Copper-mediated Regioselective C–H Cyanation of Phenols with Assistance of Bipyridine-type Bidentate Auxiliary

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A Cu-mediated *ortho*-selective C–H cyanation of phenols with ethyl cyanoformate as the cyano source has been developed. The key to success is the introduction of 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) bidentate auxiliary on the phenol oxygen, which is easily attachable, detachable, and recyclable. The newly developed protocol is tolerant of several carbonyl functional groups, which are incompatible with previous Lewis-acid-promoted cyanation of phenols.

Keywords: Bidentate Auxiliary, Copper, C–H Functionalization

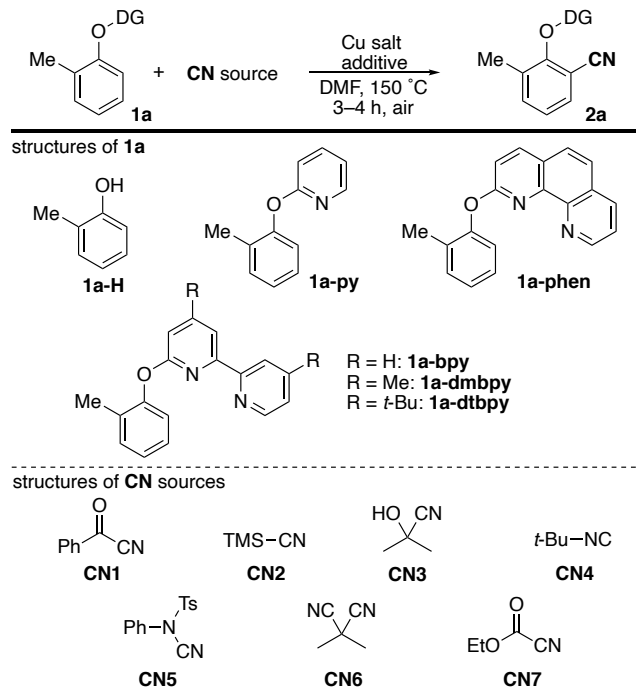
Aromatic nitriles constitute an important class of compounds in organic chemistry because they are frequently occurring in biologically active compounds[1] as well as valuable synthetic intermediates for amines, carbonyls, and *N*-heterocycles.[2] Accordingly, the development of aromatic cyanation reactions has been one of the longstanding research subjects in organic synthesis. In addition to the classical Sandmeyer reaction,[3] the currently most reliable strategy is the transition-metal-catalyzed cyanation of aryl (pseudo)halides and aryl metals with suitable nucleophilic and electrophilic CN sources.[4] However, tedious preactivation, such as halogenation and stoichiometric metalation, of aromatic compounds are inevitable and sometimes problematic. To address the aforementioned problems, synthetic chemists focused on the metal-mediated directed C–H activation[5] and developed the C–H cyanation of benzamides, oximes, arylpyridines, azobenzenes, naphthylamines, arylphosphates, and electron-rich (hetero)arenes under Ru,[6] Rh,[7] Co,[8] and Cu[9] catalysis. The Lewis-acid-mediated electrophilic cyanation[10] and organic photoredox catalyst-promoted C–H cyanation[11] of electron-rich (hetero)arenes are also good alternatives. Despite the above certain advances, the regioselective C–H cyanation of phenols still remains less explored.[12] The *ortho*-selective C–H cyanation of free phenols is possible by the two-step procedure, i.e., alkylation with MeSCN and base-mediated hydrolysis, which was originally developed by Sugasawa[13] and recently revisited by Yang and Zhao.[14] However, these strategies rely on excess amount of strongly acidic promotors such as $AlCl_3$, BCl_3, BF_3, and their combinations and thus suffer from low functional group compatibility.

Meanwhile, our group recently focused on the unique bidentate coordinating ability of phenanthroline and bipyridine and succeeded in the development of Cu-mediated highly *ortho*-selective C–H amination, sulfenylation, selenation, and (hetero)arylation of phenols with the assistance of phenanthroline- and bipyridine-type bidentate auxiliaries.[15] During the continuing interest in this chemistry, we envisioned the directed C–H cyanation of phenols. Herein, we report a Cu/bipyridine-type auxiliary-promoted highly *ortho*-selective C–H cyanation of phenols with ethyl cyanoformate as the CN source. The key to success is the introduction of 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy) bidentate auxiliary, which is readily attachable, detachable, and recyclable. The newly developed conditions are tolerant of several carbonyl functional groups, which are incompatible with the reported Lewis-acid-promoted cyanation protocols.[13,14]

Our optimization studies commenced with the previously successful phenanthroline-substituted *ortho*-cresol derivative **1a-phen**[15a-15d] (0.10 mmol) and benzoyl cyanide **CN1**[9e] (0.15 mmol) as the CN donor (Table 1, Entry 1). However, under the reported $Cu(OAc)_2$-mediated conditions in heated DMF (150 °C, air),[15a,15b] no cyanated product was detected. As far as we examined, condition modifications did not form **2a-phen** at all; only decomposition of **1a-phen** was observed. Thus, we switched attention to the relatively flexible but more stable 2,2'-bipyridine (bpy)-substituted substrate **1a-bpy**.[15d] Gratifyingly, the targeted **2a-bpy** was obtained in 42% ^{1}H NMR yield (Entry 2). Screening of several nucleophilic and electrophilic CN reagents **CN2**–**7** did not increase the yield (Entries 3–8). At this point, the careful investigation of the crude reaction mixture revealed the major side reaction was the C–H acetoxylation. The acetate-free conditions combined with $Cu(OTf)_2$ and ethyl cyanoformate (**CN7**) gave no acetoxylated byproduct, but the yield of **2a-bpy** was lower (Entry 9). On the other hand, negligible or no formation of **2a-bpy** was observed by the combination of $Cu(OTf)_2$ and **CN1** or **CN2** (data not shown). To improve the reaction efficiency, we next tested some additives and found AgOAc to uniquely accelerate the reaction (Entries 10–13). Additional fine tuning of its amount further improved the yield to 70% (Entry 14). Under conditions of Entry 14, we reinvestigated several related auxiliaries. The simple *ortho*-cresol (**1a-H**) and monodentate **1a-py** resulted in decomposition and no reaction, respectively (Entries 15 and 16), whereas the cyanated product was obtained albeit in 23% ^{1}H NMR yield from the firstly tested **1a-phen** (Entry 17). On the other hand, the introduction of substituents at the 4,4' positions of bpy auxiliary greatly affected the reaction: the 4,4'-dimethyl-2,2'-bipyridine auxiliary (**1a-dmbpy**) decreased the yield compared to the parent bpy (Entry 18), while the substitution of *tert*-butyl groups (**1a-dtbpy**) enhanced the reaction to afford the C–H cyanated product **2a-dtbpy** in 89% ^{1}H NMR yield (84% isolated yield; Entry 19).

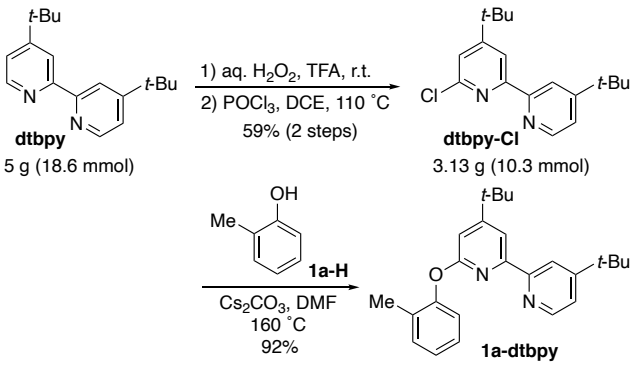
The starting substrate **1a-dtbpy** was readily synthesized by condensation of **1a-H** and 4,4'-di-*tert*-butyl-6-chloro-2,2'-bipyridine (**dtbpy-Cl**), which was prepared from the commercially available 4,4'-di-*tert*-butyl-2,2'-bipyridine (**dtbpy**) on a gram scale via *N*-oxidation and deoxychlorination (Scheme 1). Some additional observations are to be noted: the reaction under N_2 conditions largely dropped the yield (<15%) while a similar product yield was obtained under O_2 atmosphere; no catalytic turnover in Cu was observed even with the Ag-based additive; no reaction occurred without any Cu salts (data not shown).

Table 1. Optimization studies for Cu-mediated *ortho*-selective C–H cyanation of phenol derivatives **1a**.[a]

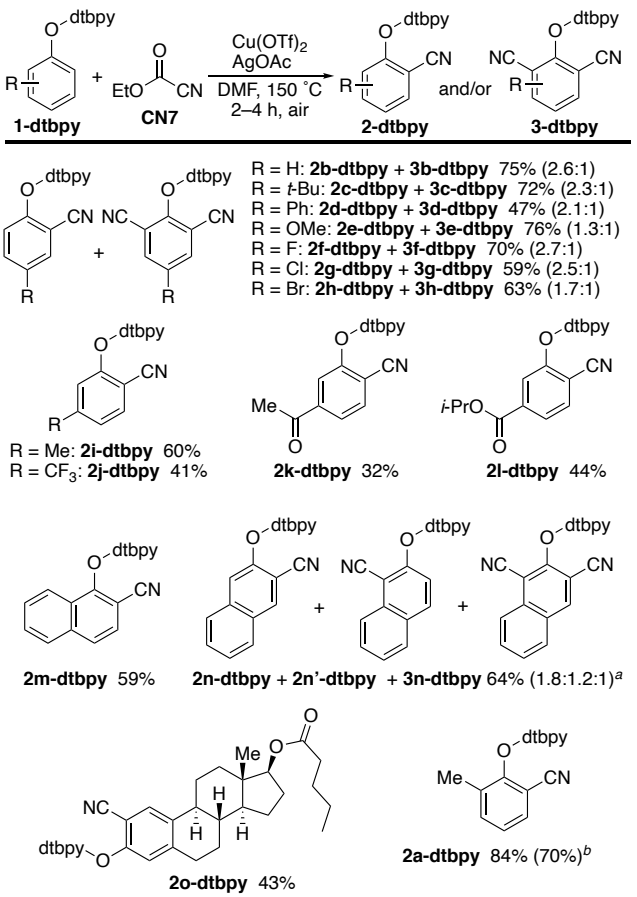


Entry	1a	CN	Cu salt	additive	2a, yield[b]
1	**1a-phen**	**CN1**	$Cu(OAc)_2$	none	**2a-phen**, 0
2	**1a-bpy**	**CN1**	$Cu(OAc)_2$	none	**2a-bpy**, 42
3	**1a-bpy**	**CN2**	$Cu(OAc)_2$	none	**2a-bpy**, 31
3	**1a-bpy**	**CN3**	$Cu(OAc)_2$	none	**2a-bpy**, 5
4	**1a-bpy**	**CN4**	$Cu(OAc)_2$	none	**2a-bpy**, 9
5	**1a-bpy**	**CN5**	$Cu(OAc)_2$	none	**2a-bpy**, <10
6	**1a-bpy**	**CN6**	$Cu(OAc)_2$	none	**2a-bpy**, 17
7	**1a-bpy**	**CN7**	$Cu(OAc)_2$	none	**2a-bpy**, 30
8	**1a-bpy**	**CN7**	$Cu(OTf)_2$	none	**2a-bpy**, 21
9	**1a-bpy**	**CN7**	$Cu(OTf)_2$	MnO_2	**2a-bpy**, 16
10	**1a-bpy**	**CN7**	$Cu(OTf)_2$	AgO	**2a-bpy**, 20
11	**1a-bpy**	**CN7**	$Cu(OTf)_2$	Ag_2CO_3	**2a-bpy**, 23
12	**1a-bpy**	**CN7**	$Cu(OTf)_2$	AgOAc	**2a-bpy**, 61
13	**1a-bpy**	**CN7**	$Cu(OTf)_2$	AgOAc[c]	**2a-bpy**, 70
14	**1a-H**	**CN7**	$Cu(OTf)_2$	AgOAc[c]	**2a-H**, 0
15	**1a-py**	**CN7**	$Cu(OTf)_2$	AgOAc[c]	**2a-py**, 0
16	**1a-phen**	**CN7**	$Cu(OTf)_2$	AgOAc[c]	**2a-phen**, 23
17	**1a-dmbpy**	**CN7**	$Cu(OTf)_2$	AgOAc[c]	**2a-dmbpy**, 29
18	**1a-dtbpy**	**CN7**	$Cu(OTf)_2$	AgOAc[c]	**2a-dtbpy**, 89 (84)

[a]Conditions: **1a** (0.10 mmol), CN source (0.15 mmol), Cu salt (0.10 mmol), additive (0.10 mmol), DMF (1.0 mL), 150 ˚C, 3–4 h, air. [b]Estimated by ^{1}H NMR with dibenzyl ether as the internal standard. Isolated yields are in parentheses. [c]With 0.060 mmol of AgOAc.



Scheme 1. Preparation of starting substrate **1a-dtbpy**.

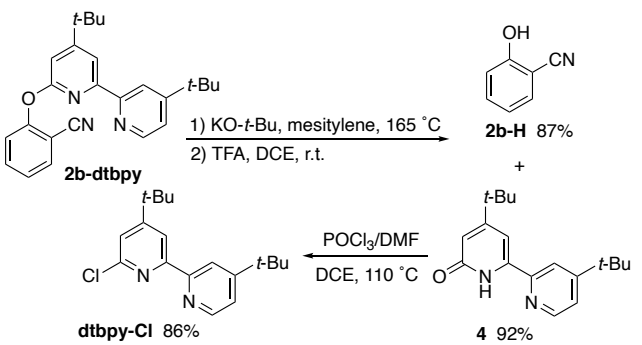


Scheme 2. Cu-mediated *ortho*-selective C–H cyanation of phenol derivatives **1-dtbpy** with ethyl cyanoformate **CN7**. Conditions: **1-dtbpy** (0.10 mmol), **CN7** (0.15 mmol), $Cu(OTf)_2$ (0.10 mmol), AgOAc (0.060 mmol), DMF (1.0 mL), 150 ˚C, 2–4 h, air. Isolated yields are shown. The ratios of **2-dtbpy** and **3-dtbpy** are indicated in parentheses. [a]The ratio of **2n-dtbpy**:**2n'-dtbpy**:**3n-dtbpy** is shown in parentheses. [b]On a 1.0 mmol scale. For 16 h. dtbpy = 4,4'-di-*tert*-butyl-2,2'-bipyridine-6-yl.

With the optimal conditions in hand (Table 1, Entry 19), we then examined the scope of dtbpy-substituted phenol

derivatives **1-dtbpy** (Scheme 2). In the case of the nonsubstituted and *para*-substituted phenol derivatives, a separable mixture of mono- and dicyanated products was obtained in a good combined yield (**2b**–**2h-dtbpy** and **3b**–**3h-dtbpy**). Notably, the C–H cyanation at the *ortho* position preferably occurred over the classical Rosenmund-von Braun reaction[4a,4b] at the C–Cl and C–Br moieties (**2g–h-dtbpy** and **3g–h-dtbpy**), which can be good synthetic handles for further manipulations. When the *meta*-substituted substrates were employed, the more sterically accessible *ortho* positions were selectively functionalized to produce the monocyanated products **2i**–**2l-dtbpy**. It should be noted that the targeted products were formed even from the substrates bearing strong Lewis-acid-labile ketone and ester groups (**2k**–**2l-dtbpy**) albeit with the moderate yields because of the competitive decomposition of substrates. The higher fused naphthol derivatives were also amenable to the reaction (**2m-dtbpy** and **2n-dtbpy**), but in the case of the 2-naphthol the regioisomeric **2n'-dtbpy** as well as dicyanated **3n-dtbpy** was also formed. Moreover, the complex steroid-type substrate underwent the regioselective C–H cyanation to afford **2o-dtbpy** in a synthetically useful yield. Additionally, the reaction could also be conducted on a 1.0 mmol scale (**2a-dtbpy**), indicating the good reproducibility of the process.

The dtbpy auxiliary was easily removed from the C–H cyanated product (Scheme 3). The KO-*t*-Bu-promoted alcoholysis of **2b-dtbpy** was followed by treatment with TFA to furnish the corresponding free OH *ortho*-cyanated phenol **2b-H** in 87% yield. Concurrently, the auxiliary was recovered in the pyridone form **4** (92%), which can be recycled via conversion back into the directing group precursor **dtbpy-Cl**.



Scheme 3. Removal and recycle of dtbpy auxiliary.

Although the detailed reaction mechanism is unclear at this stage, on the basis of our previous work[15,16] and literature information,[17] the possible reaction course involves 1) *N,N*-bidentately coordinating dtbpy-directed, Cu-promoted *ortho* C–H cleavage,[18] 2) ligand exchange with the cyanide on Cu, 3) oxidation of Cu(II) to Cu(III), and 4) reductive elimination of aryl–CN. The molecular oxygen in air and AgOAc additive can accelerate the aforementioned Cu(II) to Cu(III) oxidation step.[19] Ethyl cyanoformate (**CN7**) gradually generates the cyanide anion in situ to suitably control the concentration of CN.[20] Apparently, the bidentate coordinating nature of auxiliary is essential (Table 1, Entry 16 vs Entries 14, 17, 18, and 19), but the better performance of dtbpy auxiliary than phenanthroline and nonsubstituted bipyridine auxiliaries can be attributed to the higher stability under reaction conditions rather than the directing ability in the C–H cleavage step.[21]

In conclusion, we have developed a copper-mediated regioselective C–H cyanation of phenol derivatives with ethyl cyanoformate. The use of bipyridine-based bidentately coordinating auxiliary, 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbpy), enables the directed C–H cyanation at the *ortho* position. The developed protocol can also be applicable to phenol substrates bearing acid-labile carbonyl functional groups, which are challenging substrates in the reported strong Lewis-acid-mediated conditions. The dtbpy auxiliary is readily accessible and easily attachable, detachable, and recyclable, thus providing robust and practical access to the *ortho*-cyanophenols of prevalent motif in natural products and pharmaceutical agents.[22] Further investigations into the detailed reaction mechanism and development of related bidentate auxiliaries for more challenging C–H functionalizations of oxygenated molecules are ongoing in our laboratory.

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Supporting Information is available on http://dx.doi.org/xxxx.

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21 We performed the deuterium incorporation tests with **1a-phen**, **1a-bpy**, and **1a-dtbpy**, and the highest deuterium content was observed with **1a-phen**, suggesting that the directing ability of auxiliary is less important in the C–H cyanation reaction. On the other hand, no deuterium incorporation was observed in the case of **1a-py**. See the Supporting Information for more details.

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Graphical Abstract

Textual Information

Description (if any)	
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Authors' Names	Rikuo Kajiwara, Koji Hirano, and Masahiro Miura

Graphical Information