JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/ja511011m • Publication Date (Web): 04 Dec 2014

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Co(III)-Catalyzed C–H Activation/Formal S_N-type Reactions: Selective and Efficient Cyanation, Halogenation and Allylation

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Supporting Information Placeholder

ABSTRACT: The first cobalt-catalyzed cyanation, halogenation and allylation via C–H activation have been realized. These formal S_N-type reactions generate valuable (hetero)aryl/alkenyl nitriles, iodides, and bromides as well as allylated indoles using a bench-stable Co(III)-catalyst. High regio- and mono-selectivity were achieved for these reactions. Additionally, allylation proceeded efficiently with a turnover number (TON) of 2200 at room temperature, which is unprecedented for this Co(III)-catalyst. Alkenyl substrates and amides have been successfully utilized in Cp*Co(III)-catalyzed C–H activation for the first time.

Nucleophilic substitution (S_N) is a fundamental reaction class in chemistry (Figure 1A).[1] Various kinds of stoichiometric organometallic reagents have been applied as nucleophiles in S_N-type reactions. However, many of them are expensive, sensitive or difficult to prepare and handle. An alternative approach is to generate nucleophilic organometallic species in situ under catalytic conditions with a suitable transition metal catalyst. Due to the high atom- and step-economy, the most attractive method to access such species is C–H activation.[2] Organometallic species generated in this way have been successfully employed in cross-couplings and nucleophilic addition or substitution with different electrophiles.[2]

Compared to noble metals, 1st row transition metals are more earth-abundant, easily available, and inexpensive. As such, their use as catalysts attracts increasing attention, especially for C–H activation reactions.[3,4] For example, various kinds of C–C and C–heteroatom bond forming reactions have been developed via cobalt-catalyzed C–H activation.[4,5,6] Among these transformations, a few examples of coupling reactions with electrophiles have been reported recently (Figure 1B).[5] Pioneered by Nakamura, Ackermann, and Yoshikai, cobalt-catalyzed efficient and selective C–H activation/coupling reactions have been realized with alkyl/aryl halides, phenol, and benzyl alcohol derivatives under mild reaction conditions. Grignard reagents were used as bases and reductants to generate reactive low-valent cobalt-catalysts from precatalysts. Although many functional groups could be tolerated, reactive Grignard reagents induced some undesirable coupling reactions or dehydrohalogenation of the electrophiles. Therefore, it is appealing to develop other catalytic systems without using Grignard reagents. Herein, we report the first cobalt-catalyzed cyanation, halogenation and allylation reactions via C–H activation (Figure 1C). These Cp*Co(III)-catalyzed formal S_N-type reactions do not require the use of reactive Grignard reagents, and are highly selective, efficient (with a TON of 2200), scalable and robust. Furthermore, we report the first Cp*Co(III)-catalyzed C–H activation proceeding at room temperature.[7]

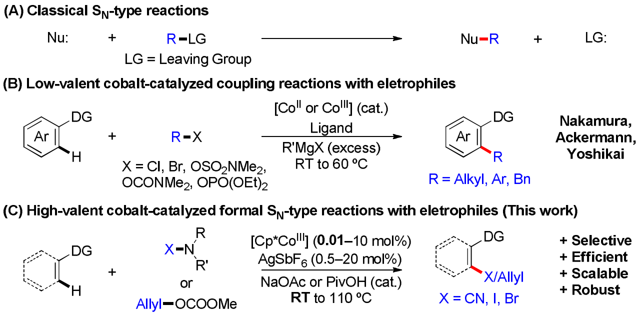


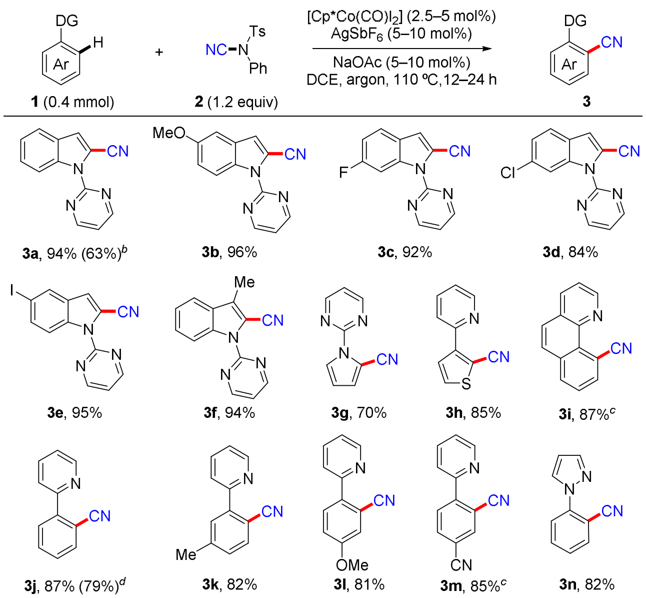
Figure 1. Cobalt-catalyzed coupling and formal S_N-type reactions with electrophiles via C–H activation. DG = directing group.

Our group has been working in the area of Rh(III)-catalyzed C–H activation for several years.[8] Although much progress has been made, the relatively high price of Rh-catalysts and curiosity about the reactivity and selectivity of its lighter congener led us to investigate Co(III)-catalysis. Very recently, the group of Kanai and Matsunaga has pioneered and contributed greatly to this field.[6] With well-defined Cp*Co(III)-catalyst precursors, they have developed insertion reactions of unsaturated moieties (imines, enones and alkynes) and nitrogen (with azides as N source) into aryl C–H bonds. They also developed an unprecedented indole C2-alkenylation/intramolecular addition to generate important pyrroloindolones. We were interested in the behavior of the Cp*Co(III)-catalyst in *intermolecular formal S_N-type reactions*[2s] with electrophilic cyanation, halogenation and allylation reagents, which might be not compatible with Grignard reagents in the low-valent cobalt catalysis.[5] Moreover, valuable organo-nitriles and -halides as well as allylated arenes could be generated, common motifs in many bioactive molecules[9] and organic synthesis.[10]

We first tested cyanation due to its high value and the ease of derivatization of organo-nitriles.[11] Direct functionalization of the indole motif is highly important and thus attracts much attention. Due to its inherent nucleophilicity at the C3 position, there are several reports on electrophilic C3-cyanation.[12] We expected to overcome this reactivity to achieve the selective directed C2-cyanation using the bench-stable complex [Cp*Co(CO)I$_2$] as the catalyst.[6d] Due to its low toxicity, ease of handling, and stability,[13] *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) **2** was chosen as the reaction partner. To our delight, after an extensive screen of reaction conditions we successfully realized a highly selective and efficient C2-cyanation of *N*-(2-pyrimidinyl)indole **1a** to give **3a** in the presence of catalytic amounts of AgSbF$_6$ and NaOAc (Scheme 1). No reaction was observed in the absence of the Co(III)-catalyst or using 1-cyanopyrrolidine as the CN-source. Moreover, 63% yield was obtained using only 0.5 mol% of the Co(III)-catalyst.

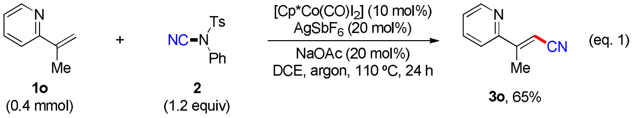
Under the optimized reaction conditions, other indoles with different substituents were tested (Scheme 1). Many functional groups, for example methoxy (**3b**), fluoro (**3c**), chloro (**3d**) and iodo (**3e**) were tolerated, which provides great opportunities for further functionalizations. To our delight, the substrate **1f** with a methyl group at the C3-position gave the desired product **3f** in an excellent yield despite the steric hindrance.

Scheme 1. Cobalt-Catalyzed C–H Cyanation [a]



[a] Reaction conditions: **1** (0.4 mmol), **2** (1.2 equiv), [Cp*Co(CO)I$_2$] (2.5–5.0 mol%), AgSbF$_6$ (5–10 mol%), NaOAc (5–10 mol%), DCE (3 mL), 12–24 h. [b] [Cp*Co(CO)I$_2$] (0.5 mol%), AgSbF$_6$ (1 mol%), NaOAc (2 mol%). [c] 1.5 equiv of **2**. [d] 8.0 mmol scale.

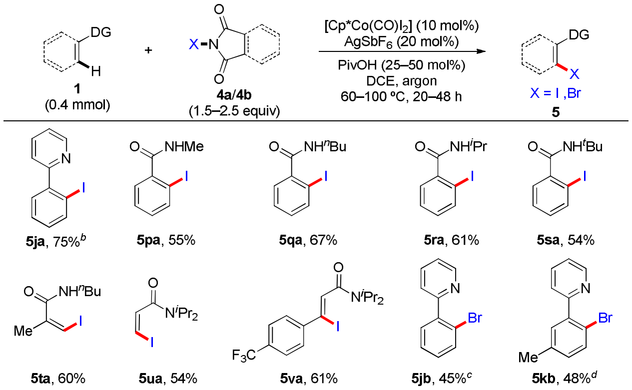
Moreover, other kinds of arenes and heteroarenes with different directing groups (DGs) were explored. *N*-(2-pyrimidinyl)pyrrole **1g** underwent selective and clean transformation to generate **3g**, albeit with a slightly lower efficiency. 2-Arylpyridines also showed good reactivity and selectivity for mono-cyanation. For these compounds, the reaction was sensitive to steric hindrance and the substrate electronics. For example, the C–H cyanation of 2-(*m*-tolyl)pyridine **1k** selectively occurred at the position with lower steric hindrance.[14] Compared to the electron-poor 2-(4-cyanophenyl)pyridine **1m**, the more electron-rich 2-(4-methoxyphenyl)pyridine **1l** showed higher reactivity, which was also demonstrated by a competition experiment (products **3l** and **3m** formed in a ratio of 29:1; please see the SI for details). Both the steric and electronic effects might contribute to the high regio- and chemo-selectivity of this transformation. A gram scale reaction of 2-phenylpyridine **1j** also proceeded with similar efficiency. Another heterocycle, the thiophene derivative **1h**, also underwent highly selective C2-cyanation in 85% yield with pyridyl as directing group. Benzo[*h*]quinoline **1i** and *N*-phenylpyrazole **1n** also showed good reactivity and selectivity in this transformation. Furthermore, a robustness screen has been done to demonstrate the good functional group tolerance.[15]



Gratifyingly, the cyanation did not only happen on (hetero)arenes but also on olefins via alkenyl C–H activation. 2-(Prop-1-en-2-yl)pyridine **1o** showed good reactivity in this reaction and a subsequent isomerization generated **3o** as the thermodynamically favored product (Eq. 1, please see the SI for details). To the best of our knowledge, this is the first reported example of Cp*Co(III)-catalyzed alkenyl C–H activation.

The success of the cyanation reaction led us to extend the method developed to other electrophiles containing N-based leaving groups. Since organo-halides are powerful substrates, the selective halogenation of C–H bonds is an important transformation,[16] especially when using commercially available and less toxic halogen sources such as *N*-iodosuccinimide (NIS, **4a**) and *N*-bromophthalimide (NBP, **4b**). We proposed selective halogenation could be possible with Cp*Co(III)-catalysis. Indeed, under reaction conditions similar to the cyanation reaction, **1j** underwent selective mono-iodination at 70 °C to give **5ja** in good yield (Scheme 2).[17]

Scheme 2. Cobalt-Catalyzed C–H Halogenation [a]

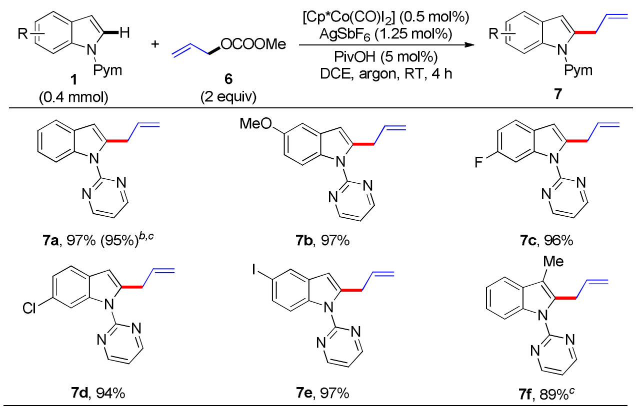


[a] Reaction conditions: **1** (0.4 mmol), **4** (1.5–2.5 equiv), [Cp*Co(CO)I$_2$] (10 mol%), AgSbF$_6$ (20 mol%), PivOH (25–50 mol%), DCE (2 mL), 20–48 h. [b] NaOAc (20 mol%) was used instead of PivOH. [c] 3.0 equiv of **1j**, NMR yield. [d] 2.0 equiv of **1k**.

When we moved on to test other kinds of substrates with different directing groups, pivalic acid was found to promote the iodination and higher conversions than with sodium acetate were achieved. The role of the acid might be the activation of NIS through protonation, increasing its electrophilicity, or the generation of a highly reactive cobalt catalyst with a vacant site for coordination.[18] Under the slightly modified reaction conditions, *N*-alkylbenzamides (**1p**, **1q**, **1r**, and **1s**), which have not yet been successfully applied in Cp*Co(III)-catalyzed C–H activation,[19] showed moderate to good reactivity to generate mono-iodinated products (**5pa**, **5qa**, **5ra**, and **5sa**).[20] It is noteworthy that benzamides are highly important and useful functional groups in medicinal and material chemistry.[5a] Selective mono-iodination was also observed for olefins via alkenyl C–H activation. Thus, acrylamides (**1t**, **1u**, and **1v**) reacted under these reaction conditions to selectively generate **5ta**, **5ua**, and **5va** in moderate yields. No desired product was detected in the absence of the Co(III)-catalyst. Furthermore, bromination was tested to generate aryl bromides. Selective mono-bromination of **1j** and **1k** occurred with moderate yields using NBP **4b** as the bromination reagent.[21]

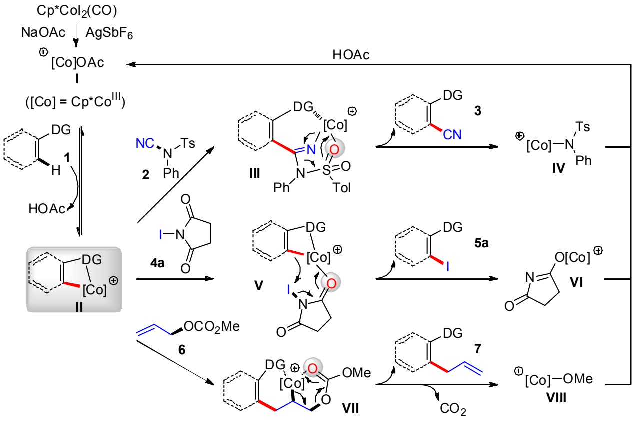
Based on the success of S_N2-type reactions, related S_N2'-type transformations were further considered. Due to the importance of the allyl motif in bioactive compounds and the ease of subsequent functionalization, allylation reactions attract much attention,[22] especially the aryl C–H bond allylation.[23] However, there is no report of allylation via cobalt-catalyzed C–H activation. Thus, the high value of C2-allylated indole structures[9b] made us wonder if Cp*Co(III)-catalyzed formal S_N-type reactions with readily available allyl carbonate **6** could selectively generate 2-allylindoles **7** (Scheme 3).[24] Gratifyingly, the reaction proceeded selectively, with negligible amount of the alternative isomer resulting from double bond migration (less than 1% yield for all cases). To our delight, this transformation took place efficiently even at room temperature, which is unprecedented for Cp*Co(III)-catalyzed C–H activation. No reaction occurred when cobalt or silver was omitted. Moreover, an excellent yield was obtained for the allylation of **1a** with as low as 0.2 mol% catalyst loading. This means a TON of 474 was obtained. We found that, if given time, the turnover number can reach an impressive 2200 at room temperature (please see the SI for details). Reported turnover numbers of this level are rare in the field of C–H activation/C–C bond formation.

Scheme 3. Cobalt-Catalyzed C–H Allylation [a]



[a] Reaction conditions: **1** (0.4 mmol), **6** (2 equiv), [Cp*Co(CO)I$_2$] (0.5 mol%), AgSbF$_6$ (1.25 mol%), PivOH (5 mol%), DCE (2 mL), RT, 4 h. [b] **1** (1 mmol), [Cp*Co(CO)I$_2$] (0.2 mol%), AgSbF$_6$ (0.5 mol%), PivOH (2 mol%), DCE (5 mL). [c] 8 h. Pym = 2-pyrimidinyl. RT = room temperature.

Scheme 4. Proposed mechanisms



Preliminary mechanistic experiments indicated that the C–H activation was reversible both in the presence or absence of the cyanation reagent NCTS **2** even at room temperature (please see the SI for details). Based on previous reports[6] and our results, we propose the following mechanism (Scheme 4). First of all, the active Cp*Co(III)-catalyst **I** is generated in situ in the presence of AgSbF$_6$ and a carboxylate source (NaOAc or PivOH) with release of the CO ligand.[23] Coordination of the Co(III)-catalyst to the directing group (DG) (**1**) promotes the C–H activation and generates the cobaltacycle **II**. For the cyanation, coordination of the sulfonamide or cyano groups of NCTS to the Co(III)-center may assist the insertion of the C≡N group into the C–Co bond to generate **III**. This assertion is supported by the fact that 1-cyanopyrrolidine, which does not possess a sulfonamide group, showed no reactivity. This is followed by release of the desired product **3** and regeneration of the Co(III)-catalyst **I** from **IV** by ligand exchange. For the halogenation with NIS, nucleophilic attack of the C–Co bond to the I–N bond (**V**) is proposed to generate the C–I bond in products **5a**, which is similarly promoted by the interaction of Co with one carbonyl group (**V**). For the allylation, a similar coordination of the carbonyl group to Co is proposed to direct the selective insertion, facilitate the β-O elimination and supress the unproductive β-H elimination.

In conclusion, we have developed the first cobalt-catalyzed C–H cyanation, halogenation and allylation reactions. Various kinds of arenes, heteroarenes and alkenes directly undergo such regio- and chemoselective formal S$_N$-type reactions with good functional group tolerance. Alkenyl substrates and amides have been successfully utilized in Cp*Co(III)-catalyzed C–H activation for the first time. Furthermore, C–H activation occurred efficiently at room temperature using 0.01–0.5 mol% of a bench-stable Cp*Co(III)-catalyst. A turnover number (TON) of 2200 was obtained. Valuable organo-nitriles, -iodides, and -bromides as well as allylated indoles have been generated from easily available starting materials. The coordination of oxygen in the leaving group (LG) towards cobalt is proposed to play a vital role in ensuring selectivity and reactivity in these transformations.

ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures; characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

This paper is dedicated to Professor Lixin Dai and Professor Chengye Yuan on the Occasion of their 90th birthdays. We thank Mr. Jan Paulmann, Dr. Matthew Hopkinson, Mr. Nils Schröder, Mr. Basudev Sahoo, Mr. Fabian Lied, and Ms. R. Aleyda Garza Sánchez for kind help and discussions. We are very grateful to the Alexander von Humboldt Foundation (D.G.Y.), the São Paulo Research Foundation (grant 2013/14209-9, F. de A.), SFB858 (S.V.C.), the European Research Council (ERC) under the European Community's Seventh Framework Program (FP7 2007-2013)/ERC grant agreement no 25936, and the DFG (Leibniz award) (F.G.) for generous financial support.

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(20) These amides showed low to moderate conversions in the abovementioned cyanation. On the other hand, the heterocyclic compounds, which showed good reactivity in the cyanation reactions (Scheme 1), were not further investigated due to uncatalyzed background reactions.

(21) Using the preformed cationic Co(III)-complex $[Cp^*Co(MeCN)_3(SbF_6)_2]$ instead of $[Cp^*Co(CO)I_2]$ and $AgSbF_6$, similar reactivity is observed in the halogenation reactions, e.g. 50% isolated yield for the substrate **1k**, supporting the intermediacy of **I**.

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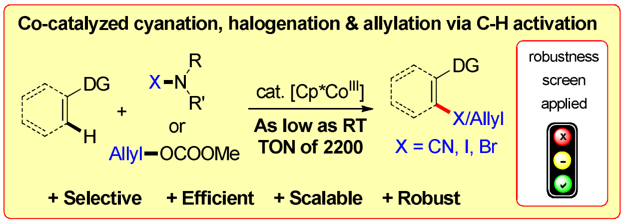
Co-catalyzed cyanation, halogenation & allylation via C-H activation
DG
H
+
X
N
R
R'
or
Allyl
OCOOMe
cat. [Cp*Co^{III}]
As low as RT
TON of 2200
DG
X/Allyl
X = CN, I, Br
robustness screen applied
+ Selective
+ Efficient
+ Scalable
+ Robust