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Cobalt-Catalyzed C−H Cyanation of (Hetero)arenes and 6-Arylpurines with *N*-Cyanosuccinimide as a New Cyanating Agent

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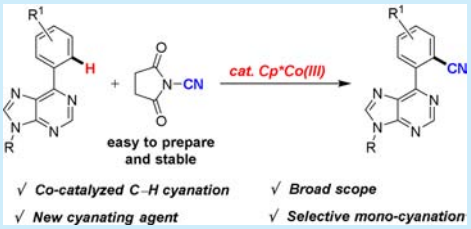
Supporting Information

ABSTRACT: A cobalt-catalyzed C−H cyanation reaction of arenes has been developed using *N*-cyanosuccinimide as a new electrophilic cyanating agent. The reaction proceeds with high selectivity to afford monocyanated products with excellent functional group tolerance. Substrate scope was found to be broad enough to include a wide range of heterocycles including 6-arylpurines.



During the past decades, significant progress has been made in the area of C−H bond functionalization,[1] and this method now offers a straightforward synthetic tool in organic synthesis as an alternative to the traditional cross-coupling reactions requiring prefunctionalized starting materials. The majority of the currently developed C−H activation methods employ precious transition-metal catalysts such as Pd, Rh, Ru, or Ir. Since the first-row transition metals are more abundant and cheap compared to their 4d or 5d metal congeners, developments of efficient catalytic systems based on the first row metals are of special interest.[2] Among the first row metals, cobalt has emerged especially as one of the most promising species for the direct C−H functionalization, leading to synthetically useful and cost-effective transformations.[3] Benzonitriles, on the other hand, represent an important structural motif frequently found in a variety of natural products, pharmaceuticals, and agrochemicals.[4] Although transition-metal-catalyzed/mediated cyanation of aryl (pseudo)halides has been well established,[5] direct introduction of a cyano unit in arenes via C−H bond activation strategy would be a more beneficial approach, thus avoiding the use of prefunctionalized substrates.[6]

In recent years, Rh-[7] and Ru[8]-catalyzed electrophilic C−H cyanation has been developed using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS). Since these procedures show attractive features such as broad substrate scope and/or external oxidant-free conditions, investigation of NCTS variants using inexpensive first-row transition-metal catalysts is highly desirable.[9] In continuation of our efforts in developing more efficient and selective cyanation methods,[10] described herein is the cobalt-catalyzed C−H cyanation[11] using *N*-cyanosuccinimide as a new electrophilic cyanating reagent[12] that is easy to prepare and bench-stable (Scheme 1).

We commenced our study by examining a series of *N*-cyanoimides in a reaction with 2-phenylpyridine (**1a**) under the perspective cobalt catalytic systems (Table 1).

When *N*-cyanophthalimide (**2a**) was subjected to conditions using Cp*Co(CO)I_2 as a catalyst, the desired cyanated product (**3aa**) was formed in 31% yield at 120 °C (entry 1). In this case, a cationic cobalt catalyst was generated in situ upon treatment of the cobalt precursor with a silver salt, which is the same system employed by the Kanai and co-workers in the direct C−H amidation of indoles with sulfonyl azides.[13] In order to improve the reaction efficiency, we examined additive effects to reveal that product yield could be increased by the addition of silver acetate (entries 2−4).[1f] At this stage, we decided to further examine additional analogous electrophilic cyanating reagents. While cyanation with *N*-cyanophthalimide substituted with 5-nitro (**2b**) was sluggish (entry 5), an analogue (**2c**) bearing a methyl group was more efficient (entry 6). More pleasingly, when *N*-cyanosuccinimide (**2d**) was employed under otherwise identical conditions, product (**3aa**) was obtained in 80% yield (entry 7). It is noteworthy that this cyanating reagent (**2d**) displays such attractive features such as easy preparation and being bench stable, thus not requiring a special precaution for the cyanation reaction. In addition, it generates a byproduct (succinimide) that is easily removed by a simple basic workup, thus making the purification process convenient. Solvents other than 1,2-dicloroethane were less effective as shown in entries 8−10. The cyanation did not take place in the absence of cobalt catalyst or $AgNTf_2$. In addition, the use of other cobalt species such as

Scheme 1. Co-Catalyzed C−H Cyanation with *N*-Cyanosuccinimide

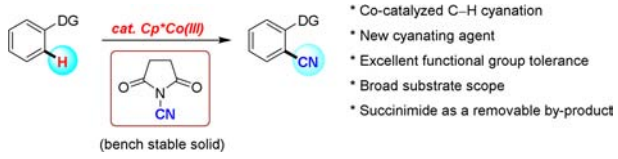


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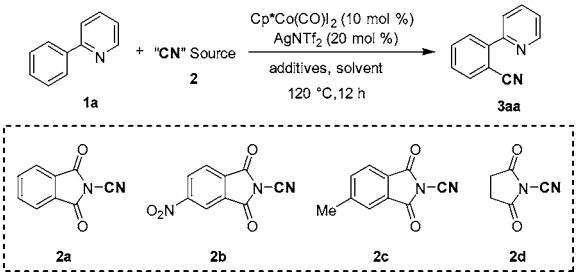
Table 1. Optimization of Reaction Conditions[a]



entry	"CN" source	additives	solvent	yield[b,c] (%)
1	**2a**		1,2-DCE	31
2	**2a**	NaOAc	1,2-DCE	58
3	**2a**	$Cu(OAc)_2$	1,2-DCE	25
4	**2a**	AgOAc	1,2-DCE	66
5	**2b**	AgOAc	1,2-DCE	42
6	**2c**	AgOAc	1,2-DCE	74
7	**2d**	AgOAc	1,2-DCE	**80** (74)
8	**2d**	AgOAc	1,4-dioxane	67
9	**2d**	AgOAc	THF	60
10	**2d**	AgOAc	acetone	38

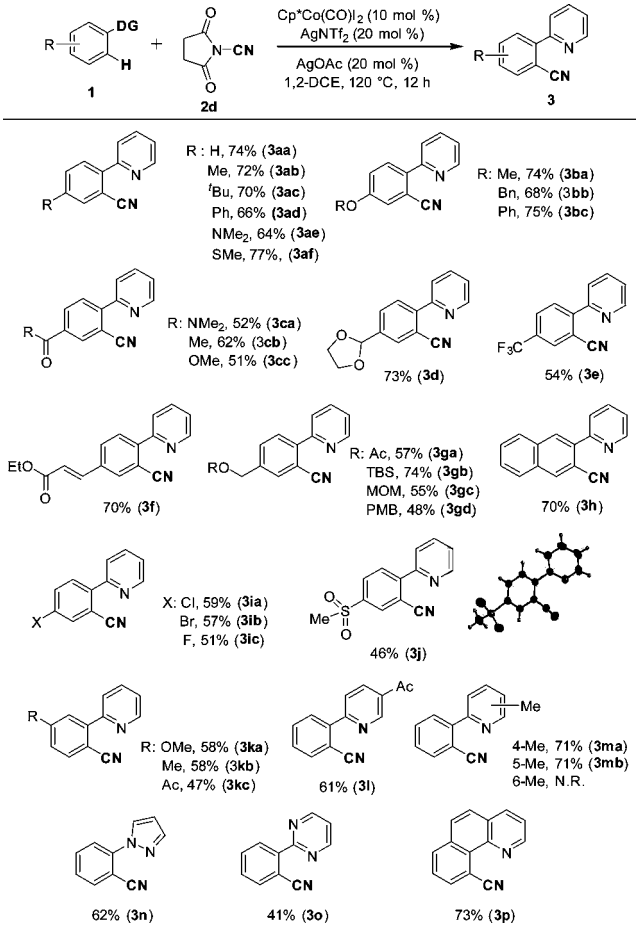
[a]Reaction conditions: **1a** (0.10 mmol), **2** (1.5 equiv), Cp*Co(CO)I_2 (10 mol %), $AgNTf_2$ (20 mol %), and additives (20 mol %) in 1,2-DCE (0.5 mL) at 120 °C for 12 h. [b]Yields are based on crude ^{1}H NMR (internal standard: 1,1,2,2 tetrachloroethane). [c]Isolated yield in parentheses.

$Co(OAc)_2$ or $Co(acac)_3$ was ineffective (see the Supporting Information for details).

With the optimized conditions in hands, the scope of substrates was next investigated (Scheme 2). As anticipated, 2-phenylpyridine derivatives bearing a range of functional groups were readily cyanated. While electron-donating groups led to higher product yields in general, reaction of a substrate bearing an amino group was also facile (**3ae**). Intriguingly, a sulfide group did not deteriorate the cyanation (**3af**). A range of ethers such as alkoxy, benzyloxy, and phenoxy was compatible with the present conditions (**3ba**–**bc**). Synthetically versatile groups including amide, ketone, and ester were also tolerated (**3ca**–**cc**). Note that cyanation took place selectively at the C–H bonds *ortho* to the 2-pyridyl moiety even in the presence of those carbonyl groups, which were shown to work as effective directing groups in the Rh, Ru, or Ir catalyst systems.[14] Substrates bearing acetal and CF_3 groups underwent the cyanation in moderate to good yields (**3d** and **3e**). Cinnamate was smoothly cyanated under the present cobalt catalytic system (**3f**). Functional group compatibility of the present cyanation conditions was additionally proven by examining various hydroxyl-protecting groups such acetate, silyl, methoxymethyl (MOM), and *p*-methoxybenzyl (PMB) (**3ga**–**gd**). 2-(2-Naphthalenyl)pyridine was cyanated selectively at the C-3 position in good yield (**3h**). Substrates bearing halides like F, Cl, or Br also underwent the cyanation without difficulty (**3ia**–**ic**), thus offering an opportunity for additional functionalizations. In addition, cyanation of a substrate containing methanesulfonyl group proceeded smoothly and the structure of product **3j** was confirmed by an X-ray crystallographic analysis. Compounds containing *meta*-substituents were selectively cyanated at the sterically less encumbered position irrespective of the electronic property (**3ka**–**kc**).

We subsequently examined the scope of pyridine and additional directing groups under the present cobalt catalytic system. While the electronic nature of substituents did not

Scheme 2. Scope of Arene Substrates[a]



[a]Reaction conditions: **1** (0.10 mmol), **2d** (1.5 equiv), Cp*Co(CO)I_2 (10 mol %), $AgNTf_2$ (20 mol %), and AgOAc (20 mol %) in 1,2-DCE (0.5 mL) at 120 °C for 12 h; isolated yields are given.

change the reaction efficiency (**3l**) very much, their position was found to be more important. For instance, whereas a methyl group at the 4- or 5-position in pyridine did not affect the reaction (**3ma**,**mb**), cyanation of 6-methyl-2-phenylpyridine did not take place. *N*-Heterocycle derivatives such as pyrazole (**3n**) and pyrimidine (**3o**) worked well as effective directing groups. In addition, cyanation of benzo[*h*]quinoline was smooth (**3p**).

We also examined the feasibility of the Co catalyst system in the cyanation of heterocyclic C–H bonds (Scheme 3). Since heteroaryl nitriles play an important role in medicinal chemistry,[15] the successful cyanation of these substrates was anticipated to be highly promising. Indeed, we were pleased to observe that thiophenyl C–H bonds were selectively cyanated (**5a** and **5ba**). It should be noted that in the case of **5a**, the cyanation occurred exclusively at the 2-position of thienyl moiety. Direct cyanation of furanyl (**5bb**) and pyrrolyl (**5c**) C–H bonds was also facile when pyridyl and pyrimidyl were used as directing groups, respectively. In addition, benzo- and dibenzo-fused substrates were reacted without difficulty (**5da**–**eb**). Indole was cyanated at the C-2 position when pyridyl or pyrimidyl groups were employed as directing groups (**5fa** and **5fb**, respectively). An indolone derivative was cyanated exclusively at the C-2 position in high yield, and the structure of its product (**5g**) was confirmed by an X-ray crystallographic analysis.

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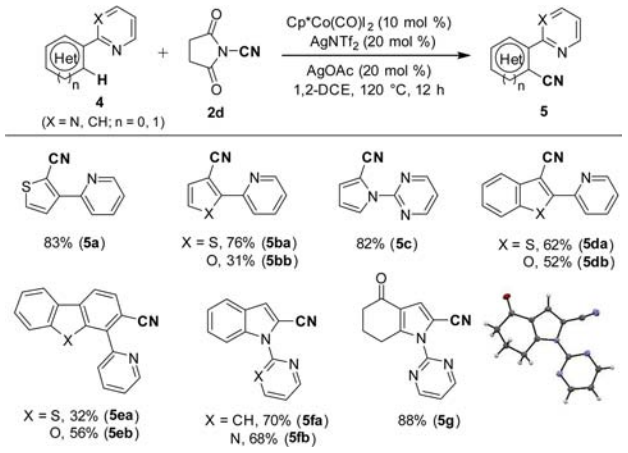
Scheme 3. Scope of Heteroarenes[a]

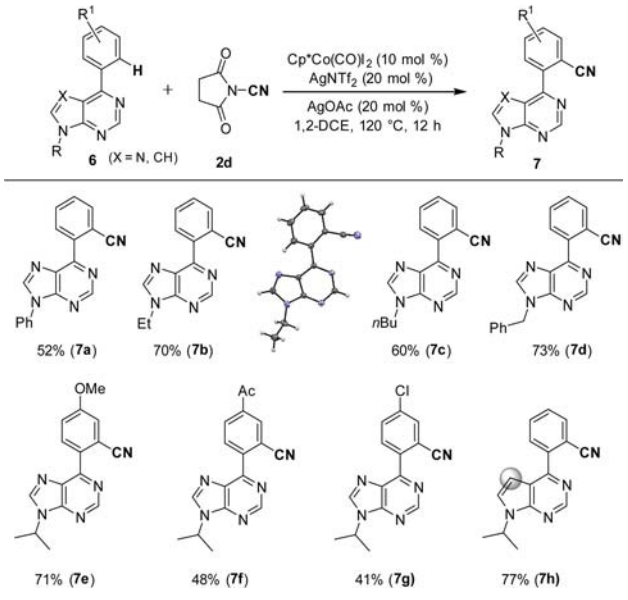


[a]Reaction conditions: **4** (0.10 mmol), **2d** (1.5 equiv), Cp*Co(CO)I_2 (10 mol %), $AgNTf_2$ (20 mol %), and AgOAc (20 mol %) in 1,2-DCE (0.5 mL) at 120 °C for 12 h; isolated yields are given.

6-Arylpurines represent a unique class of heterocyclic compounds displaying a wide range of biological activities.[16] In this regard, a selective installation of useful functional groups in 6-arylpurines is important. However, only a few examples of direct C−H functionalization of 6-arylpurines[17] have been reported, including our own.[17d] In this regard, we prepared a series of 6-arylpurine derivatives to test our working hypothesis of utilizing a purinyl moiety as a directing group for the direct C−H cyanation at the aryl pendant.

To our delight, 6-arylpurines were selectively cyanated under the present cobalt catalyst system (Scheme 4). The *N*9-substituents did not significantly change the reaction efficiency. In fact, 6-phenylpurines bearing *N*9-phenyl, ethyl, and butyl groups were all smoothly cyanated leading to the desired products (**7a**−**c**) in moderate to good yields, and the solid

Scheme 4. Scope of 6-Arylpurines[a]

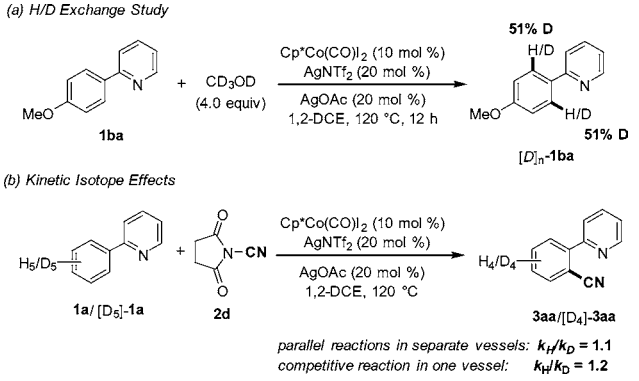


[a]Reaction conditions: **6** (0.10 mmol), **2d** (1.5 equiv), Cp*Co(CO)I_2 (10 mol %), $AgNTf_2$ (20 mol %), and AgOAc (20 mol %) in 1,2-DCE (0.5 mL) at 120 °C for 12 h; isolated yields are given.

structure of **7b** was confirmed by an X-ray diffraction analysis. Cyanation with a removable *N*9-substituent (e.g., benzyl) was also facile (**7d**). Electronic effects of the aryl side were examined to reveal that electron-donating groups facilitated the cyanation more efficiently (**7e**−**g**). It was interesting to observe that a purinyl analogue devoid of *N*7-nitrogen was cyanated in good yield (**7h**), implying that the *N*5-nitrogen atom rather than *N*7 in purine works as a directing group.[17d]

To gain mechanistic insights, preliminary experiments were briefly carried out (Scheme 5). A substrate **1ba** was found to

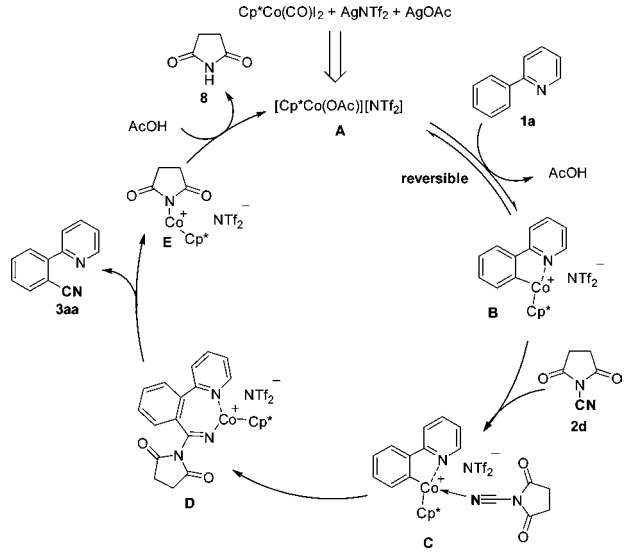
Scheme 5. Preliminary Mechanistic Experiments



undergo a notable H/D exchange by the cobalt catalyst system in the presence of CD_3OD (Scheme 5a), implying that the C−H activation step would be reversible. Additionally, the observed low values of intermolecular kinetic isotope effect in parallel reactions in separate vessels ($k_H/k_D \approx 1.1$) and competitive experiment ($k_H/k_D \approx 1.2$) suggests that the C−H bond cleavage may not be involved in the rate-limiting step although it is not conclusive at the present stage (Scheme 5b).

A plausible mechanism of the present Co-catalyzed cyanation is proposed in Scheme 6 based on the preliminary experiments and the relevant Rh- or Ru-catalyzed reactions.[7,8] First, a cationic Co(III) species **A** generated in situ from Cp*Co(CO)I_2 and $AgNTf_2$ in the presence of AgOAc reacts reversibly with 2-phenylpyridine (**1a**) to form a cobaltacycle **B**. Coordination of a

Scheme 6. Proposed Mechanism



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cyanating reagent (**2d**) to the cobalt center of **B** and subsequent migratory insertion of cyano (CN) moiety into the metallacycle would lead to a key imido intermediate **D**. A cyanated product (**3aa**) will be liberated from **D** giving rise to a succinimido cobalt complex (**E**) that is subsequently converted to a catalytically active species **A** with the concomitant release of a byproduct (succinimide, **8**).

In conclusion, Co-catalyzed C−H cyanation of (hetero)arenes has been developed by using *N*-cyanosuccinimide as a convenient cyanating reagent that is easy to prepare, bench stable, and gives succinimide as a readily removable byproduct. The reaction proceeds efficiently over a broad range of substrates, including various heterocycles, such as 6-arylpurines, with excellent functional group tolerance.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and characterization of new compounds (^{1}H, ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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