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Cobalt(III)-Catalyzed C2-Selective C−H Alkynylation of Indoles

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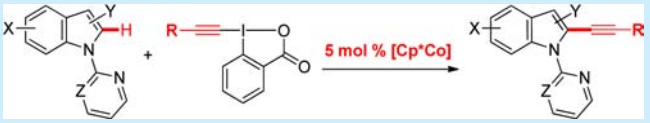
Supporting Information

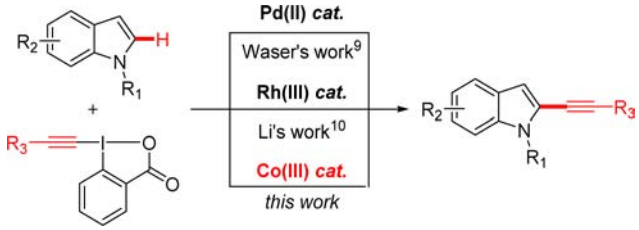
ABSTRACT: A cobalt(III)-catalyzed C-2 selective C−H alkynylation of indoles using hypervalent iodine-alkyne reagents is described. A broad range of synthetically useful functional groups (−F, −Cl, −Br, $-CO_2Me$, −CN) were tolerated, providing an efficient and robust protocol for the synthesis of C-2 alkynylated indoles. The pyrimidyl and silyl protecting groups could be easily removed to give the corresponding 2-ethynyl-1*H*-indole.



Indole is a privileged structural motif widely found in natural products, marketed drugs, agrochemicals, fragrances, and material sciences.[1] Consequently, tremendous efforts have been devoted to the effective synthesis and functionalization of indoles.[2] Over the past few decades, transition-metal-catalyzed C−H functionalization has emerged as an attractive, economical, and environmentally benign alternative to the classical synthetic methods, allowing the expeditious formation of diverse indoles.[3] In particular, the direct C−H functionalization of indoles has witnessed great success for the late-stage modification of the preexistent indole nucleus.[4]

Alkynylindoles are versatile building blocks in organic synthesis, pharmaceuticals, biochemistry, and functional materials. However, compared with the well-studied arylation, alkylation, and vinylation,[5] the direct alkynylation of the indole nucleus is largely underexplored.[6−11] The C3-selective alkynylation of indoles was first reported by Gu and coworkers using bromoalkynes and a Pd catalyst in 2009.[6] Shortly after, Waser reported a gold-catalyzed C3-selective alkynylation of indoles under different mechanisms, respectively.[7a] These reactions proceeded with electrophilic metalation at C3, due to the high nucleophilic reactivity at this position. In 2010, the Li group reported a Pd-catalyzed C2-selective Heck−Cassar−Sonogashira type alkynylation of indoles with various terminal alkynes.[8] However, only 3-methylindoles were employed as substrates. The C2 selective alkynylation of indoles that do not possess substituents at the C3-position is extremely difficult.[9−11] Generally, two kinds of strategies have been employed to achieve the selectivity, including a postulated electrophilic metalation at C3 followed by metal migration,[9] and the introduction of directing groups.[10] In 2013, Waser and coworkers reported the first example of Pd-catalyzed C2 alkynylation of indoles using alkynylated hypervalent iodine reagents (TIPS-EBX), under typically very mild conditions (Scheme 1).[9] In 2014, the Li research group described several excellent examples of the direct C2 alkynylation of these heterocyclic compounds by Cp*Rh(III) catalysis with low a catalyst loading (Scheme 1).[10] However, these established methods relied on the use of expensive second-row transition-metal catalysts. Therefore, the development of C2-selective alkynylation of indoles with abundant first-row transition metals would be highly desirable yet challenging.

Scheme 1. C2-Selective Alkynylation of Indoles



Recently, high-valent Cp*Co(III) catalysts have been identified as robust, powerful, and cheap metal catalysts in C−H alkylations, alkenylations, arylations, amidations, cyanations, and halogenations.[12−17] However, to the best of our knowledge, Co(III)-catalyzed C−H alkynylation has not been realized. As part of our continuing efforts on the synthesis of aryl alkynes via C−H alkynylation,[18] we report herein a Cp*Co(III)-catalyzed C−H alkynylation with TIPS-EBX[19] to furnish C-2 alkynylated indoles under simple and redox-neutral reaction conditions (Scheme 1). The pyrimidyl and silyl protecting groups could be easily removed to give the corresponding 2-ethynyl-1*H*-indole.

Our initial investigation focused on the reaction of (pyrimidin-2-yl)-1*H*-indole (**1a**) and 1-[(triisopropylsilyl)-ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS-EBX) (**2a**), which was first reported by Waser in the alkynylation of indoles with gold or palladium catalysis[7,9,19] and further applied to Rh(III)- or Ir(III)-catalyzed C−H alkynylation by Loh,[20] Li,[10,21] and Glorius.[22] *N*-Pyrimidyl was selected as a directing group to ensure the C2-selectivity.[23] The desired alkynylated product **3a** was obtained in 5% yield when $[Cp^*Co(CO)I_2]$ was used in the presence of silver fluoride and potassium acetate at 80 °C (Table 1, entry 1). Surprisingly, $AgSbF_6$, a well-known additive in Rh(III)-catalyzed C−H activation reactions, did not give any desired product (entry 2). Next, various additives were

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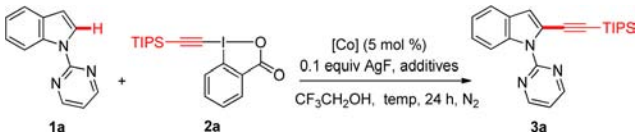
Table 1. Optimization of the Reaction Conditions[a]



entry	[Co]	additives (equiv)	temp (°C)	yield (%)[b]
1[c]	[CoCp*(CO)I_2]	KOAc (1)	80	5
2[d]	[CoCp*(CO)I_2]	KOAc (1)	80	0
3	[CoCp*(CO)I_2]	$Mg(OCH_3)_2$ (1)	80	35
4[c]	[CoCp*(CO)I_2]	$Mg(OCH_3)_2$ (1)	100	45
5[c]	[CoCp*(CO)I_2]	$Mg(OCH_3)_2$ (3)	100	78
6	[CoCp*(CO)I_2]	$Mg(OCH_3)_2$ (3)	110	84[e]
7	–	$Mg(OCH_3)_2$ (3)	110	0
8	$[Cp^*_2Co]PF_6$	$Mg(OCH_3)_2$ (3)	110	0

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), [CoCp*(CO)I_2] (5 mol %), CF_3CH_2OH (1 mL), at temp (°C) for 24 h under nitrogen. [b]^1H NMR yields using 1,3,5-trimethoxybenzene as the internal standard. [c]0.2 equiv of AgF. [d]0.2 equiv of $AgSbF_6$. [e]Isolated yield.

examined, and $Mg(OCH_3)_2$ was demonstrated to be effective, affording the desired product **3a** in 35% yield (entry 3). Although the exact role of $Mg(OCH_3)_2$ is unclear at this stage, we hypothesized that it may activate TIPS-EBX.[10] A significant improvement in yield was observed by increasing the amount of $Mg(OCH_3)_2$ to 3.0 equiv and the temperature to 100 °C (entry 5, 78%). The reaction proceeded better with a reduced AgF loading at 110 °C, affording the alkynylated product **3a** in 84% isolated yield (entry 6). Control experiments revealed that the alkynylation did not occur in the absence of the [CoCp*(CO)I_2] catalyst (entry 7). Commercially available Co(III) salts, such as $[Cp^*_2Co]PF_6$, did not promote the reaction (entry 8). Based on these optimization studies, we confirmed that 5 mol % [CoCp*(CO)I_2], 10 mol % AgF, and 3 equiv of $Mg(OCH_3)_2$ in CF_3CH_2OH at 110 °C offer the best conditions for this C–H alkynylation reaction (entry 6).

With the optimized reaction conditions in hand, the scope of this reaction was examined with various indoles. As shown in Figure 1, C2-selective alkynylation of indoles proceeded well to give the desired products irrespective of various substitution patterns on the phenyl ring. Both electron-donating and -withdrawing substituents, such as methoxy (**3e** and **4d**), methyl (**3g**–**3j**, **4f**), fluoro (**3b** and **4b**), chloro (**3c**), bromo (**3d** and **4c**), methoxycarbonyl (**3f** and **4e**), and cyano (**3k**), were compatible with this protocol, providing alkynylindoles in moderate to good yields. However, with a 3-cyanoindole substrate, the reactivity decreased significantly, and the alkynylated product **3k** was obtained in only 29% yield, perhaps because of the combination of both steric hindrance and strong electron deficiency. When the directing group was changed from *N*-pyrimidyl to *N*-pyridyl, the desired product **3l** was obtained in comparable yield (**3l**, 50%). The TBDPS protected alkyne reagent, TBDPS-EBX, was also compatible with the optimized conditions, affording the corresponding products in moderate yields (**4a**–**4f**, 32–59% yields). Although only moderate yields were obtained in some cases, the starting materials could be recovered. Finally, we also examined other alkynylated hypervalent iodine reagents. The presence of the bulky silyl groups are essential for the success of the reaction, and no alkynylated products were observed when alkyl or aryl substituted alkynylation reagents were used. Given the ready

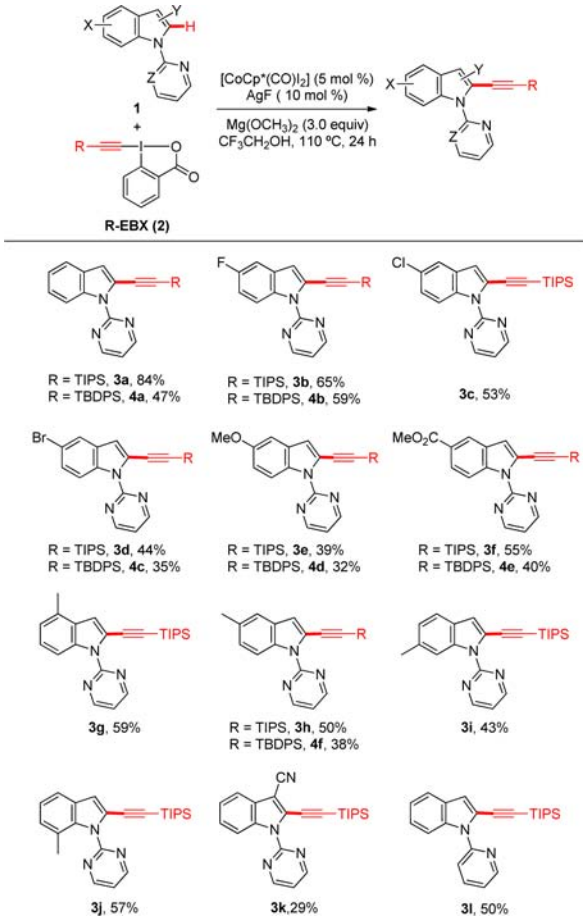


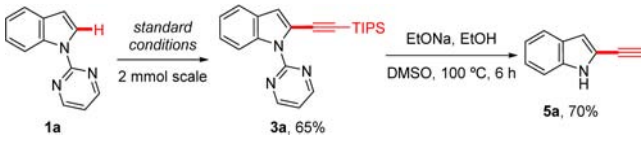
Figure 1. Substrate scope for cobalt-catalyzed C2-selective C–H alkynylation of indoles. Reaction conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), [CoCp*(CO)I_2] (5 mol %), CF_3CH_2OH (1 mL), at 110 °C for 24 h under nitrogen. Isolated yields are presented.

removal of the silyl group and the versatility of the resulting terminal alkynes, we anticipated that synthetic applications via a desilylation/metal-mediated coupling sequence would be feasible.

To highlight the synthetic utility of this procedure, a 2 mmol scale reaction was conducted using **1a** as substrate, and the reaction proceeded smoothly to give the alkynylated product **3a** in 65% yield. Furthermore, the *N*-pyrimidyl directing group and triisopropylsilyl protecting group could be easily removed from **3a** in one pot,[23] affording 2-ethynyl-1*H*-indole **5a** in 70% yield (Scheme 2). Although the sterically bulky silyl groups are crucial for the reaction, the silyl groups can be easily removed to give the terminal alkyne, which could be used for further derivation.

Although the detailed mechansim is not clear, a plausible catalytic cycle based on related Rh(III)-catalyzed alkynylation was proposed in Scheme 3.[10,20,21] Initially, the active Cp*Co-

Scheme 2. Gram-Scale Synthesis and Removal of the Protecting Groups



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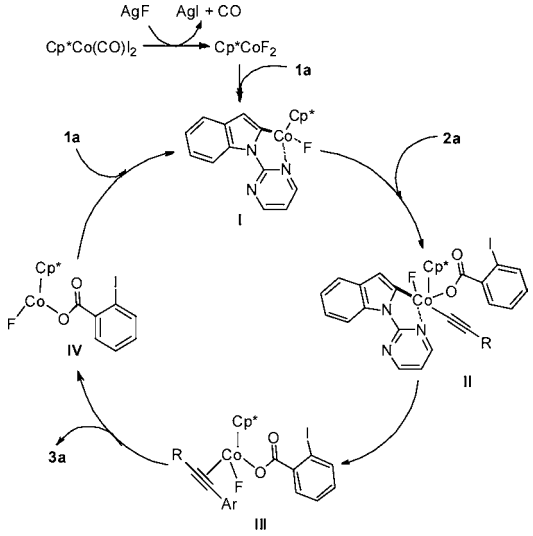
Scheme 3. Proposed Mechanism



(III) catalyst is generated in situ in the presence of AgF. *Ortho*-C−H activation affords cobaltacylce **I**, and subsequent oxidative addition of hypervalent iodine-alkyne reagent **2a** leads to the formation of a putative Co(V) alkynyl intermediate **II**. The alkynylated product **3a** is afforded via reductive elimination followed by protonolysis of Co(III) intermediate **III** to give the active Co(III) catalyst **IV**. However, a mechanistic pathway that involves transmetalation between cobaltacycle **I** and the hypervalent iodine-alkyne reagents cannot be excluded at this stage.[10]

In conclusion, we have observed the cobalt(III) catalyzed C2-selective alkynylation of indoles with alkynylated hypervalent iodine reagents. The reaction demonstrates good functional group compatibility. Further, the pyrimidyl directing group and triisopropylsilyl protecting group can be removed easily in one pot, providing a useful tool for the synthesis of diverse 2-ethynyl-1*H*-indoles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02038.

Experimental details and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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