論文の内容の要旨

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)

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Research background

Transition metal-catalyzed directed C-H bond functionalization has emerged as a powerful synthetic methodology that is potentially superior to traditional organic reactions using stoichiometric amounts of activating reagents. Cationic Cp*Rh^{III} complexes are widely utilized for various C-C, C-N, and many other C-X bond formation. Despite their utility in C-H functionalization, however, the need for expensive and precious rhodium sources is economically and environmentally disadvantageous. Recently, a cationic [Cp*Co^{III}(C$_6$H$_6$)](PF$_6$)$_2$ complex **a** was reported for the addition of 2-phenylpyridines[1] and indoles[2] to imines.

The synthetic procedure of the **a** was rather lengthy and the catalytic activity was also moderate in many reactions. Thus, further studies to find out new readily available, yet more reactive Co(III)-complexes were required. As my Ph.D work, I developed readily available Cp*Co^{III} complexes for C-H bond functionalization and expanded the scopes of Cp*Co^{III} catalysis.
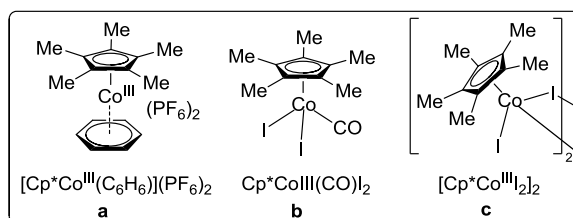
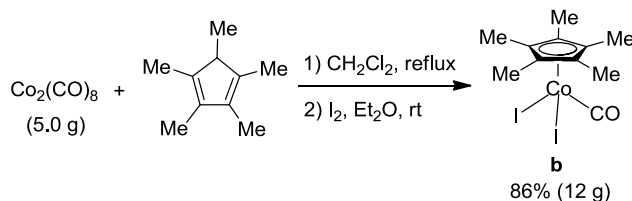## (1) Amidation reactions with sulfonyl azides

Chang and coworkers recently reported Cp*Rh^{III}-catalyzed C-H amidation reactions using sulfonyl azides as amine sources.[3] The results led me to evaluate the catalytic activity of cationic Cp*Co^{III} complexes for the same reaction. The reactivity of the **a** was, however, poor, and C-2 selective C-H
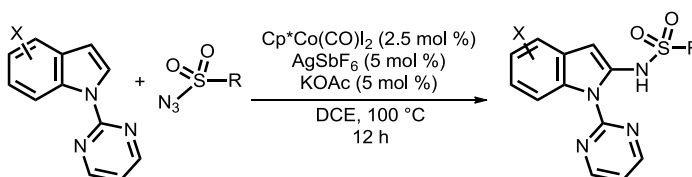
**Scheme 1.** Cp*Co(III)-catalyzed C2-selective amidation

amidation of indole with sulfonyl azide resulted in 4% yield. I assumed that the poor activity of the **a** was due to the thermal instability of the PF$_6$ ion under the present reaction conditions. Trials to exchange the counter ion of the cationic **a** 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 found that a Cp*Co(CO)I$_2$ complex **b** in combination with a suitable Ag salt was effective. The reaction under **b** + Ag-salt proceeded with excellent selectivity and high functional group tolerance, furnishing the C-2 amidated indoles in up to 98% yield **(Scheme 1)**. The **b** was 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)**.

Scheme 2. Preparation of Cp*Co(CO)I$_2$ complex

## (2) Amidation reactions with phosphoryl azides

The Cp*Co(CO)I$_2$ complex **b** was useful for generating an active cationic cobalt(III) species in situ as described in section (1). Safety issues, however, remained problematic; toxic carbon monoxide was inevitably released during the reaction process, and all reaction vessels had to be handled carefully. Thus, further studies are needed to avoid the safety issues in future industrial applications of the

Scheme 3. Preparation of [Cp*CoI$_2$]$_2$ complex

cobalt(III) catalysis. Thus, I also synthesized an air-stable dimeric [Cp*CoI$_2$]$_2$ complex **c**, and evaluated its activity (**Scheme 3**).
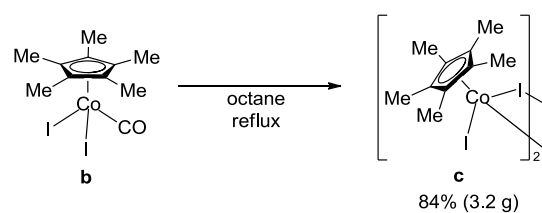
Phosphoramidates are important structural units found in many biologically active compounds. In addition, phosphoramidates are useful synthetic intermediates for various nitrogen-containing heterocycles. The Cp*Ir(III)-based strategy pioneered by Chang and coworkers provides a highly efficient approach for the synthesis of various phosphoramidates from arenes.[4] Because indoles were not used in recent reports of Cp*Ir(III)-catalysis, I selected C-H phosphoramidation reaction of indoles **4** with phosphoryl azides **5** as a target reaction to broaden the scope of C-H phosphoramidation reactions.

The substrate scope of the phosphoramidation of indoles under the optimized conditions is summarized in **Table 1**. Various indoles bearing electron-donating (Me, MeO, and BnO) and electron-withdrawing groups (halogen and CO$_2$Me) 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. 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 1.** The scope of indoles moiety and phosphoryl azides
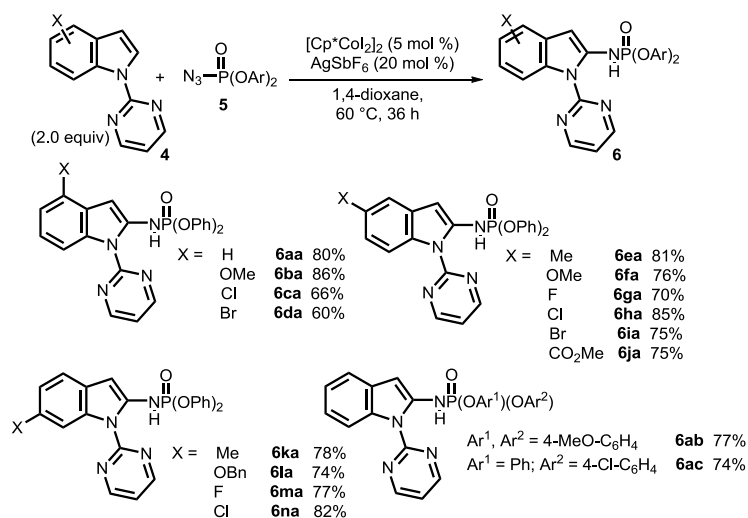
(3) Regioselective formation of isoquinolines with terminal alkynes

Isoquinoline is an important and common structure seen in a series of biologically active alkaloids. Cyclization reactions of oxime derivatives and alkynes via C-H activation to give isoquinolines without any external oxidants[5] are reported to be catalyzed by various transition metal catalysts. In 2010, Chiba and co-workers reported a Cp*Rh^{III}-catalyzed annulation reaction of *O*-acyloximes with internal alkynes. Around the
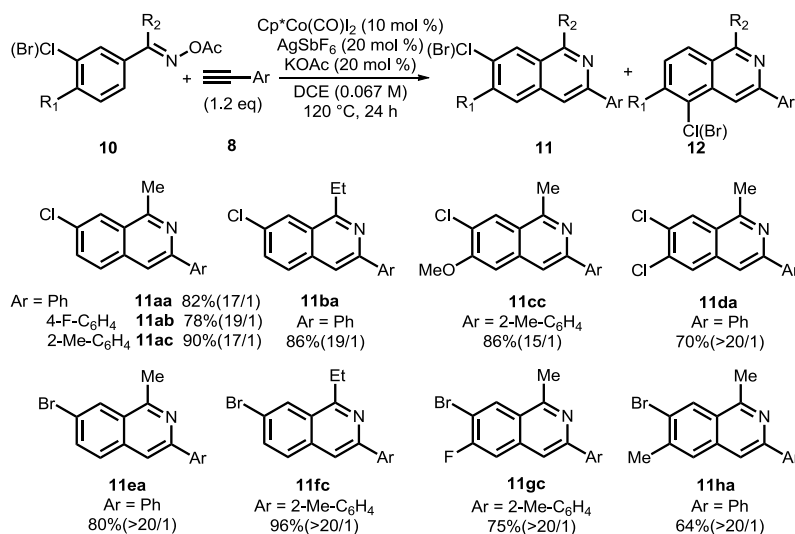
same time, Zhao, Jia, Li, and co-wokers reported the reaction with unactivated oximes under the similar conditions. The substrate scope, however, was limited to internal alkynes in both cases. Regioselectivity of the C-H activation step to form a metallacycle is also a difficult issue when *m*-substituted oxime derivatives are used as a substrate. Only very limited substrates bearing methyl or alkoxy groups showed sufficient selectivity so far. I succeeded in a Cp*Co[III]-catalyzed regioselective cyclization reaction of *O*-acyloximes and terminal alkynes. This is the first report on cobalt-catalyzed C-H bond functionalization reactions utilizing the internal oxidizing directing groups. *m*-Cl- and *m*-Br-substituted *O*-acyloximes generally prefer the reaction at the less hindered site under Cp*Co[III] catalysis while Cp*Rh[III] and Ru[II] showed low selectivity.

The scope of *para*-substituted *O*-acyloximes **7** and terminal alkynes **8** is summarized in **Table 2**. 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 2. The scope of *para*-substituted *O*-acyloxime with terminal alkyne
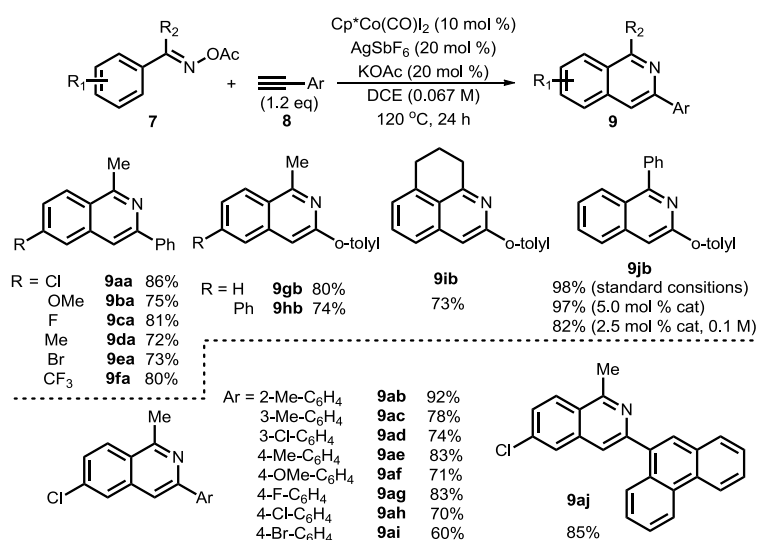
The scope of *meta*-Cl or Br substituted *O*-acyloximes **10** and terminal alkynes **8** is summarized in **Table 3**. *O*-acyloximes bearing chloro or bromo substituents at the *meta*-position generally showed high regioselectivity, and the less hindered C-H bonds were functionalized (**11aa-11ac, 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 3 The scope of *meta*-Cl, Br substituted *O*-acyloxime with terminal alkyne

Ar = Ph	**11aa**	82%(17/1)
4-F-C$_6$H$_4$	**11ab**	78%(19/1)
2-Me-C$_6$H$_4$	**11ac**	90%(17/1)

11ba
Ar = Ph
86%(19/1)

11cc
Ar = 2-Me-C$_6$H$_4$
86%(15/1)

11da
Ar = Ph
70%(>20/1)

11ea
Ar = Ph
80%(>20/1)

11fc
Ar = 2-Me-C$_6$H$_4$
96%(>20/1)

11gc
Ar = 2-Me-C$_6$H$_4$
75%(>20/1)

11ha
Ar = Ph
64%(>20/1)

To gain insight into the reaction mechanism and the origin of high regioselectivity, I performed experimental mechanistic studies. When *O*-acyloxime **8a** and CD$_3$CO$_2$D was subjected to the optimized reaction conditions using Cp*Co(CO)I$_2$ complex, selective deuterium incorporation was observed at the less hindered position. On the other hand, Cp*Rh^{III} catalyst promoted non selective H/D exchange under the same conditions (**Scheme 4**). This high selectivity of the Cp*Co^{III} catalyst would reflect the smaller ionic radius of cobalt compared with rhodium.
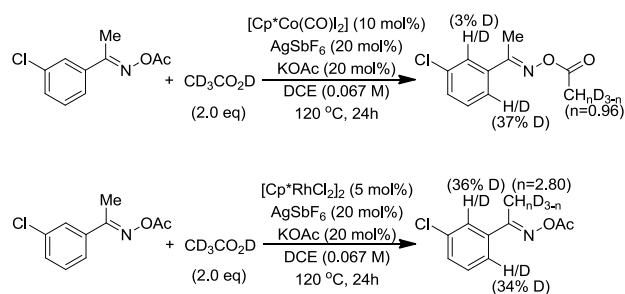
Scheme 4. H/D exchange experiments

Summary

Air-stable and readily available Cp*Co(CO)I$_2$ complex **b** and dimeric [Cp*CoI$_2$]$_2$ complex **c** were obtained from commercially available materials with high yield in large scale. C-2 selective C-H bond amidation of indoles with sulfonyl azides and phosphoryl azides showed excellent selectivity and high functional group tolerance, furnishing the C-2 amidated indoles in good yields.[6,7] When using *meta*-chloro or bromo substituted aryl ketone *O*-acyloximes, Cp*Co(III) showed excellent regioselectivity over Cp*Rh(III), furnishing the C-7 chloro or bromo substituted isoquinolines in good yields.[8] In these three transformations I investigated, the original cationic [Cp*Co^{III}(C$_6$H$_6$)](PF$_6$)$_2$ complex **a** was not effective and the use of newly developed method to generate cationic cobalt(III) complexes *in situ* was critical to obtain high catalytic activity.

References

[1] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Angew. Chem. Int. Ed.* **2013**, *52*, 2207. [2] T. Yoshino, H. Ikemoto, S. Matsunaga, M. Kanai, *Chem. Eur. J.* **2013**, *19*, 9142. [3] J. Y. Kim, S. H. Park, J. Ryu, S. H. Cho, S. H. Kim, S. Chang, *J. Am. Chem. Soc.* **2012**, *134*, 9110. [4] H. Kim, J. Park, J. G. Kim and S. Chang, *Org. Lett.,* **2014**, *16*, 5466. [5] Reviews on oxidative C-H bond functionalization reactions without external oxidant: a) J. Mo, L. Wang, Y. Liu, X. Cui, *Synthesis*, **2015**, *47*, 439; b) H. Huang, X. Ji, W. Wu, H. Jiang, *Chem. Soc. Rev.,* **2015**, *44*, 1155. [6] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Adv. Synth. Catal*., **2014**, *356*, 1491. [7] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Chem. Commun.* **2015**, *51*, 4649. [8] B. Sun, T. Yoshino, S. Matsunaga, M. Kanai, *Manuscript in preparation.*