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**Cp*Co**

Catalyzed Site-Selective C-H Activation of Unsymmetrical O-Acylloximes: Multi-substituted Isoquinoline Synthesis from Terminal and Internal Alkynes

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

**Abstract:** 
*Cp*Co** 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** catalysis, and reactions with terminal as well as internal alkynes afforded products in up to 98% yield. The *Cp*Co** catalyst exhibited high site selectivity (15:1 → 20:1), whereas *Cp*Rh** catalysts exhibited low selectivity and/or yield when unsymmetrical O-acyloximes and terminal alkynes were used. Deuteration labeling studies indicated a clear difference in the site selectivity of the C-H activation step between the *Cp*Co** catalyst and the *Cp*Rh** catalyst.

Transition metal-catalyzed C-H bond functionalization is an atom- and step-economical organic transformation that has emerged over the last two decades.[5] 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** 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** complexes, however, can be an obstacle for large scale application for producing valuable materials and biologically active compounds. In this context, in 2013 we began to investigate *Cp*Co** catalysis as an inexpensive alternative to *Cp*Rh** catalysis.[5,6] Since then, we and other groups revealed that several *Cp*Co** complexes indeed catalyze various C-H bond functionalization reactions[7] that have already been established with *Cp*Rh** catalysts. On the other hand, reports on the unique catalytic activity of *Cp*Co** in comparison with *Cp*Rh** catalysts are still limited.[6] Our group utilized the high nucleophilicity of alkanyl-Co** species in a one-pot pyrroloindoline synthesis.[8] Glorius et al. also utilized the high Lewis acidity of a cationic Co** to produce 6H-pyrido[2,1-a]isoquinolin-6-ones.[9] More recently, our group[9] and Glorius’ group[8d] independently utilized the oxophilic property of Co** in dehydrative C-H allylation with free allylic alcohols. Herein we describe our efforts to further explore the unique catalytic activity of *Cp*Co** over *Cp*Rh**. *Cp*Co** 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**-catalyzed annihilation reaction of O-acyloximes with internal alkynes (Scheme 1a).[13,14] Zhao, Jia, Li, and co-workers also reported the reaction with oximes under *Cp*Rh** catalysis.[15] 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 alkoy 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** catalyst than with the *Cp*Rh** catalyst, because the ionic radius of cobalt is smaller than that of rhodium. Thereby, *Cp*Co** would efficiently differentiate the steric difference in unsymmetrical m-substituted oxime derivatives.

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(C6H4)][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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**Scheme 1.** *Cp*Rh**- and *Cp*Co**-catalyzed isoquinoline synthesis; site selectivity with unsymmetrical oxime derivatives and alkynes.
The reaction was run using 1a (0.15 mmol) and 2a (0.18 mmol) in CH2Cl2 unless otherwise noted. [b] Combines 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,b. [e] Reactions were run using 1 (0.15 mmol), 2 (0.18 mmol), Cp*Co(CO)I2 (10 mol %), AgSbF6 (20 mol %), and KOAc (20 mol %) in CH2Cl2 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. [f] CsOAc (20 mol %) was used instead of KOAc. 1 (0.10 mmol) and 2 (0.15 mmol) were used. [g] Reaction was run at 80°C. [h] Reaction was run at 100°C.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst [mol %]</th>
<th>Ag-salt [mol %]</th>
<th>Base [mol %]</th>
<th>T [°C]</th>
<th>Yield [%][1]</th>
<th>Ratio 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Cp*Co(CO)I2][PF6]Br (10)</td>
<td>None</td>
<td>KOAc (20)</td>
<td>120</td>
<td>46</td>
<td>14/1</td>
</tr>
<tr>
<td>2</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgPF6 (20)</td>
<td>KOAc (20)</td>
<td>120</td>
<td>73</td>
<td>17/1</td>
</tr>
<tr>
<td>3</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgBF4 (20)</td>
<td>KOAc (20)</td>
<td>120</td>
<td>65</td>
<td>19/1</td>
</tr>
<tr>
<td>4</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgNTf2 (20)</td>
<td>KOAc (20)</td>
<td>120</td>
<td>70</td>
<td>16/1</td>
</tr>
<tr>
<td>5</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgSbF6 (20)</td>
<td>KOAc (20)</td>
<td>120</td>
<td>82</td>
<td>17/1</td>
</tr>
<tr>
<td>6</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgSbF6 (20)</td>
<td>K2CO3 (20)</td>
<td>120</td>
<td>71</td>
<td>13/1</td>
</tr>
<tr>
<td>7</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgSbF6 (20)</td>
<td>Cs2CO3 (20)</td>
<td>120</td>
<td>63</td>
<td>19/1</td>
</tr>
<tr>
<td>8</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgSbF6 (20)</td>
<td>CsOAc (20)</td>
<td>120</td>
<td>64</td>
<td>17/1</td>
</tr>
<tr>
<td>9</td>
<td>Cp*Co(CO)I2 (10)</td>
<td>AgSbF6 (20)</td>
<td>None</td>
<td>120</td>
<td>55</td>
<td>17/1</td>
</tr>
<tr>
<td>10[b]</td>
<td>[Cp*RhCl2(PF6)]Br (2.5)</td>
<td>None</td>
<td>NaOAc (30)</td>
<td>60</td>
<td>trace</td>
<td>N.D.</td>
</tr>
<tr>
<td>11[b]</td>
<td>[Cp*RhCl2(PF6)]Br (2.5)</td>
<td>None</td>
<td>CsOAc (30)</td>
<td>80</td>
<td>trace</td>
<td>N.D.</td>
</tr>
<tr>
<td>12</td>
<td>[Cp*RhCl2(PF6)]Br (5)</td>
<td>AgSbF6 (20)</td>
<td>KOAc (20)</td>
<td>80</td>
<td>trace</td>
<td>N.D.</td>
</tr>
<tr>
<td>13</td>
<td>[Cp*RhCl2(PF6)]Br (5)</td>
<td>AgSbF6 (20)</td>
<td>KOAc (20)</td>
<td>120</td>
<td>11</td>
<td>1/1.3</td>
</tr>
<tr>
<td>14</td>
<td>[Cp*RhCl2(PF6)]Br (5)</td>
<td>AgSbF6 (20)</td>
<td>K2CO3 (20)</td>
<td>120</td>
<td>9</td>
<td>1/1.6</td>
</tr>
<tr>
<td>15</td>
<td>[Cp*RhCl2(PF6)]Br (5)</td>
<td>AgSbF6 (20)</td>
<td>Cs2CO3 (20)</td>
<td>120</td>
<td>28</td>
<td>1/1.3</td>
</tr>
<tr>
<td>16</td>
<td>[Cp*RhCl2(PF6)]Br (5)</td>
<td>AgSbF6 (20)</td>
<td>CsOAc (20)</td>
<td>120</td>
<td>13</td>
<td>1/1.3</td>
</tr>
</tbody>
</table>

[a] Reactions were run using 1a (0.15 mmol) and 2a (0.18 mmol) in CH2Cl2 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).
conditions using CsOAc as a base, terminal alkyl alkynes 2d-2g also afforded products with high terminal selectivity (>20:1) and good to moderate yield (3hd, 3kd, 3md-3mg). We evaluated the reactivity of the Cp*RhIII 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*RhII also resulted in low site-selectivity when using m-Br substituted O-acyloxime 1b and internal alkyne 2h (3bb/4bb = 2.7/1).[13a] The Cp*CoIII catalyst exhibited much superior site-selectivity using either aryl or alkyl internal alkynes (2h and 2i), and a broad range of unsymmetrical substituted O-acyloximes afforded products 3ah-3ki with >20:1 site selectivity and 45-97% yield.

Table 3. Scope of terminal alkynes.[4]

<table>
<thead>
<tr>
<th>Alkynes</th>
<th>Products</th>
<th>Site Selectivity</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a-2r</td>
<td>Y</td>
<td>Z</td>
<td>R'</td>
</tr>
<tr>
<td>1n-1w</td>
<td>R: Ph</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>3na</td>
<td>R: Ph, Y</td>
<td>81%</td>
<td></td>
</tr>
<tr>
<td>3nb</td>
<td>R: Ph</td>
<td>92%(88%)</td>
<td></td>
</tr>
<tr>
<td>3nc</td>
<td>R: Ph</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>3nd</td>
<td>R: Ph</td>
<td>&gt;20/1</td>
<td></td>
</tr>
<tr>
<td>3ne</td>
<td>R: Ph</td>
<td>72%</td>
<td></td>
</tr>
<tr>
<td>3nf</td>
<td>R: Ph</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>3ng</td>
<td>R: Ph</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>3nh</td>
<td>R: Ph</td>
<td>85%</td>
<td></td>
</tr>
<tr>
<td>3ni</td>
<td>R: Ph</td>
<td>70%</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reactions were run using 1 (0.15 mmol), 2 (0.18 mmol), Cp*Co(CO)I2 (10 mol %), AgSbF6 (20 mol %), and KOAc (20 mol %) in CICH2CH2Cl 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 when using 1m (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*RhIII exhibited only modest to poor reactivity with terminal alkynes,[16,16] we further examined the synthetic utility of the Cp*CoIII 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-acyloxymes, 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*CoIII catalysis in comparison with Cp*RhIII catalysis was confirmed by deuterium exchange experiments, shown in Scheme 2. When O-acyloxime 1a was subjected to the optimized reaction conditions using Cp*CoIII in the presence of CD3CO2D, selective deuterium incorporation was observed at the less hindered position (Scheme 2a; 37% D vs 3% D). On the other hand, the Cp*RhIII catalyst promoted non-selective H/D exchange under the same conditions (Scheme 2b; 34% D vs 36% D). The results clearly indicated that Cp*CoIII more efficiently differentiated the steric difference in unsymmetrical m-substituted O-acyloxime than did Cp*RhIII. We assume that steric repulsion between the Cp ligand and substrates would be larger with the Cp*CoIII catalyst than with the Cp*RhIII catalyst, because the ionic radius of cobalt is smaller than that of rhodium.[11] Further mechanistic studies, however, are required to clarify the precise origin of the high site-selectivity.

Possible reaction pathways to form isoquinolines 3 are summarized in Figure 1. Coordination of O-acyloxime 1a to the CoIII 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), followed by acetate-assisted C-H activation (II), giving acetoxy isoquinolinium cation (III) and subsequent reduction of the intermediate (III) by the resulting CoIII species. In path (b), a concerted C-N bond formation and N-O bond cleavage process would provide isoquinoline 3 and regenerate the catalyst.[11d] Path (c) involves formal oxidative addition of the N-O bond to the CoIII center to give CoIV species (IV), which undergoes reductive elimination leading to 3. At present, it is difficult to determine which pathway is more plausible under Cp*CoIII.

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catalysis. On the other hand, we ruled out the possibility of the reaction via 6τ-electrocyclization of ortho-alkenylation intermediate V (path d) 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*CoIII catalysis](image)

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

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


1,3-Dienes were used as alternative substrates to overcome the difficulty in using terminal alkyl alkynes under Cpt"Rh catalysts, see ref. [13].

A few terminal alkynes were successfully used as substrates in the reaction of benzophenone-derived oximes under Ru"I-catalysis, see ref. [14]. When we used less reactive meta-substituted oxime and terminal alkyne 2a, however, Ru"I-catalyst, [RuCl₂(p-cymene)], gave isoquinolines in less than 5% yield and low 3aa/4aa ratio (1.2:1).


6α-Electrocyclization was proposed under Rh(II) catalysis, see: a) D. A. Colby, R. G. Bergman, J. A. Ellman, J. Am. Chem. Soc. 2008, 130, 3645. See also ref. [16].
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Cp*CoIII-Catalyzed Site-Selective C-H Activation of Unsymmetrical O-Acyloximes: Multi-substituted Isoquinoline Synthesis from Terminal and Internal Alkynes