**:**4bh** = 2.7/1).[13a] The Cp*Co^{III} catalyst exhibited much superior site-selectivity using either aryl or alkyl internal alkynes (**2h** and **2i**), and a broad range of unsymmetrically substituted *O*-acyloximes afforded products **3ah**-**3ki** with >20:1 site selectivity and 45-97% yield.

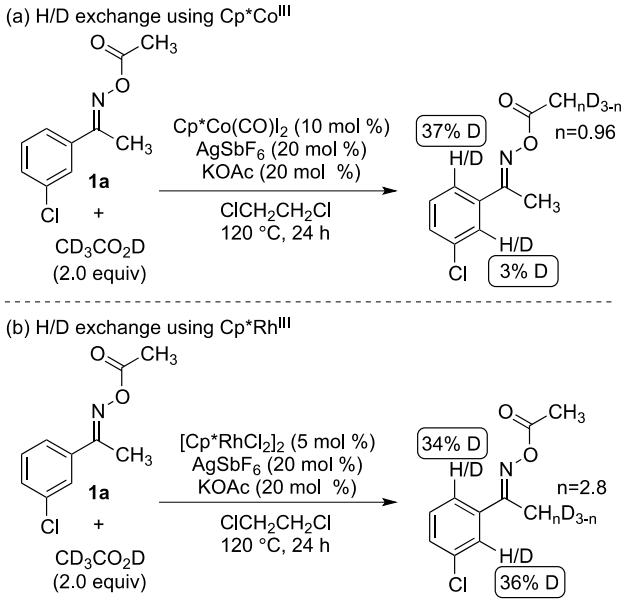
Table 3. Scope of terminal alkynes **2**.[a]



[a] Reactions were run using **1** (0.15 mmol), **2** (0.18 mmol), Cp*Co(CO)I_2 (10 mol %), $AgSbF_6$ (20 mol %), and KOAc (20 mol %) in $ClCH_2CH_2Cl$ at 120 °C for 24 h unless otherwise noted. Isolated yield of **3** was determined after purification by silica gel column chromatography. [b] Yield in parenthesis was obtained using **1n** (5.0 mmol, 1.06 g) and **2b** (6.0 mmol). [c] CsOAc (20 mol %) was used instead of KOAc. **1** (0.10 mmol) and **2** (0.15 mmol) were used.

Because Cp*Rh^{III} exhibited only modest to poor reactivity with terminal alkynes,[15,16] we further examined the synthetic utility of the Cp*Co^{III} with various terminal alkynes and symmetrical *O*-acyloximes. Aryl, alkyl, heteroaryl, and ferrocenyl terminal alkynes reacted smoothly with *O*-acyloxime **1n**, giving products **3na**–**3nr** in 52-92% yield (Table 3). The reaction also proceeded in gram-scale without difficulty, and **3nb** was obtained in 88% yield. Regarding the scope of symmetrical *O*-acyloximes, **1o**-**1u** gave **3oa**-**3ub** in 72-81% yield. An *ortho*-substituted bicyclic *O*-acyloxime **1v** gave **3vb** in 73% yield, and a benzophenone-derived *O*-acyloxime **1w** also afforded the product in excellent yield (**3wb**, 98%). With **1w** and **2b** as model substrates, we attempted to reduce the catalyst loading. The reaction proceeded smoothly with 5.0 mol % of the cobalt catalyst, and **3wb** was obtained in 97% yield. Decreasing the catalyst loading to 2.5 mol % resulted in diminished reactivity, but an acceptable yield (82%) was obtained.

High site-selectivity in C-H bond activation step under Cp*Co^{III} catalysis in comparison with Cp*Rh^{III} catalysis was confirmed by deuterium exchange experiments, shown in Scheme 2. When *O*-acyloxime **1a** was subjected to the optimized reaction conditions using Cp*Co^{III} in the presence of CD_3CO_2D, selective deuterium incorporation was observed at the less hindered position (Scheme 2a; 37%D vs 3%D). On the other hand, the Cp*Rh^{III} catalyst promoted non-selective H/D exchange under the same conditions (Scheme 2b; 34%D vs 36%D). The results clearly indicated that Cp*Co^{III} more efficiently differentiated the steric difference in unsymmetrical *m*-substituted *O*-acyloxime than did Cp*Rh^{III}. We assume that steric repulsion between the Cp* ligand and substrates would be larger with the Cp*Co^{III} catalyst than that with the Cp*Rh^{III} catalyst, because the ionic radius of cobalt is smaller than that of rhodium.[17] Further mechanistic studies, however, are required to clarify the precise origin of the high site-selectivity.



Scheme 2. H/D exchange experiments under (a) Cp*Co^{III} catalysis and (b) Cp*Rh^{III} catalysis.

Possible reaction pathways to form isoquinolines **3** are summarized in Figure 1. Coordination of *O*-acyloxime **1a** to the Co^{III} center, followed by acetate-assisted C-H activation[18] at sterically less hindered site, gives 5-membered metallacycle (**I**). Alkyne insertion leads to a common intermediate (**II**). Path (a) consists of reductive elimination of the C-N bond to form the *N*-acetoxyisoquinolinium cation (**III**) and subsequent reduction of the intermediate (**III**) by the resulting Co^{I} species. In path (b), a concerted C-N bond formation and N-O bond cleavage process would provide isoquinoline **3** and regenerate the catalyst.[11a] Path (c) involves formal oxidative addition of the N-O bond to the Co^{III} center to give Co^{V} species (**IV**),[7o] which undergoes reductive elimination leading to **3**. At present, it is difficult to determine which pathway is more plausible under Cp*Co^{III}

catalysis. On the other hand, we ruled out the possibility of the reaction via 6π-electrocyclization of *ortho*-alkenylated intermediate **V** (path d)[14b,19], because **3** was not obtained when separately synthesized intermediate **V** (X = Cl, R = Ph) was subjected to the reaction conditions.

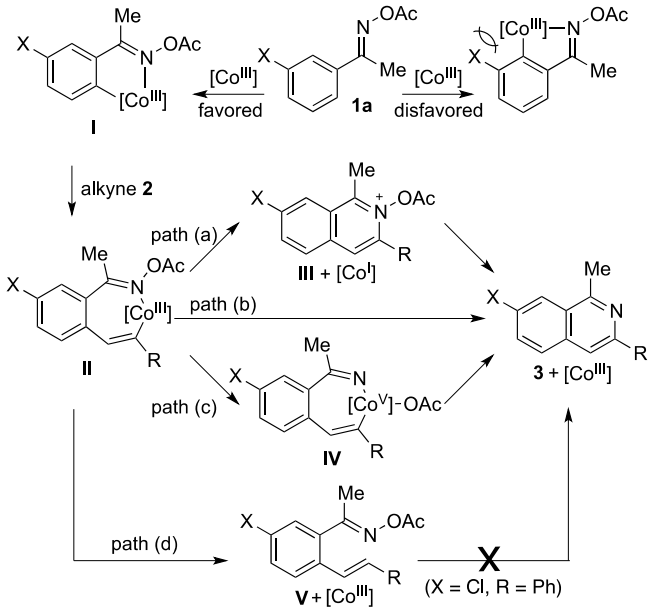


Figure 1. Possible reaction pathways to form isoquinolines under Cp*Co^{III} catalysis

In summary, we demonstrated the unique catalytic activity of the Cp*Co^{III} complex for multi-substituted isoquinoline synthesis from *O*-acyloximes **1** and terminal as well as internal alkynes **2** via site-selective C-H bond activation. The Cp*Co^{III} catalyst exhibited much higher site selectivity for unsymmetrical *O*-acyloximes and higher reactivity towards terminal alkynes than Cp*Rh^{III} catalysts. An oxidizing directing group bearing an N-O bond was successfully utilized as an internal oxidant in Cp*Co^{III}-catalyzed oxidative C-H bond functionalization reactions. Further mechanistic studies as well as trials to broaden the unique catalytic activity of Cp*Co^{III} catalysis are actively ongoing in our group.

Acknowledgements

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Keywords: catalysis • C-H activation • cobalt • first-row transition metal• isoquinoline

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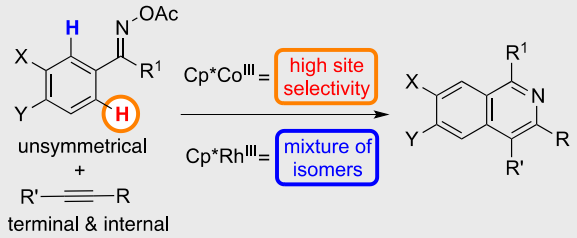

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