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Copper-mediated cyanation of aryl boronic acids using benzyl cyanide

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ABSTRACT

An efficient copper-mediated synthesis of aryl nitriles from aryl boronic acids has been achieved using benzyl cyanide as a user-friendly cyanide source. Various aryl boronic acids underwent the reaction smoothly, affording the corresponding aryl nitriles in moderate to good yields. *tert*-Butyl hydroperoxide (TBHP) was found to be a critical agent facilitating the cyanation reaction.

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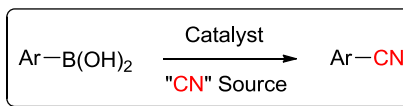
1. Introduction

Aryl nitriles are known to be important organic compounds widely existing in nature products, pharmaceuticals, dyes, and herbicides.¹ Furthermore, due to the tunable reactivity of the cyano group, aryl nitriles have been utilized as key synthetic intermediates for the preparation of other organic compounds, such as aldehydes, carboxylic acids, amines, amidines, amides, and tetrazoles.²

Among various methods, the Sandmeyer and Rosenmund-von Braun reactions have been widely used in aromatic cyanation.³ However, the most commonly used metal cyanides, such as KCN, NaCN, CuCN, Zn(CN)₂, are extremely toxic.⁴ In 2004, K₄[Fe(CN)₆] was shown to be a safety cyanide reagent by Beller et al. and thereafter was widely used for cyanations.⁵ In addition to inorganic cyanating reagents, many other CN-containing organic compounds have also been exploited as CN source, including acetone cyanohydrin, trimethylsilyl cyanide (TMSCN), CH₃CN, propanedinitrile, ethyl cyanoacetate, and isocyanide.⁶ Intriguingly, non-CN-containing systems, such as CH₃NO₂, *N,N*-dimethylformamide (DMF) only,⁷ and DMF or dimethyl sulfoxide (DMSO) plus ammonium salts,⁸ have also been employed as CN sources.

Among various Pd and Cu-catalyzed aromatic cyanation reactions,⁹ the cyanation of aryl boronic acids has been increasingly

interested due to the good starting material availability and operational feasibility (Scheme 1). Liebeskind et al. have reported a palladium-catalyzed copper(I)-mediated cyanation of boronic acids using benzylthiocyanate.¹⁰ Hartwig et al. have shown a copper-mediated cyanation of arenes via iridium-catalyzed borylation.¹¹ Cheng et al. demonstrated a copper-mediated cyanation of boronic acids with CuCN and TMSCN.¹² In addition to the above mentioned aromatic cyanations using conventional cyanide sources, Beller et al. disclosed a rhodium-catalyzed cyanation of aryl and alkenyl boronic using *N*-cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS).¹³ More recently, Chang et al. demonstrated that similar conversion could also be achieved using a combination of DMF and NH₄I as the cyanide source.^{8d}



Previous work:

Liebeskind's: Pd(PPh₃)₄, CuTC, "RSCN"

Hartwig's: Cu(NO₃)₂·3H₂O, "Zn(CN)₂"

Cheng's: "CuCN" or CuI, "TMSCN"

Beller's: {Rh(OH)(cod)}₂, "NCTS"

Chang's: Cu(NO₃)₂·3H₂O, "DMF+NH₄I"

This work:

CuI, TBHP, "PhCH₂CN"

Scheme 1. Cyanation of boronic acids using various cyanating agents.

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Our group has utilized readily available benzyl cyanide as a viable agent for the cyanation of arenes, aryl halides, and indoles.¹⁴ Kwong et al. applied this reagent in the cyanation of 3-cyanoindole derivatives.¹⁵ Herein, we disclose a copper-mediated cyanation of aryl boronic acids using benzyl cyanide.

2. Results and discussion

Our original experiment was taken with 4-biphenylboronic acid (**1a**), benzyl cyanide (**2a**), and cuprous iodide (CuI). Unfortunately, only trace amount of the expected 4-phenylbenzotrile (**3a**) was detected when the mixture was reacted in DMF at 130 °C under air (Table 1, entry 1). According to GC analysis of the reaction mixture, 4-iodobiphenyl and biphenyl were identified as the major components, which were presumably formed from the iodination and hydrogenation of **1a**, respectively.

Table 1
Optimization of reaction conditions for the preparation of **3a**^a

Entry	Cu (equiv)	Oxidant (equiv)	Solvent	T (°C)	3a (%) ^b
1	CuI (1.5)	None	DMF	130	Trace
2	CuI (1.5)	TBHP (2.0)	DMF	130	78
3	CuBr (1.5)	TBHP (2.0)	DMF	130	12
4	CuCl (1.5)	TBHP (2.0)	DMF	130	Trace
5	Cu ₂ O (1.5)	TBHP (2.0)	DMF	130	Trace
6	Cu(OAc) ₂ (1.5)	TBHP (2.0)	DMF	130	Trace
7	CuCl ₂ (1.5)	TBHP (2.0)	DMF	130	Trace
8	CuI (1.5)	DTBP (2.0)	DMF	130	11
9	CuI (1.5)	BPO (2.0)	DMF	130	70
10	CuI (1.5)	TBHP (1.0)	DMF	130	61
11	CuI (1.5)	TBHP (4.0)	DMF	130	53
12	CuI (1.5)	TBHP (2.0)	DMF	110	55
13	CuI (1.5)	TBHP (2.0)	DMF	80	22
14	CuI (1.0)	TBHP (2.0)	DMF	130	75
15	CuI (0.4)	TBHP (2.0)	DMF	130	56
16	CuI (0.2)	TBHP (2.0)	DMF	130	17
17	CuI (1.0)	TBHP (2.0)	Dioxane	130	0
18	CuI (1.0)	TBHP (2.0)	NMP	130	56
19	CuI (1.0)	TBHP (2.0)	DMSO	130	74
20	CuI (1.0)	TBHP (2.0)	DMAc	130	82
21 ^c	CuI (1.0)	TBHP (2.0)	DMAc	130	70

^a Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), Cu source, oxidant, air, solvent (2 mL), 20 h.

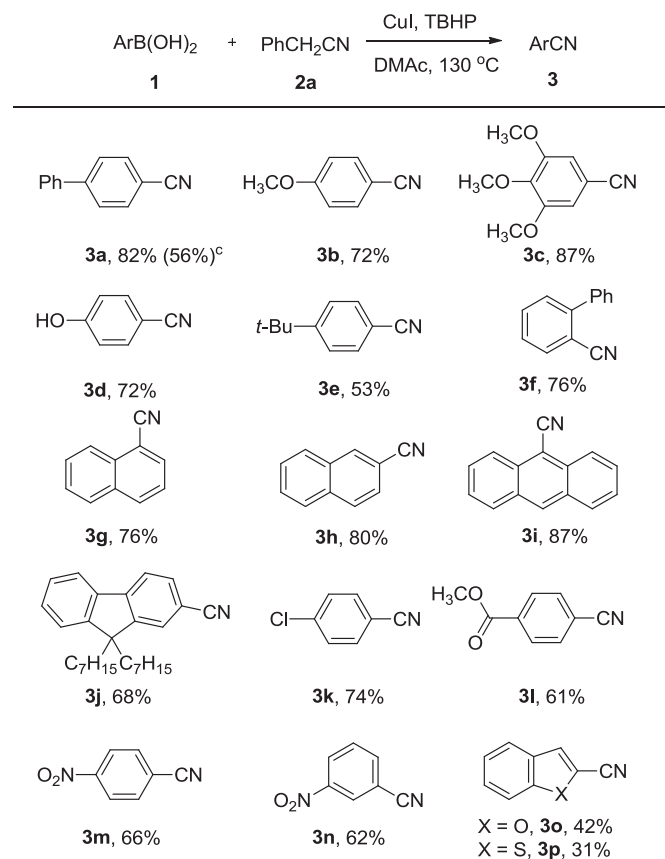
^b Isolated yields.

^c Under N₂ atmosphere. TBHP=*tert*-butyl hydroperoxide, DTBP=*di-tert*-butylperoxide, BPO=benzoyl peroxide. NMP=*N*-methyl-2-pyrrolidone, DMSO=dimethyl sulfoxide, DMAc=*N,N*-dimethylacetamide. TBHP represents 70% aqueous solution.

To our delight, the yield of **3a** was found to increase to 78% when we applied 2 equiv of *tert*-butyl hydroperoxide aqueous solution (TBHP) as an oxidant to promote the benzylic oxidation of **2a** (Table 1, entry 2). Further reaction condition screening showed CuI to be optimal among different copper sources (Table 1, entries 2–7). Other oxidants, such as di-*tert*-butylperoxide (DTBP) and benzoyl peroxide (BPO), could also serve as oxidizing agents in the reaction, which, however, led to inferior yields (Table 1, entries 8, 9). Although we tried to alter the reaction temperatures and proportions of substrates and reagents, such attempts did not provide additional improvement to reaction yields (Table 1, entries 10–16). We also examined the solvent effects in this reaction. As expected, low polar solvents, such as 1,4-dioxane, led to dramatic decrease in reaction yield possibly due to low solubility of CuI in these solvents (Table 1, entry 17). In comparison, high reaction yields were generally enabled by polar solvents, among which *N,N*-dimethylacetamide (DMAc) was found to be the optimal solvent affording **3a**

with 82% yield (Table 1, entry 20). It was notable that a nice yield (70%) of 4-phenylbenzotrile could be obtained when the reaction was taken under N₂ atmosphere (Table 1, entry 21).

With the optimal conditions in hand, we explored the substrate scope of the present reaction (Scheme 2). Aryl boronic acids bearing strong electron-donating and moderate electron-withdrawing substituents (OR and Cl, respectively) gave the corresponding aryl



^a Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), CuI (0.5 mmol), TBHP (aq. 1 mmol), air, DMAc (2 mL), 130 °C, 20 h. ^b Isolated yields based on **1**. ^c The reaction was carried out on 6 mmol scale.

Scheme 2. Substrate scope of cyanation of aryl boronic acids^{a,b}.

nitriles in good yields. 4-*tert*-butyl-phenyl boronic acid furnished the cyanation product in only 53% yield. In contrast, the introduction of the NO₂ and ester groups onto the aromatic ring led to dramatic decrease in reaction yields. Both *ortho*- and *para*-phenyl substituted boronic acids underwent reaction smoothly, indicating the insignificant role of steric effects in reaction yields. For fused aryl rings, such as naphthalene, anthracene, and fluorene derivatives, moderate to excellent yields were obtained. In addition, heterocyclic boronic acids could also be used as the substrates, affording the corresponding aryl nitriles **3o** and **3p** in relatively lower yields. To demonstrate the feasibility of the present protocol, a gram-scale reaction was carried out with 6 mmol 4-biphenylboronic acid, which gave desired product in 56% yield. In addition to aryl boronic acids, we have also attempted the cyanation of aryl boronic esters, which generally demonstrated similar reactivity to the parent boronic acids (Scheme 3).

To gain mechanistic insight into the reaction, we carried out cyanation reaction with different benzyl nitriles as the CN sources. As shown in Scheme 4, the cyanation was sluggish when NO₂-substituted benzyl nitrile was employed. Presumably, the strong electron-withdrawing ability of the *para* NO₂ group can inhibit the

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