C–H Activation | Hot Paper

DOI: 10.1002/ange.201409247

Cobalt-Catalyzed C–H Cyanation of Arenes and Heteroarenes**

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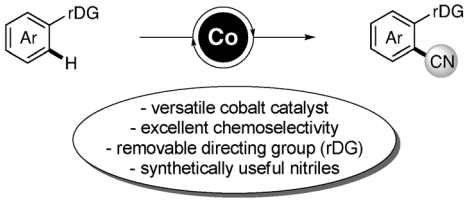
Abstract: *Carboxylate assistance proved to be the key for the success of efficient cobalt(III)-catalyzed C–H cyanations. Thus, an in situ generated cationic cobalt complex was identified as a versatile catalyst for the site-selective synthesis of various aromatic and heteroaromatic nitriles with ample substrate scope.*

Benzonitriles are key structural motifs in numerous important drugs, agrochemicals, and natural products.[1–3] The cyano group also serves as one of the most useful functional groups in organic synthesis, and can be easily transformed into substituted amines, ketones, or aldehydes.[4] The most common procedures for the synthesis of aryl nitriles rely on classical approaches, including the Sandmeyer[5] or the Rosenmund–von Braun reaction.[6,7] These transformations face severe limitations, such as the use of (super)stoichiometric amounts of mostly toxic metal cyanides and harsh reaction conditions. Alternatively, in recent years, transition-metal-catalyzed cyanations of aryl halides or boronic acids have been elegantly developed by the groups of Beller, Buchwald, Gelman, and others.[8] Despite its practical importance, this strategy requires prefunctionalized substrates, the preparation of which calls for tedious functional-group interconversions and leads to undesired waste formation.

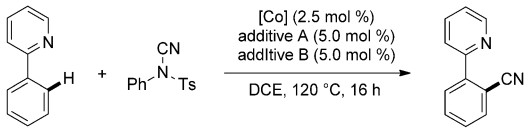
Functionalizations of unactivated C–H bonds provide a means for improving the step- and atom-economy in organic synthesis.[9] While most advances in C–H activation chemistry have been accomplished with expensive second-row transition-metal catalysts, largely based on rhodium, palladium, or ruthenium complexes, more naturally abundant first-row transition-metal compounds have witnessed considerable recent attention.[10] Particularly, inexpensive cobalt catalysts,[11–13] including high-valent [Cp*Co^{III}] derivatives,[13c,d] have in the past few years been identified as increasingly viable tools for the site-selective functionalization of unactivated C–H bonds, yet almost exclusively leading to alkylations, alkenylations, and arylations.[11–13] Considering the practical importance of aryl cyanides, we were attracted to devising reaction conditions for the first cobalt-catalyzed C–H cyanations with the readily available *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS; **2**).[14] In this context it is noteworthy that direct cyanations with **2** have thus far only been accomplished with significantly more expensive rhodium[15–18] or ruthenium[19] catalysts.[20] Within our program on carboxylate-assisted C–H activations,[21,22] we report on unprecedented cobalt-catalyzed C–H cyanations which are accomplished through carboxylate assistance,[22] and provide expedient access to diversely decorated benzonitriles with ample scope (Scheme 1).

We initiated our studies by varying reaction conditions for the envisioned C–H cyanation of substrate **1a** (Table 1). Initial experiments indicated [Cp*CoI$_2$(CO)][23] to be an efficient catalyst in the presence of cocatalytic amounts of $AgSbF_6$ and NaOAc (entry 1), while other cobalt sources were found to be less effective (entries 2–5). These results are indicative of the in situ generation of cationic cobalt(III) acetate[22] catalysts. Among a representative set of acetate additives, KOAc provided optimal results. Notably, omission



Scheme 1. Cobalt-catalyzed C–H cyanation.

Table 1: Optimization of cobalt-catalyzed C–H cyanation.[a]



1a 2 3a

Entry	[Co]	Additive A	Additive B	Yield [%][b]
1	[Cp*CoI$_2$(CO)]	$AgSbF_6$	NaOAc	83
2	[Cp*CoI$_2$(CO)]	AgOAc	NaOAc	0
3	[CoI$_2$]	$AgSbF_6$	NaOAc	0
4	[Co(acac)$_2$]	$AgSbF_6$	NaOAc	0
5	[Cp*CoCl$_2$]$_2$	$AgSbF_6$	KOAc	30
6	[Cp*CoI$_2$(CO)]	$AgSbF_6$	AgOAc	66
7	[Cp*CoI$_2$(CO)]	–	KOAc	0
8	[Cp*CoI$_2$(CO)]	$AgSbF_6$	–	33
9	–	$AgSbF_6$	KOAc	0
10	[Cp*CoI$_2$(CO)]	$AgSbF_6$	KOAc	90
11	[Cp*CoI$_2$(CO)]	$AgSbF_6$	KOAc	93[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), [Cp*CoI$_2$(CO)] (2.5 mol%), additive A (5.0 mol%), additive B (5.0 mol%), DCE (2.0 mL), 120°C, 16 h. [b] Yield of isolated product. [c] **2** (1.5 mmol). DCE = 1,2-dichloroethane, Cp* = C_5Me_5.

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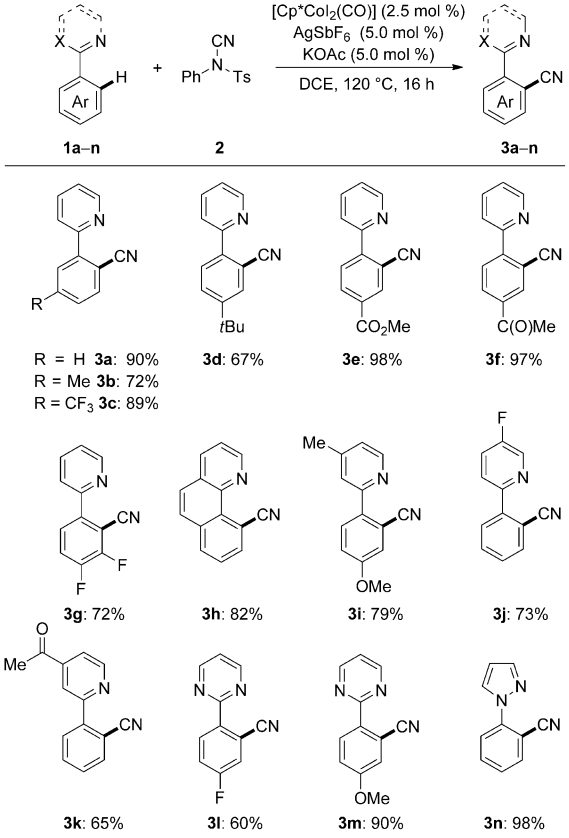
[**] Generous support by the European Research Council under the European Community's Seventh Framework Program (FP7 2007–2013)/ERC Grant agreement no. 307535, and the Chinese Scholarship Program (fellowship to J.L.) is gratefully acknowledged.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201409247.

of either of the catalyst's components resulted in significantly reduced yields of the desired product **3a** (entries 6–10). A C–H cyanation with an excess **2** furnished the monocyanated arene **3a** as the sole product (entry 11), thereby highlighting the excellent chemoselectivity of the cobalt(III) catalyst.

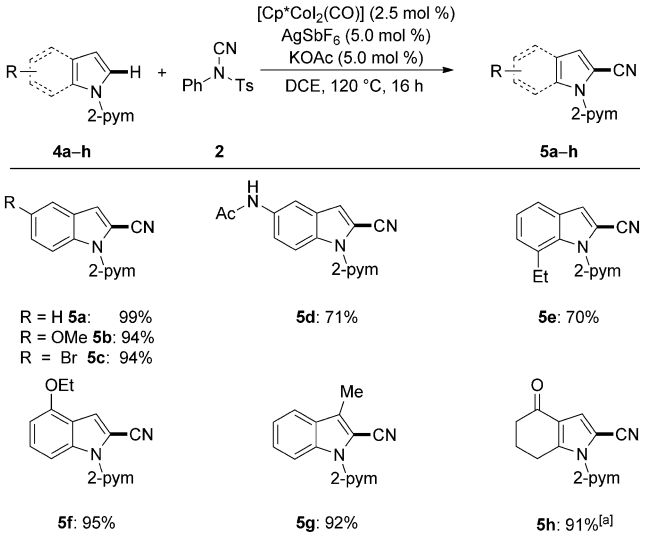
With the optimized cobalt(III) catalyst in hand, we tested its substrate scope with various N-heteroarylarenes (Scheme 2). The chelation-assisted C–H cyanation of the



Scheme 2. Substrate scope of cobalt-catalyzed C–H cyanation.

meta-disubstituted arenes **1a–c** proceeded with excellent levels of site selectivity at the less sterically hindered position. Importantly, the cobalt catalyst displayed a remarkable chemoselectivity wherein a number of valuable electrophilic groups, such as esters or ketones, were well tolerated. The fluoro substituent in the substrate **1g** featured a considerable secondary directing group effect,[12,24] thus leading to the site-selective formation of **3g** as the sole product. A variation of the substitution pattern on the Lewis-basic pyridine moiety proved to be viable, but did not significantly alter the catalytic efficacy. We were pleased to observe that synthetically useful heterocycles, such as pyridines (py), pyrimidine (pym), and pyrazole, could be utilized as the selectivity ensuring entities. In contrast, arenes displaying oximes or esters have thus far not been suitable substrates.

Thereafter, we exploited the use of the pyrimidine group for the direct cyanation of the biologically active indole[25] derivatives **4**[26] by a removable directing group approach (Scheme 3). Interestingly, indoles bearing various 5-substitu-

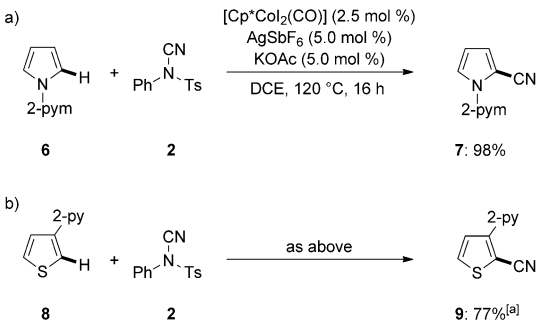


Scheme 3. Cobalt-catalyzed C–H cyanation of the indoles **1**.[a] [Cp*CoI_2(CO)] (5.0 mol%), $AgSbF_6$ (10 mol%), KOAc (10 mol%).

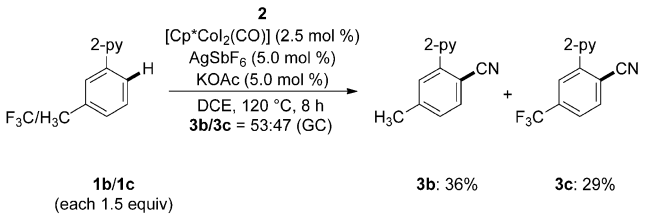
ents, such as bromo or amido groups, were efficiently cyanated, and should allow the synthesis of serotonin derivatives in a step-economical fashion. Substitution on the aromatic moiety of the substrates **4** was generally well tolerated by the C–H functionalization catalyst (**5a–f**). Likewise, the sterically more congested 3-substituted indole **4g** delivered the desired cyanated product **5g** with an excellent yield upon isolation. Even the sensitive ketone functionality on the tetrahydroindole **4h** remained untouched by the cobalt catalyst.

The versatile cobalt catalyst was not restricted to cyanations on the indole heterocycle. Indeed, the direct C–H functionalization of pyrroles (**6**; Scheme 4a) and thiophenes (**8**; Scheme 4b) occurred with excellent levels of efficacy and positional selectivity as well.

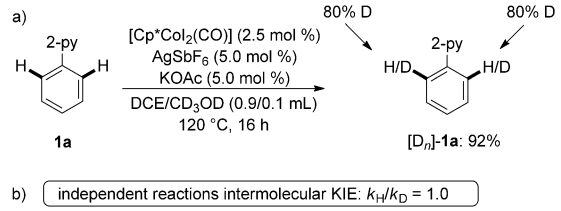
Intrigued by the outstanding catalytic activity of the cobalt catalyst through mechanistically unusual carboxylate assistance, we sought to unravel the mode of action. To this end, intermolecular competition experiments between the differently substituted arenes **1** highlighted a slight preference in the C–H cyanation for the more electron-rich substrate **1b** (Scheme 5).



Scheme 4. Cobalt-catalyzed C–H cyanation of the heteroarenes **6** and **8**.[a] 21% of the 2,4-dicyanated product also isolated.



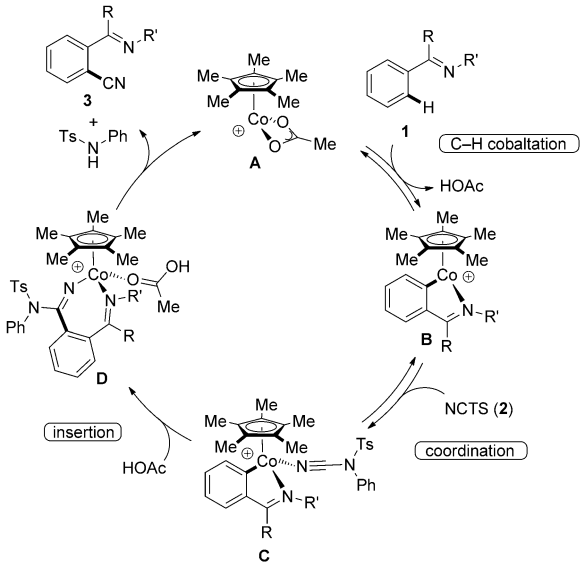
Scheme 5. Competition experiment between different arenes **1**.



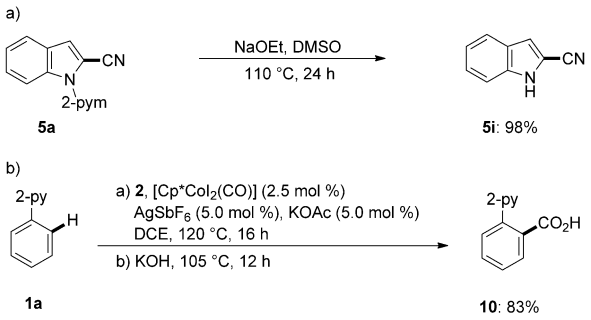
Scheme 6. Cobalt-catalyzed H–D exchange on the arene **1a**.

The use of a deuterated cosolvent clearly indicated a significant H–D exchange solely occurring in the *ortho* position of **1a** (Scheme 6a). Accordingly, cobalt-catalyzed C–H cyanations with isotopically labeled substrates led to a minor kinetic isotope effect (KIE) of $k_H/k_D \approx 1.0$ and $k_H/k_D \approx 1.1$ for the inter- and intramolecular KIE, respectively (Scheme 6b).[27] This data is in agreement with the C–H metalation step not being rate-determining. Moreover, a Hammett plot correlation[28] (σ_m) was indicative of a change in the rate-determining reaction step depending on the substitution pattern of the arene.[27]

Based on our mechanistic studies, we propose the catalytic cycle to initiate by a reversible C–H metalation, thus yielding the cyclometalated complex **B** (Scheme 7). Subsequent coordination and insertion of **2** furnish the key intermediates **C** and **D**, respectively. Finally, β elimination provides the



Scheme 7. Proposed catalytic cycle.

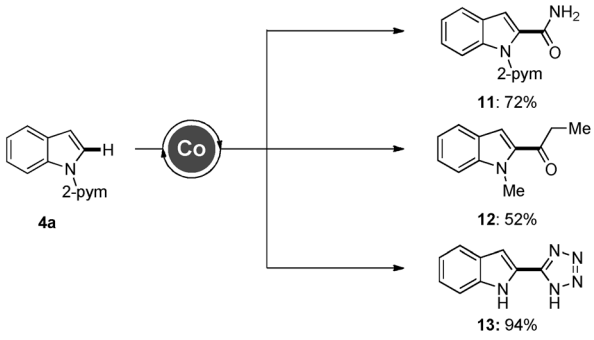


Scheme 8. a) Removal of directing group. b) Cobalt-catalyzed one-pot synthesis of the carboxylic acid **10a**. DMSO = dimethylsulfoxide.

desired product **3**, while proto-demetalation regenerates the catalytically active cobalt(III) carboxylate catalyst **A**.

To illustrate the unique potential of the cobalt(III)-catalyzed cyanation protocol, we removed the directing group on the indole **5a** (Scheme 8a),[26] and devised a reaction sequence which resulted in the formal direct carboxylation of unactivated C–H bonds.[29] Thus, a one-pot procedure initiated by the cobalt-catalyzed C–H cyanation, along with a facile base-mediated saponification, delivered the desired carboxylic acid **10** in high yield (Scheme 8b).

Finally, we exploited the cobalt-catalyzed C–H cyanation for the synthesis of the decorated indoles **11**–**13** (Scheme 9). Particularly, the high-yielding preparation of the 2-tetrazolyl-derivative **13** should prove instrumental for the design of novel bioactive drugs.



Scheme 9. Cobalt-catalyzed C–H activation towards substituted indoles.[27]

In summary, we have reported on the first cobalt-catalyzed cyanation of unactivated C–H bonds. Thus, carboxylate assistance led to a highly active cationic cobalt(III) catalyst for the direct cyanation of arenes and heteroarenes with ample scope. The optimized catalytic system tolerated various functional groups and proved applicable to removable directing groups. Mechanistic studies revealed an effective cobalt catalyst for the site-selective *ortho* deuteration of heteroarylarenes by reversible C–H activation. The development of related cobalt(III)-catalyzed transformations, such as halogenations, is currently ongoing in our laboratories and will be reported in due course.

Received: September 18, 2014
Revised: October 25, 2014
Published online: November 17, 2014

Keywords: C–H activation · cobalt · cyanides · heterocycles · synthetic methods

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