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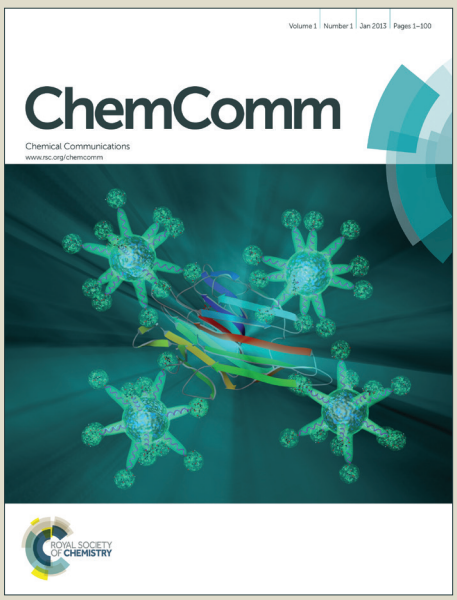

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A Cp^*CoI_2-dimer as a precursor for cationic Co(III)-catalysis: application to C-H phosphoramidation of indoles

Cite this: DOI: 10.1039/x0xx00000x

Received ooth December 2014,
Accepted ooth January 2015

DOI: 10.1039/x0xx00000x

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C2-Selective indole C-H phosphoramidation was achieved under improved Cp*Co(III) catalysis. A cationic Co(III) species generated in situ from a Cp^*CoI_2-dimer showed the best catalytic activity, giving phosphoramidated indoles in 60-86% yield.

Transition metal-catalyzed C-H bond functionalization reactions are powerful and potentially superior to traditional organic reactions using stoichiometric activating reagents. Among the various transition metal catalysts developed for C-H bond functionalization reactions, cationic Cp*Rh(III) and Cp*Ir(III) complexes are widely applied for various C-C, C-N, and many other C-X bond-forming reactions.[1] Despite their high catalytic activity and broad reaction scope, however, the use of expensive and precious rhodium and iridium metal sources is somewhat disadvantageous. Thus, the development of an alternative catalyst with readily available base metal sources is highly desirable.[2] Since our first report on the utility of a cationic Cp*Co(III)-arene complex **1a** in 2013 (Fig. 1),[3] we and others have expended tremendous effort to broaden the scope of Co(III)-catalysis.[4,5] The development of a readily available, stable, and easy-to-handle catalyst is in high demand to further enhance the application of cationic Cp*Co(III) catalysis. Toward this aim, we previously reported the synthesis and application of a $Cp^*Co(CO)I_2$ complex.[6] The $Cp^*Co(CO)I_2$ complex **1b** was useful for generating an active cationic Co(III) species in situ. 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 Co(III) catalysis. Herein, we describe the utility of an air-stable dimeric $[Cp^*CoI_2]_2$ complex **1c**, which is readily available in multi-gram quantity. The dimeric $[Cp^*CoI_2]_2$ **1c** showed superior performance in comparison with previously reported Co(III) complexes.

Phosphoramidates are important structural units found in many biologically active compounds,[7] such as agrocin 84,[8a] microcin C7,[8b] and phosmidosine antibiotics,[8c] and pro-nucleotides as prodrugs of antiviral and antitumor agents.[8d] In addition, phosphoramidates are useful synthetic intermediates for synthesizing various nitrogen-containing heterocycles.[9] Conventional methods for phosphoramidates rely on P-N bond formation, while the C-H bond phosphoramidation strategy is less studied. Recently, a couple of C-H phosphoramidation reactions with phosphoryl azides were disclosed under transition metal catalysis.[10-13] Among them, the Cp*Ir(III)-based strategy pioneered by Chang and coworkers provides a highly efficient approach for the synthesis of various phosphoramidates from arenes.[12] Because indoles were not used in recent reports of Cp*Ir(III)-catalysis, we selected C-H phosphoramidation reaction of indoles **2** with phosphoryl azides **3** as a target reaction to broaden the scope of C-H phosphoramidation reactions.[14]

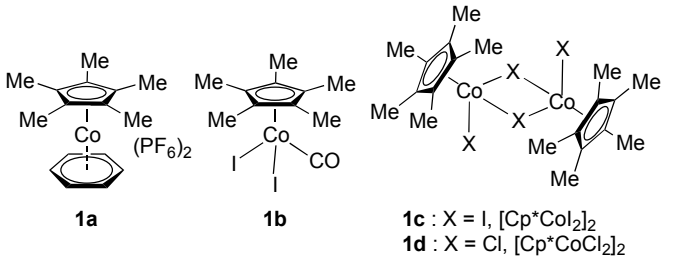
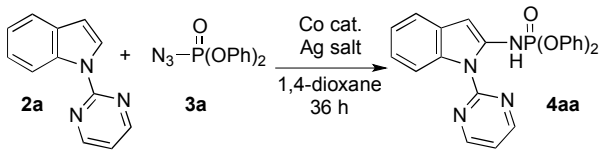


Fig. 1 Structures of Cp*Co(III) complexes **1a**-**1d**.

Initial optimization studies using indole **2a** and azide **3a**[15] are summarized in Table 1. The original cationic Cp*Co-arene complex **1a** did not afford any product (entry 1). In situ generation of an active cationic Cp*Co(III) species was effective, and the combination of $Cp^*Co(CO)I_2$ **1b** and $AgSbF_6$ gave the desired product **4aa**, albeit in moderate yield (entry 2, 34%). The yield was improved by changing the catalyst precursor to a dimeric iodide complex $[Cp^*CoI_2]_2$ **1c** (50%, entry 3), while $[Cp^*CoCl_2]_2$ **1d**[3] resulted in poor yield (4%, entry 4).[16] Because dimeric $[Cp^*CoI_2]_2$ **1c** was synthesized by thermal decarbonylation of **1b** in a gram scale,[17] it was necessary to carefully perform the decarbonylation process. Once dimeric $[Cp^*CoI_2]_2$ **1c** was obtained, however, **1c** itself was air-stable and easy-to-handle. Other silver salts (entries 5-6) as well as other solvents did not improve the yield. In contrast to our previous studies on indole functionalization,[4a,6] the addition of KOAc was not effective (entry 7). While higher temperature decreased the yield, probably due to the thermal instability of **3a** (entries 8-9), a higher concentration improved the yield (entries 10-

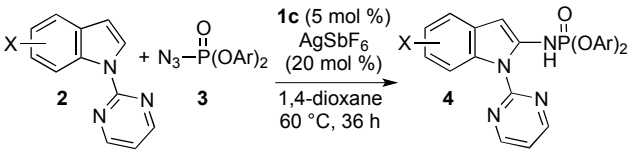
Table 1 Optimization of reaction conditions[a]

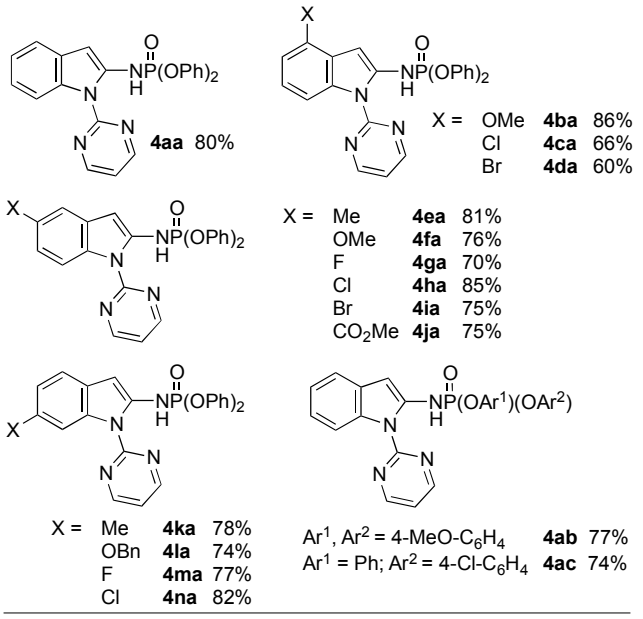


Entry	Co cat. (x mol %)	Ag salt (y mol %)	Temp (°C)	Conc. (M)	Yield (%)[b]
1	**1a** (10)	none	60	0.2	0
2	**1b** (10)	$AgSbF_6$ (20)	60	0.2	34
3	**1c** (5)	$AgSbF_6$ (20)	60	0.2	50
4	**1d** (5)	$AgSbF_6$ (20)	60	0.2	4
5	**1c** (5)	$AgPF_6$ (20)	60	0.2	trace
6	**1c** (5)	$AgBF_4$ (20)	60	0.2	5
7[c]	**1c** (5)	$AgSbF_6$ (20)	60	0.2	45
8	**1c** (5)	$AgSbF_6$ (20)	80	0.2	17
9	**1c** (5)	$AgSbF_6$ (20)	100	0.2	0
10	**1c** (5)	$AgSbF_6$ (20)	60	1.0	79
11	**1c** (5)	$AgSbF_6$ (20)	60	2.0	86 (80)[d]
12	none	$AgSbF_6$ (20)	60	2.0	0
13	**1c** (5)	none	60	2.0	trace
14	$Co(acac)_3$ (10)	none	60	2.0	0
15	$Co(NH_3)_6Cl_3$ (10)	none	60	2.0	0
16	CoI_2 (10)	$AgSbF_6$ (20)	60	2.0	0

[a] Reactions were run using 2 equiv of **2a**. [b] Yield of **4aa** was determined by ^{1}H NMR analysis of crude reaction mixture with an internal standard. [c] KOAc (20 mol %) was added. [d] Isolated yield of **4aa** was determined after purification by silica gel column chromatography.

Table 2 Substrate scope of phosphoramidation of indoles **2** with phosphoryl azides **3**[a]



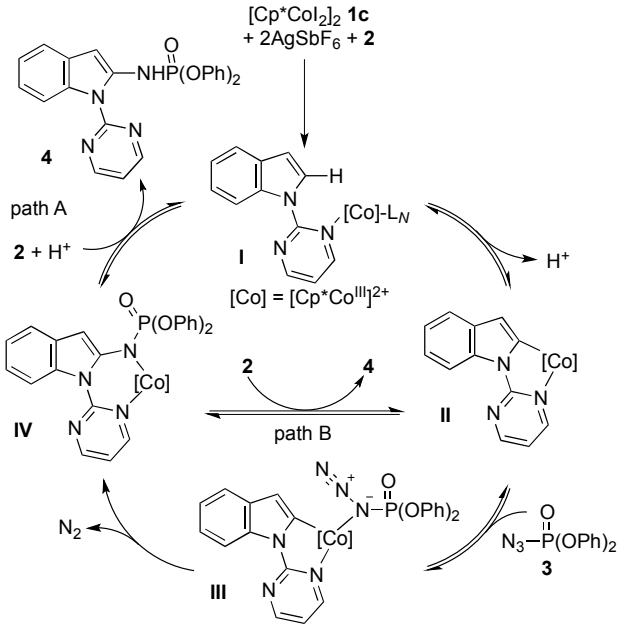


[a]Reactions were run using **2** (0.80 mmol), **3** (0.40 mmol), **1c** (5 mol %), and $AgSbF_6$ (20 mol %) in 1,4-dioxane (2.0 M) at 60 °C for 36 h. Isolated yield of **4** was determined after purification by silica gel column chromatography.

11). In entry 11, **4aa** was obtained in 86% yield (80% isolated yield) at 2.0 M in 1,4-dioxane at 60 °C. The reaction was completely C2-selective, and no regioisomeric product was detected under the optimized reaction conditions. Negative control experiments in entries 12-13 indicated that both complex **1c** and $AgSbF_6$ are essential to promote the reaction. Neither other Co(III)-salts nor in situ-generated cationic Co(II)-species promoted the reaction (entries 14-16), suggesting that the use of cationic Co(III) species was essential to promote the reaction.

The substrate scope of the phosphoramidation of indoles under the optimized conditions is summarized in Table 2.[18] Various indoles bearing electron-donating (Me, MeO, and BnO) and electron-withdrawing groups (halogen and CO_2Me) at either the C4-, C5-, or C6-position afforded products **4aa**–**4na** 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, our reaction conditions are complementary to the intra- and intermolecular alkane amidation reaction via an outersphere mechanism under Co- and Ru-porphyrin catalysis.[11b] With regard to the scope of the phosphoryl azide, an electron-donating MeO-substituent and an electron-withdrawing Cl-substituent were compatible (**4ab**, 77%; **4ac**, 74%). On the other hand, diethyl phosphoryl azide did not afford desired phosphoramidation product.

A plausible reaction mechanism is depicted in Scheme 1, based on the previously reported Cp*Co(III)-catalyzed C-H bond functionalization reaction of indoles[4] and the mechanistic studies by Chang and coworkers on the Cp*Rh(III)-catalyzed[19] C-H bond amidation reactions. Initial halide abstraction from $[Cp^*CoI_2]_2$ **1c** by $AgSbF_6$ in the presence of the pyrimidyl-protected indole **2** would form cationic complex **I**. A C-H bond activation step to afford metalacycle **II** would proceed via either electrophilic aromatic substitution mechanism or concerted metalation-deprotonation



Scheme 1 Plausible catalytic cycle.

(CMD)[20] assisted by some basic functional groups. Coordination of phosphoryl azide **3** (**III**) followed by C-N bond formation with release of N_2 gave **IV**. Although stepwise C-N bond formation

through a Rh(V)-nitrenoid species rather than concerted C-N bond formation was supported in the Cp*Rh^{III}-catalyzed amidation reaction,[18] we cannot yet conclude which mechanism is plausible, either nitrenoid formation or concerted substitution, for the Cp*Co(III) catalysis. Because there is no evidence for the formation of a high valent, possibly unstable, Co(V) intermediate under the present reaction conditions, further studies are required to clarify the reaction pathway. Protonation by the acidic proton released in the C-H bond metalation step (path A) or direct deprotonation from a C-H bond of another substrate **2** (path B) would dissociate the product **4**.

In conclusion, an improved cationic Cp*Co(III) catalyst generated from $[Cp^*CoI_2]_2$ **1c** and $AgSbF_6$ exhibited higher catalytic activity than those from other Cp*Co(III)-complexes. Directing group-assisted C-H bond metalation realized high regio- and chemoselectivity under mild conditions, and the C2-selective C-H bond phosphoramidation reaction of 2-pyrimidyl-protected indoles proceeded in 60–86% yield. Studies of the reaction mechanism as well as further applications of Cp*Co(III)-catalysis are actively ongoing in our group.

Notes and references

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† Financial support was in part provided by ACT-C from JST, Grant-in-Aid for Scientific Research on Innovative Areas from MEXT and the Naito foundation. Electronic Supplementary Information (ESI) available: [experimental details, including procedures, characterization of new products, ^{1}H and ^{13}C NMR charts,]. See DOI: 10.1039/c000000x/

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17 For detailed procedure, see Electronic Supplementary Information. See also, S. A. Frith and J. Spencer in: *Inorganic Syntheses: Reagents for Transition Metal Complex and Organometallic Syntheses*, Vol. 28, (Ed.: R. J. Angelici), Inorganic Syntheses, Inc., pp 273–277.

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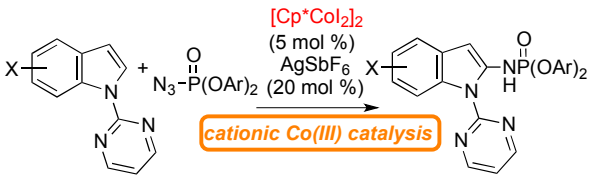
Graphical Abstracts:



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