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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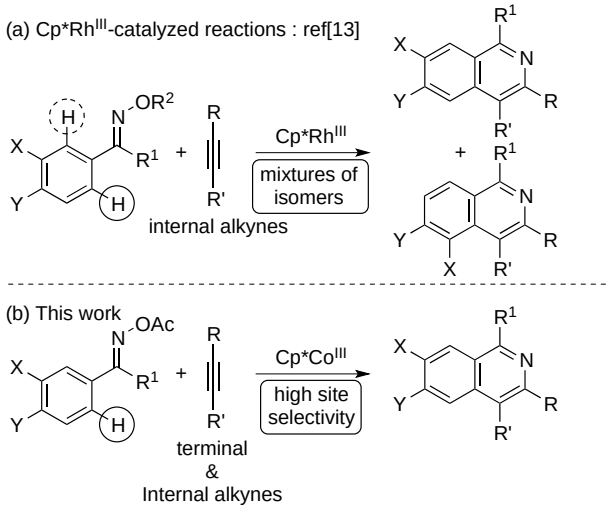
Abstract: *Cp*Co^{III}-catalyzed isoquinoline synthesis via site-selective C-H activation of O-acyloximes is described. C-H activation of various unsymmetrically substituted O-acyloximes selectively occurred at a sterically less hindered site under Cp*Co^{III} catalysis, and reactions with terminal as 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 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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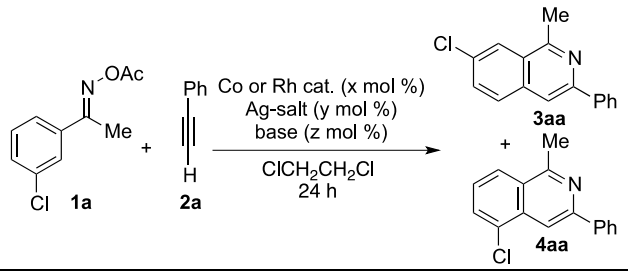
(entry 1, **3aa**:**4aa** = 14/1). The less hindered C-H bond was selectively functionalized under Cp*Co^{III} catalysis. *In situ* generation of an active catalyst using Cp*Co(CO)I_2 and cationic Ag salts showed higher reactivity (entries 2–5), and $AgSbF_6$ afforded the best result (82% isolated yield, 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

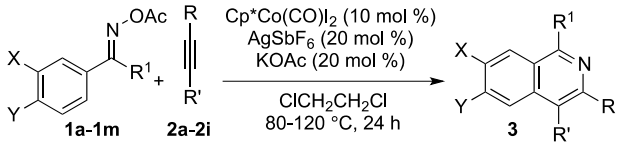
Table 1. Optimization studies and control experiments.[a]



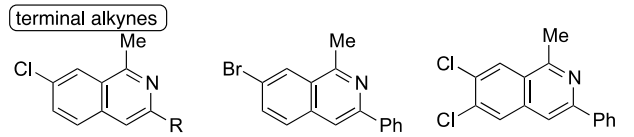
Entry	Catalyst [mol %]	Ag-salt [mol %]	Base [mol %]	*T* [°C]	Yield [%][b]	Ratio of **3**/**4**
1	$[Cp^*Co(C_6H_6)][PF_6]_2$ (10)	None	KOAc (20)	120	46	14/1
2	Cp*Co(CO)I_2 (10)	$AgPF_6$ (20)	KOAc (20)	120	73	17/1
3	Cp*Co(CO)I_2 (10)	$AgBF_4$ (20)	KOAc (20)	120	65	19/1
4	Cp*Co(CO)I_2 (10)	$AgNTf_2$ (20)	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]).

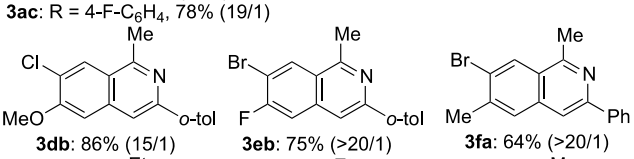
Table 2. Scope of unsymmetrical *O*-acyloximes **1**.[a]



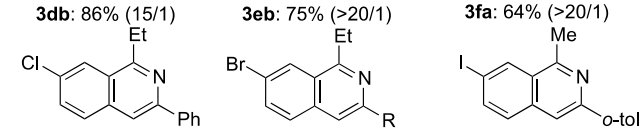
terminal alkynes



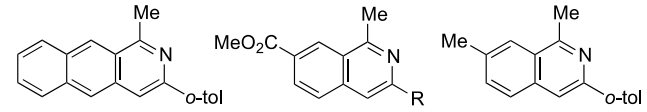
3aa: R = Ph, 82% (17/1)
3ab: R = *o*-tol, 90% (17/1)
3ac: R = 4-F-C_6H_4, 78% (19/1)
3ba: 80% (>20/1)
3ca: 70% (>20/1)



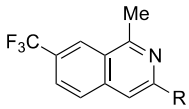
3db: 86% (15/1)
3eb: 75% (>20/1)
3fa: 64% (>20/1)



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

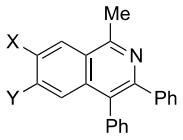


3jb: 79% (>20/1)
3kb: R = *o*-tol, 91% (>20/1)
3kd: R = -CH_2CH_2Ph, 66% (>20/1)[b]
3lb: 75% (>20/1)

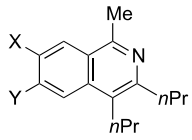


3mb: R = *o*-tol, 93% (>20/1)
3md: R = -CH_2CH_2Ph, 70% (>20/1)[b]
3me: R = *n*Pr, 88% (>20/1)[b]
3mf: R = *n*Pent, 86% (>20/1)[b]
3mg: R = *cyclo*Hex, 68% (>20/1)[b]

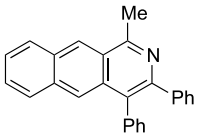
internal alkynes



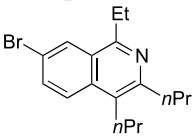
3ah: X = Cl, Y = H, 94% (>20/1)[b,c]
3bh: X = Br, Y = H, 92% (>20/1)[b,c]
3ch: X = Cl, Y = Cl, 86% (>20/1)[b,d]
3fh: X = Br, Y = Me, 72% (>20/1)[b,c]
3ih: X = I, Y = H, 45% (>20/1)[b,c]
3kh: X = CO_2Me, Y = H, 90% (>20/1)[b,c]
3lh: X = Me, Y = H, 78% (>20/1)[b,d]
3mh: X = CF_3, Y = H, 97% (>20/1)[b,c]



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]



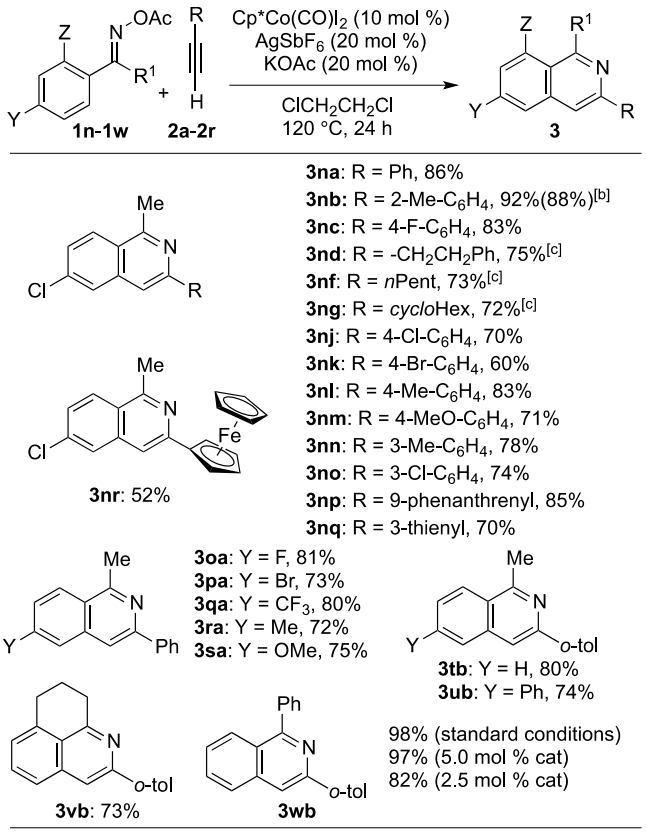
3hi: 85% (>20/1)[b,d]

[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.

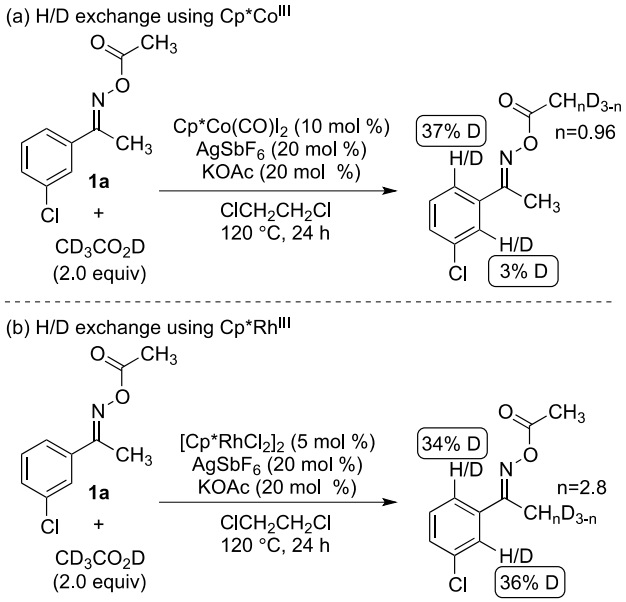
Table 3. Scope of terminal alkynes **2**.[a]



[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.

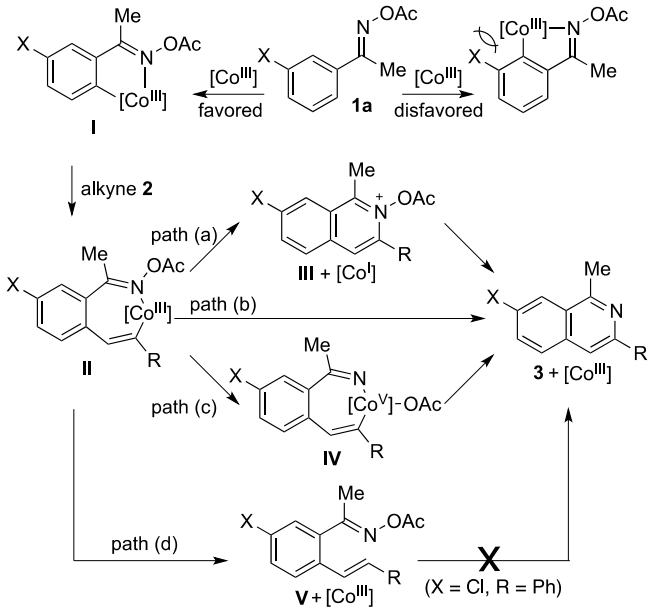


Figure 1. Possible reaction pathways to form isoquinolines under Cp*Co^{III} catalysis

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.

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

[1] B. M. Trost, *Science* **1991**, *254*, 1471.

[2] P. A. Wender, B. L. Miller, *Nature* **2009**, *460*, 197.

[3] Selected recent reviews on C-H bond functionalization: a) L. Ackermann, *Org. Process Res. Dev.* **2015**, *19*, 260. b) G. Rouquet, N. Chatani, *Angew. Chem.* **2013**, *125*, 11942; *Angew. Chem. Int. Ed.* **2013**, *52*, 11726; b) P. B. Arockiam, C. Bruneau, P. H. Dixneuf, *Chem. Rev.* **2012**, *112*, 5879; c) J. Wencel-Delord, F. Glorius, *Nature Chem.* **2013**, *5*, 369; d) K. M. Engle, T.-S. Mei, M. Wasa, J.-Q. Yu, *Acc. Chem. Res.* **2012**, *45*, 788; e) J. Yamaguchi, A. D. Yamaguchi, K. Itami, *Angew. Chem. Int. Ed.* **2012**, *51*, 8960; *Angew. Chem.* **2012**, *124*, 9092; f) B.-J. Li, Z.-J. Shi, *Chem. Soc. Rev.* **2012**, *41*, 5588; g) S. H. Cho, J. Y. Kim, J. Kwak, S. Chang, *Chem. Soc. Rev.* **2011**, *40*, 5068.

[4] Reviews on Cp*Rh^{III}-catalyzed C-H functionalization: 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; e) N. Kuhl, N. Schröder, F. Glorius, *Adv. Synth. Catal.* **2014**, *356*, 1443; f) G. Song, X. Li, *Acc. Chem. Res.* **2015**, *48*, 1007; g) B. Ye, N. Cramer, *Acc. Chem. Res.* **2015**, *48*, 1308.

[5] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207; *Angew. Chem.* **2013**, *125*, 2263.

[6] Reviews on cobalt-catalyzed C-H bond functionalization reactions: a) N. Yoshikai, *Synlett* **2011**, 1047; b) K. Gao, N. Yoshikai, *Acc. Chem. Res.* **2014**, *47*, 1208; a review on first-row transition metal-catalyzed C-H bond functionalization reactions: c) A. A. Kulkarni, O. Daugulis, *Synthesis* **2009**, 4087.

[7] a) T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142; b) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal.* **2014**, *356*, 1491; c) D.-G. Yu, T. Gensch, F. de Azambuja, S. Vásquez-Céspedes, F. Glorius, *J. Am. Chem. Soc.* **2014**, *136*, 17722; d) T. M. Figg, S. Park, J. Park, S. Chang, D. G. Musaev, *Organometallics* **2014**, *33*, 4076; e) J. R. Hummel, J. A. Ellman, *J. Am. Chem. Soc.* **2015**, *137*, 490; f) P. Patel, S. Chang, *ACS Catal.* **2015**, *5*, 853; g) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 3635; *Angew. Chem.* **2015**, *127*, 3706; h) B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Chem. Commun*. **2015**, *51*, 4659; i) A. B. Pawar, S. Chang, *Org. Lett.* **2015**, *17*, 660; j) J. Li, L. Ackermann, *Angew. Chem. Int. Ed.* **2015**, *54*, 8551; *Angew. Chem.* **2015**, *127*, 8671; k) J. R. Hummel, J. A. Ellman, *Org. Lett.* **2015**, *17*, 2400; l) Y. Suzuki, B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Tetrahedron* **2015**, *71*, 4552; m) M. Moselage, N. Sauermann, J. Koeller, W. Liu, D. Gelman, L. Ackermann, *Synlett* **2015**, *26*, 1596; n) X.-G. Liu, S.-S. Zhang, J.-Q. Wu, Q. Li, H. Wang, *Tetrahedron Lett.* **2015**, *56*, 4093; o) Z.-Z. Zhang, B. Liu, C.-Y. Wang, B.-F. Shi, *Org. Lett.* **2015**, *17*, published online [DOI: 10.1021/acs.orglett.5b02038].

[8] a) H. Ikemoto, T. Yoshino, K. Sakata, S. Matsunaga, M. Kanai, *J. Am. Chem. Soc.* **2014**, *136*, 5424; b) D. Zhao, J. H. Kim, L. Stegemann, C. A. Strassert, F. Glorius, *Angew. Chem. Int. Ed.* **2015**, *54*, 4508; *Angew. Chem.* **2015**, *127*, 4591; c) Y. Suzuki, B. Sun, K. Sakata, T. Yoshino, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2015**, *54*, 9944; *Angew. Chem.* **2015**, *127*, 10082; d) T. Gensch, S. Vásquez-Céspedes, D.-G. Yu, F. Glorius, *Org. Lett.* **2015**, *17*, 3714.

[9] Reviews: a) K. W. Bentley, The Isoquinoline Alkaloids, Hardwood Academic, Amsterdam, The Netherlands, **1998**, vol. 1; b) K. W. Bentley, *Nat. Prod. Rep.* **2004**, *21*, 395; c) K. W. Bentley, *Nat. Prod. Rep.* **2006**, *23*, 444.

[10] Reviews on oxidative C-H bond functionalization reactions without external oxidant: a) F. W. Patureau, F. Glorius, *Angew. Chem. Int. Ed.* **2011**, *50*, 1977; *Angew. Chem.* **2011**, *123*, 2021; b) J. Mo, L. Wang, Y. Liu, X. Cui, *Synthesis* **2015**, *47*, 439; c) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.* **2015**, *44*, 1155.

[11] For selected examples of Cp*Rh^{III}-catalyzed redox-neutral C-H bond activation/annulation reactions with internal oxidizing directing group-assistance: a) N. Guimond, C. Gouliaras, K. Fagnou, *J. Am. Chem. Soc.* **2010**, *132*, 6908; b) S. Rakshit, C. Grohmann, T. Besset, F. Glorius, *J. Am. Chem. Soc.* **2011**, *133*, 2350; c) N. Guimond, S. I. Gorelsky, K. Fagnou, *J. Am. Chem. Soc.* **2011**, *133*, 6449; d) P.C. Too, T. Noji, Y. J. Lim, X. Li, S. Chiba, *Synlett* **2011**, 2789; e) T. K. Hyster, L. Knörr, T. R. Ward, T. Rovis, *Science* **2012**, *338*, 500; f) B. Ye, N. Cramer, *Science* **2012**, *338*, 504; g) H. Wang, C. Grohmann, C. Nimphius, F. Glorius, *J. Am. Chem. Soc.* **2012**, *134*, 19592; h) J. M. Neely, T. Rovis, *J. Am. Chem. Soc.* **2013**, *135*, 66; i) D. Zhao, Z. Shi, F. Glorius, *Angew. Chem. Int. Ed.* **2013**, *52*, 12426; *Angew. Chem.* **2013**, 125, 12652; j) B. Liu, C. Song, C. Sun, S. Zhou, J. Zhu, *J. Am. Chem. Soc.* **2013**, *135*, 16625; k) C. Wang, Y. Huang, *Org. Lett.* **2013**, *15*, 5294; l) S.-C. Chuang, P. Gandeepan, C.-H. Cheng, *Org. Lett.* **2013**, *15*, 5750; m) X. Huang, J. Huang, C. Du, X. Zhang, F. Song, J. You, *Angew. Chem. Int. Ed.* **2013**, *52*, 12970; *Angew. Chem.* **2013**, 125, 13208; n) X.-C. Huang, X.-H. Yang, R.-J. Song, J.-H. Li, *J. Org. Chem.* **2014**, *79*, 1025; o) L. Zheng, R. Hua, *Chem. Eur. J.* **2014**, *20*, 2352; p) U. Sharma, Y. Park, S.

Chang, *J. Org. Chem.* **2014**, *79*, 9899; q) Z. Fan, S. Song, W. Li, K. Geng, Y. Xu, Z.-H. Miao, A. Zhang, *Org. Lett.* **2015**, *17*, 310.

[12] For examples of isoquinoline synthesis via C-H activation with stoichiometric amounts of external oxidants, see a review: a) R. He, Z.-T. Huang, Q.-Y. Zheng, C. Wang, *Tetrahedron Lett.* **2014**, *55*, 5705; For pioneering works, see also: b) T. Fukutani, N. Umeda, K. Hirano, T. Satoh, M. Miura, *Chem. Commun.* **2009**, 5141; c) N. Guimond, K. Fagnou, *J. Am. Chem. Soc.* **2009**, *131*, 12050.

[13] Cp^*Rh^{III}-catalyzed Isoquinoline synthesis via redox-neutral C-H functionalization from oxime derivatives, see: a) P. C. Too, Y.-F. Wang, S. Chiba, *Org. Lett.* **2010**, *12*, 5688; b) X. Zhang, D. Chen, M. Zhao, J. Zhao, A. Jia, X. Li, *Adv. Synth. Catal.* **2011**, *353*, 719; c) P. C. Too, S. H. Chua, S. H. Wong, S. Chiba, *J. Org. Chem.* **2011**, *76*, 6159; d) T. K. Hyster, T. Rovis, *Chem. Commun.* **2011**, *47*, 11846; e) L. Zheng, J. Ju, Y. Bin, R. Hua, *J. Org. Chem.* **2012**, *77*, 5794; f) D. Zhao, F. Lied, F. Glorius, *Chem. Sci.* **2014**, *5*, 2869; For related works, see also, g) Y.-F. Wang, K. K. Toh, J.-Y. Lee, S. Chiba, *Angew. Chem. Int. Ed.* **2011**, *50*, 5927; *Angew. Chem.* **2011**, *123*, 6049; h) S.-C. Chuang, P. Gandeepan, C.-H. Cheng, *Org. Lett.* **2013**, *15*, 5750; i) X.-C. Huang, X.-H. Yang, R.-J. Song, J.-H. Li, *J. Org. Chem.* **2014**, *79*, 1025; j) S. Zhang, D. Huang, G. Xu, S. Cao, R. Wang, S. Peng, J. Sun, *Org. Biomol. Chem.* **2015**, *13*, 7920.

[14] Isoquinoline synthesis from oxime derivatives using other transition metal catalysts, see: a) T. Gerfaud, L. Neuville, J. Zhu, *Angew. Chem. Int. Ed.* **2009**, *48*, 572; *Angew. Chem.* **2009**, *121*, 580; b) K. Parthasarathy, C.-H. Cheng, *J. Org. Chem.* **2009**, *74*, 9359; c) Y. Yoshida, T. Kurahashi, S. Matsubara, *Chem. Lett.* **2011**, *40*, 1140; d) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Org. Lett.* **2012**, *14*, 3032; e) C. Kornhaaß, J. Li, L. Ackermann, *J. Org. Chem.* **2012**, *77*, 9190; f) R. K. Chinnagolla, S. Pimparkar, M. Jeganmohan, *Chem. Commun.* **2013**, *49*, 3703; g) C. Kornhaaß, C. Kuper, L. Ackermann, *Adv. Synth. Catal.* **2014**, *356*, 1619.

[15] 1,3-Dienes were used as alternative substrates to overcome the difficulty in using terminal alkyl alkynes under Cp^*Rh^{III} catalysis, see ref [13f].

[16] A few terminal alkynes were successfully used as substrates in the reaction of benzophenone-derived oximes under Ru^{II}-catalysis, see ref [14d]. When we used less reactive *meta*-substituted oxime and terminal alkyne **2a**, however, Ru^{II}-catalyst, $[RuCl_2(p\text{-cymene})]_2$, gave isoquinolines in less than 5% yield and low **3aa**/**4aa** ratio (1.2/1).

[17] Steric factors of substituted cyclopentadienyl ligands affected site, regio, and diastereoselectivity of Rh^{III}-catalyzed C-H activation. For systematic studies in dihydroisoquinolone synthesis and cyclopropanation, see: a) T. K. Hyster, D. M. Dalton, T. Rovis, *Chem. Sci.* **2015**, *6*, 254; b) T. Piou, T. Rovis *J. Am. Chem. Soc.* **2014**, *136*, 11292.

[18] Reviews on concerted metalation-deprotonation mechanism: D. Lapointe, K. Fagnou, *Chem. Lett.* **2010**, *39*, 1118; b) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315 and references therein.

[19] 6π-Electrocyclization was proposed under Rh(I) catalysis, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 3645. See also ref [14b].

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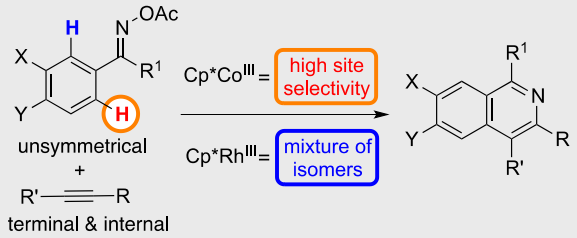

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