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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

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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 pyrrolindolone synthesis.^[8a] Glorius *et al.* also utilized the high Lewis acidity of a cationic Co^{III} to produce 6H-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(C₆H₆)](PF₆)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 $\text{Cp}^*\text{Co}^{\text{III}}$ catalysis. *In situ* generation of an active catalyst using $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ 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 $\text{Cp}^*\text{Rh}^{\text{III}}$ 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	$[\text{Cp}^*\text{Co}(\text{C}_6\text{H}_5)][\text{PF}_6]_2$ (10)	None	KOAc (20)	120	46	14/1
2	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgPF_6 (20)	KOAc (20)	120	73	17/1
3	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgBF_4 (20)	KOAc (20)	120	65	19/1
4	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgNTf_2 (20)	KOAc (20)	120	70	16/1
5	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgSbF_6 (20)	KOAc (20)	120	82 ^[c]	17/1
6	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgSbF_6 (20)	K_2CO_3 (20)	120	71	13/1
7	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgSbF_6 (20)	CsOAc (20)	120	63	19/1
8	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgSbF_6 (20)	CsOPiv (20)	120	64	17/1
9	$\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10)	AgSbF_6 (20)	None	120	55	17/1
10 ^[d]	$[\text{Cp}^*\text{RhCl}_2]_2$ (2.5)	None	NaOAc (30)	60	trace	N.D.
11 ^[d]	$[\text{Cp}^*\text{RhCl}_2]_2$ (2.5)	None	CsOAc (30)	80	trace	N.D.
12	$[\text{Cp}^*\text{RhCl}_2]_2$ (5)	AgSbF_6 (20)	KOAc (20)	80	trace	N.D.
13	$[\text{Cp}^*\text{RhCl}_2]_2$ (5)	AgSbF_6 (20)	KOAc (20)	120	11	1/1.3
14	$[\text{Cp}^*\text{RhCl}_2]_2$ (5)	AgSbF_6 (20)	K_2CO_3 (20)	120	9	1/1.6
15	$[\text{Cp}^*\text{RhCl}_2]_2$ (5)	AgSbF_6 (20)	CsOAc (20)	120	28	1/1.3
16	$[\text{Cp}^*\text{RhCl}_2]_2$ (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 $\text{ClCH}_2\text{CH}_2\text{Cl}$ unless otherwise noted. [b] Combined yield of **3aa** and **4aa** determined by ^1H 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	internal alkynes
3aa : R = Ph, 82% (17/1) 3ab : R = o-tol, 90% (17/1) 3ac : R = 4-F-C ₆ H ₄ , 78% (19/1)	3ca : 70% (>20/1) 3ba : 80% (>20/1) 3cb : 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 ₂ CH ₂ Ph, 56% (>20/1) ^[b] 3jb : 79% (>20/1) 3kb : R = o-tol, 91% (>20/1) 3ld : R = -CH ₂ CH ₂ Ph, 66% (>20/1) ^[b] 3mb : R = o-tol, 93% (>20/1) 3md : R = -CH ₂ CH ₂ Ph, 70% (>20/1) ^[b] 3me : R = nPr, 88% (>20/1) ^[b] 3mf : R = nPent, 86% (>20/1) ^[b] 3mg : R = cycloHex, 68% (>20/1) ^[b]
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 ₂ Me, 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 ₂ Me, 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), $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10 mol %), AgSbF_6 (20 mol %), and KOAc (20 mol %) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ 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 ^1H 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 $\text{Cp}^*\text{Rh}^{\text{III}}$ 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, $\text{Cp}^*\text{Rh}^{\text{III}}$ 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 $\text{Cp}^*\text{Co}^{\text{III}}$ 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]

3na : R = Ph, 86%	
3nb : R = 2-Me-C ₆ H ₄ , 92% (88%) ^[b]	
3nc : R = 4-F-C ₆ H ₄ , 83%	
3nd : R = -CH ₂ CH ₂ Ph, 75% ^[c]	
3nf : R = <i>n</i> Pent, 73% ^[c]	
3ng : R = <i>cyclo</i> Hex, 72% ^[c]	
3nj : R = 4-Cl-C ₆ H ₄ , 70%	
3nk : R = 4-Br-C ₆ H ₄ , 60%	
3nl : R = 4-Me-C ₆ H ₄ , 83%	
3nm : R = 4-MeO-C ₆ H ₄ , 71%	
3nn : R = 3-Me-C ₆ H ₄ , 78%	
3no : R = 3-Cl-C ₆ H ₄ , 74%	
3np : R = 9-phenanthrenyl, 85%	
3nq : R = 3-thienyl, 70%	
3nr : 52%	
3oa : Y = F, 81%	3tb : Y = H, 80%
3pa : Y = Br, 73%	3ub : Y = Ph, 74%
3qa : Y = CF ₃ , 80%	
3ra : Y = Me, 72%	
3sa : Y = OMe, 75%	
3vb : 73%	3wb : 98% (standard conditions) 97% (5.0 mol % cat) 82% (2.5 mol % cat)

[a] Reactions were run using **1** (0.15 mmol), **2** (0.18 mmol), $\text{Cp}^*\text{Co}(\text{CO})\text{I}_2$ (10 mol %), AgSbF_6 (20 mol %), and KOAc (20 mol %) in $\text{ClCH}_2\text{CH}_2\text{Cl}$ 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 $\text{Cp}^*\text{Rh}^{\text{III}}$ exhibited only modest to poor reactivity with terminal alkynes,^[15,16] we further examined the synthetic utility of the $\text{Cp}^*\text{Co}^{\text{III}}$ 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 $\text{Cp}^*\text{Co}^{\text{III}}$ catalysis in comparison with $\text{Cp}^*\text{Rh}^{\text{III}}$ catalysis was confirmed by deuterium exchange experiments, shown in Scheme 2. When *O*-acyloxime **1a** was subjected to the optimized reaction conditions using $\text{Cp}^*\text{Co}^{\text{III}}$ in the presence of $\text{CD}_3\text{CO}_2\text{D}$, selective deuterium incorporation was observed at the less hindered position (Scheme 2a; 37%D vs 3%D). On the other hand, the $\text{Cp}^*\text{Rh}^{\text{III}}$ catalyst promoted non-selective H/D exchange under the same conditions (Scheme 2b; 34%D vs 36%D). The results clearly indicated that $\text{Cp}^*\text{Co}^{\text{III}}$ more efficiently differentiated the steric difference in unsymmetrical *m*-substituted *O*-acyloxime than did $\text{Cp}^*\text{Rh}^{\text{III}}$. We assume that steric repulsion between the Cp^* ligand and substrates would be larger with the $\text{Cp}^*\text{Co}^{\text{III}}$ catalyst than that with the $\text{Cp}^*\text{Rh}^{\text{III}}$ 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) $\text{Cp}^*\text{Co}^{\text{III}}$ catalysis and (b) $\text{Cp}^*\text{Rh}^{\text{III}}$ 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**),^[70] which undergoes reductive elimination leading to **3**. At present, it is difficult to determine which pathway is more plausible under $\text{Cp}^*\text{Co}^{\text{III}}$

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 $\text{Cp}^*\text{Co}^{\text{III}}$ catalysis

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

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

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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