# Copper-mediated Cyanation of Aryl C–H Bond with Removable Bidenate Auxiliary Using Acetonitrile as the Cyano Source

Zhengwei Yu, Saisai Zhang and Zengming Shen*

Dedicated to Professor Xiyan Lu on the occasion of his 90th birthday

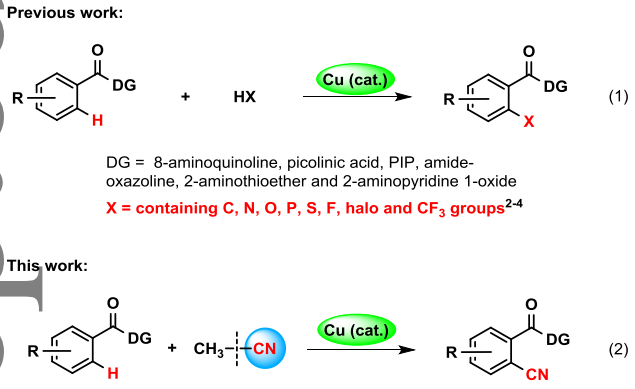
**ABSTRACT** Copper-mediated cyanation of aryl C–H bond with removable bidenate auxiliary as a directing group has been developed, in which green and cheap acetonitrile is used as the "CN" source. By switching the reaction conditions, the C–H cyanated products and *N*-Ar-phthalimides can be respectively provided in acceptable yields with high chem-selectivity. The use of quaternary ammonium salt is essential for cyanation reaction.
**KEYWORDS** cyanation, copper catalyst, aryl C–H bond activation, acetonitrile, *N*-Ar-phthalimides



## Introduction

Transition metal-catalyzed functionalization of carbon-hydrogen bonds is a challenging field in the modern organic chemistry and has achieved enormous advances in the past decades.[1] The utilization of directing groups is a sapiential strategy to assist metal-catalyzed C–H bond activation. Recently, Daugulis and co-workers first employed 8-aminoquinoline or picolinic acid as bidentate auxiliary which shows high efficiency in copper-catalyzed C–H functionalization.[2] Meanwhile, other bidentate auxiliaries, such as PIP (2-pyridinylisopropyl), amide-oxazoline, 2-aminothioether and 2-aminopyridine 1-oxide moiety, have also been introduced by Shi, Yu, Daugulis and Song respectively.[3] During the past few years, tremendous C–C, C–N, C–O, and other carbon–heteroatom bond-forming reactions have been developed by employing bidentate directing group (Scheme 1, eq. 1).[4] However, to the best of our knowledge, no examples of the cyanation of $sp^2$ C–H bond with assistance of bidentate directing group have ever been reported (Scheme 1, eq. 2).

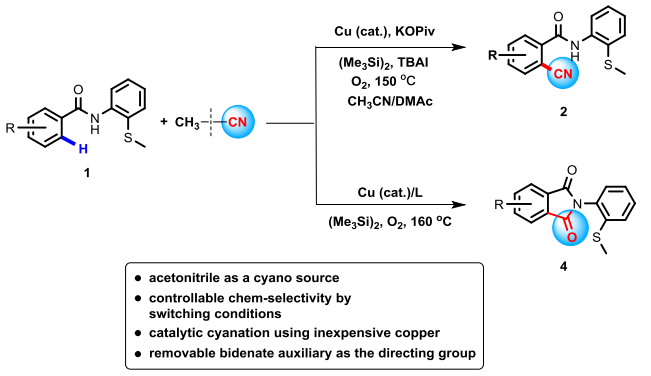
**Scheme 1** Cu-catalyzed C($sp^2$)–H bond functionalization with removable bidenate auxiliary as directing group




Aromatic nitriles are an important class of compounds found in pharmaceuticals, agrochemicals, and dyes.[5] They are also key intermediates, which can convert into a variety of functional groups such as aldehydes, amines, amidines, carboxy variants, tetrazoles and amides.[6] Notably, the first copper-promoted directed cyanation of arene C–H bonds was reported by Yu in 2006,[7] using TMSCN or $MeNO_2$ as the cyano source. Subsequently, other groups have also shown that 2-phenylpyridine derivatives enabled ortho cyanation by employing copper salts as catalysts.[8] Nevertheless, copper-catalysed cyanation also encounters a hard problem that the excess of "CN" anion is prone to coordinating with Cu catalyst strongly, leading to a rapid deactivation of copper catalyst. Consequently, the exploration of new organic cyano sources instead of cyanides, for example, NCTs, $^t$Bu-NC, benzyl cyanide, combined CN source, has been the driving force for promoting the development of cyanation reactions.[9]

From the view point of safety and atom-economy, acetonitrile is a rather good "CN" source compared to others mentioned before. In recent years, much attention has been paid in acetonitrile by C–CN cleavage strategy to develop an efficient approach for cyanation.[10] Since 2013, our group has shown that acetonitrile is a new type "CN" source and discovered two new systems [Cu (cat.)/Si and Cu (cat.)/Si/TEMPO] for the cyanation of arene C–H bonds or aryl boronic acids, in which disilane plays an essential role for enabling acetonitrile to be an efficient CN source.[11] Herein, we first report a 2-(methylthio)aniline-assisted copper-mediated C–H bond cyanation and cyclization using acetonitrile as CN source (Scheme 2).

**Scheme 2** 2-Aminothioether auxiliary assisted copper-mediated C–H bond cyanation using acetonitrile as an CN source




## Results and Discussion

Initially, we investigated the effect of the directing group on the efficiency of the cyanation reaction (Table 1). No reaction occurred when compounds **S-2**, **S-3**, **S-4** and **S-5** with different

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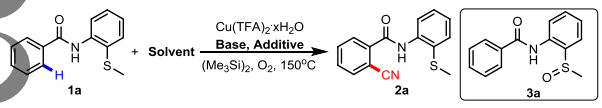
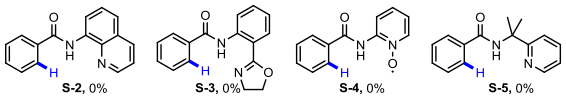
types of amides as the bidentate auxiliaries were employed as the substrates, which have been widely applied in transition metal-catalyzed C−H functionalization reactions. To our surprise, when using *N*–(2–(methylthio)phenyl)benzamide **1a** as a substrate, the reaction of **1a** and acetonitrile in the presence of $Cu(TFA)_2{\cdot}XH_2O$ and hexamethyldisilane at 150 °C gave the desired product in 5% isolated yield (entry 1). Next, we focused on the effect of bases in Cu-catalyzed cyanation reaction. It turned out that KOPiv is optimal among the screened bases (entries 2-6), providing **2a** in 40% yield (entry 2). NaOPiv was inferior to KOPiv (entry 3). Reaction with KOAc also afforded **2a** in 38% yield (entry 4), while other potassium salts with different anions could yield trace amount of product. Meanwhile, we observed a solvent effect. When DMSO was used as a co-solvent and the ratio of acetonitrile and DMSO was 2:1 (v/v'), the yield increased to 45% (entry 7). Subsequently, a series of polar solvents were examined (entries 7-10). Pleasingly, a 57% yield of the desired product **2a** was isolated when DMAc (*N,N*-dimethylacetamide) was added to the reaction (entry 11). Further screening of the solvent ratio revealed that $CH_3CN$/DMAc (2:1) is superior to others (entries 11-13). Inspired by the work regarding the amination of $sp^2$ C-H bond reported by Daugulis[2g], optimization showed that this reaction could also be improved by the addition of a quaternary ammonium salt (entries 14-15). TBAI and $TBAPF_6$ gave 62% and 60% yields, respectively. Other ammonium salts have the similar effect on the reaction (See the Supporting Information). Remarkably, the formation of sulfoxide **3a** by the oxidation of substrate **1a** was suppressed with the addition of TBAI. To our surprise, when 2 equivalents of copper salt were utilized, almost no product was generated.

**Table 1** Optimization of the conditions[a]



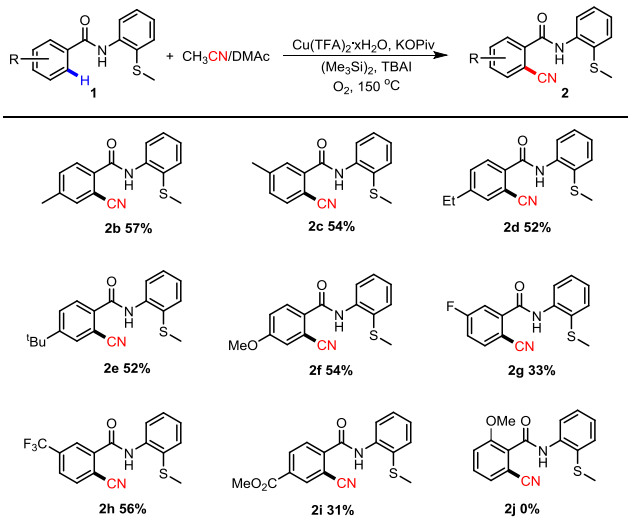

| Entry | Base | Solvent (v/v') | Additive | Yield (%)[b] |
|---|---|---|---|---|
| 1 | / | $CH_3CN$ | / | 5 |
| 2 | KOPiv | $CH_3CN$ | / | 40 |
| 3 | NaOPiv | $CH_3CN$ | / | 15 |
| 4 | KOAc | $CH_3CN$ | / | 38 |
| 5 | KOH | $CH_3CN$ | / | N.R. |
| 6 | KO$^t$Bu | $CH_3CN$ | / | N.R. |
| 7 | KOPiv | $CH_3CN$/DMSO (2:1) | / | 45 |
| 8 | KOPiv | $CH_3CN$/NMP (2:1) | / | 40 |
| 9 | KOPiv | $CH_3CN$/DCE (2:1) | / | 42 |
| 10 | KOPiv | $CH_3CN$/$CHCl_3$ (2:1) | / | 15 |
| 11 | KOPiv | $CH_3CN$/DMAc (2:1) | / | 57 |
| 12 | KOPiv | $CH_3CN$/DMAc (4:1) | / | 55 |
| 13 | KOPiv | $CH_3CN$/DMAc (1:1) | / | 42 |
| 14 | KOPiv | $CH_3CN$/DMAc (2:1) | TBAI | 62 |
| 15 | KOPiv | $CH_3CN$/DMAc (2:1) | $TBAPF_6$ | 60 |
| 16[c] | KOPiv | $CH_3CN$/DMAc (2:1) | TBAI | N.R. |




[a] Conditions:**1a** (0.15 mmol), $Cu(TFA)_2{\cdot}XH_2O$ (1 eq.), base (1 eq.), $(Me_3Si)_2$ (2 eq.), $CH_3CN$ (1 mL), additive (1 eq.), $O_2$, 150 °C, reaction time = 12 h. [b] Isolated yield. [c] $Cu(TFA)_2{\cdot}xH_2O$ (2 eq.), KOPiv = Potassium pivalate, DMSO = Dimethyl sulfoxide. NMP = 1-Methyl-2-pyrrolidinone. DCE = 1,2-Dichloroethane. DMAc = *N,N*-Dimethylacetamide.

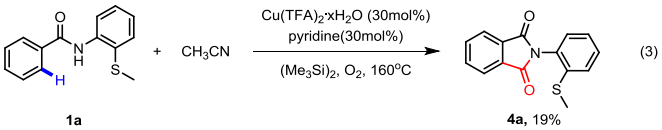
With the optimal reaction conditions in hand, we tested the cyanation reactions of a series of *N*-(2-(methylthio)phenyl)benzamide derivatives bearing different functional groups. The results are listed in Table 2. Alkyl substituents, including the bulky group such as *tert*-butyl, were tolerated well under the standard reaction conditions and generated desired products (**2b**, **2c**, **2d** and **2e**) over 50% yields. Besides alkyl groups, electron-withdrawing functional groups such as F, $CF_3$ and COOMe provided the desired products in 33%, 56% and 31% yields, respectively. Notably, 2-MeO substituted substrate **1j** did not provide the corresponding product (**2j**). This observation could be explained by OMe coordinating to Cu catalyst together with N and S atoms to prevent the C-H bond activation. Because of this phenomenon, the dicyanated product from **2** did not form during the course the cyanation reaction.

**Table 2** Scope of substrates for the synthesis of cyanated product **2**[a]



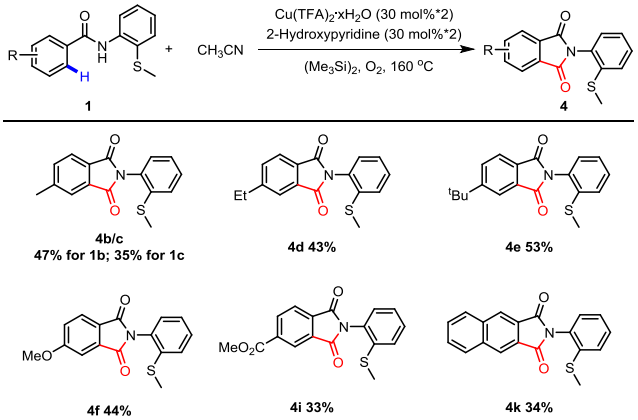

[a] Conditions: **1** (0.15 mmol), $Cu(TFA)_2{\cdot}xH_2O$ (1 eq.), KOPiv (1eq.), $(Me_3Si)_2$ (2 eq.), $CH_3CN$ (1mL), DMAc (0.5 mL), TBAI (1eq.), $O_2$, 150 °C, Reaction time = 6-24 h. [b] Isolated yield.

Interestingly, when we screened different types of bases, it was found that pyridine furnished very trace amount of **2a**. Instead, the reaction afforded a *N*-(2-(methylthio)phenyl-phthalimide **4a** in 19% yield (eq. 3). The reaction optimization for the synthesis of phthalimide was then carried out with respect to ligands, reaction




(3)

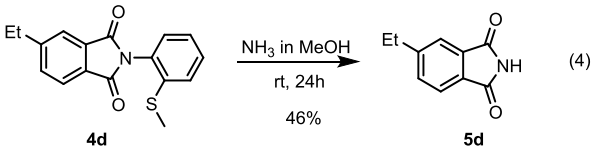
**Table 3** Scope of substrates for the synthesis of *N*-Ar-phthalimide[a]




[a] Conditions:**1** (0.15 mmol), $Cu(TFA)_2.XH_2O$ (30 mol%), 2-Hydroxypyridine (30 mol%), $(Me_3Si)_2$ (2 eq.), $CH_3CN$ (1 mL), $O^2$, 160 °C. After 24 h, add $Cu(TFA)_2.XH_2O$ (30 mol%), 2-Hydroxypyridine (30 mol%). [b] Isolated yield.

temperature and other conditions (See the Supporting Information). We found that 2-hydroxypyridine worked as the best ligand and $Cu(TFA)_2 \cdot XH_2O$ catalyst added again after 24 hours could promote this conversion.

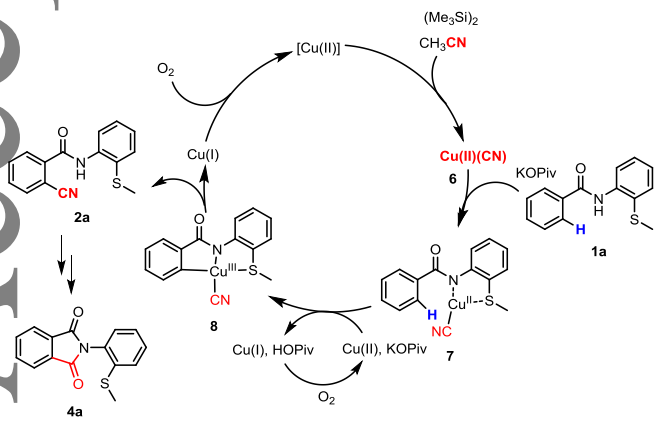
Using the newly developed protocol, we tested the versatility of substrates under the optimized reaction conditions. As shown in Table 3, the electron-donating group gave *N*-Ar-phthalimides **4** in moderate yields from 43%-53% (**4b-4f**). Meanwhile, *p*-COOMe-substituted substrate **1i** and 2-naphthamide derivative **1k** gave lower yields (33% and 34%, respectively). Furthermore, the 2-(methylthio)phenyl directing group could be efficiently removed by treatment with ammonia, affording the corresponding phthalimide derivative **5d** (eq. 4).




**4d** **5d** (4)

Although the detailed mechanism remained unclear at the current stage, a tentative mechanism is proposed on the basis of the previous reports.[11-13] As shown in Scheme 3, the Cu(II)-mediated acetonitrile C−CN cleavage with the assistance of disilane provides the copper cyanide species **6**. The complex **6** coordinates to bidentate substrate **1a**, followed by C−H activation with the assistance of KOPiv and another molecule of Cu(II) as an oxidant to give the aryl Cu(III) intermediate **8** and a Cu(I) salt. The C,N,S-pincer type intermediate **8** may stabilize the high valent Cu(III) intermediate **8** and facilitate C−Cu-CN reductive elimination. Reductive elimination of aryl Cu(III) intermediate **7** yields the corresponding cyanated product **2a** and the Cu(I) salt. Finally, the CuI species is oxidized by oxygen to regenerate the Cu(II) species. On the other hand, when changing ligand and increasing temperature, the amide group of product **2a** can attack intramolecular CN group, affording *N*-Ar-phthalimides **4a** through hydrolysis.

**Scheme 3** The tentative reaction mechanism




## Conclusions

we have developed the Cu-catalyzed protocols for the C−H bond cyanation and cyclization by employing removable bidenate 2-(methylthio)aniline as the directing group, in which green and cheap acetonitrile is used as the "CN" source. By switching the reaction conditions, the C−H cyanated products and *N*-Ar-phthalimides can be provided in acceptable yields with high chem-selectivity. The use of quaternary ammonium salt is essential for cyanation reaction.

## Experimental

**General procedure for the cyanation**. An oven-dried Schlenk tube equipped with a magnetic stir bar was evacuated and backfilled with oxygen three times. Under oxygen, corresponding starting material **1** (0.15 mmol), $Cu(TFA)_2 \cdot XH_2O$ (43.5 mg, 0.15 mmol), KOPiv (21.0 mg, 0.15 mmol), $Bu_4NI$ (55.4 mg, 0.15 mmol), $(Me_3Si)_2$ (62 µL, 0.3 mmol), $CH_3CN$ (1 mL) and *N,N*-dimethylacetamide (0.5 mL) were added into the tube. The reaction was then heated up to 150 °C for 6-24 h under an oxygen atmosphere. After completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and quenched with saturated aqueous $Na_2S$. The aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phase was dried with anhydrous magnesium sulfate. After concentration, the purification by flash chromatography gave the corresponding cyanated products **2**.

**General procedure for the synthesis of N-Ar-phthalimide derivatives**. An oven-dried Schlenk tube equipped with a magnetic stir bar was evacuated and backfilled with oxygen three times. Under oxygen, corresponding starting material **1** (0.15 mmol), $Cu(TFA)_2 \cdot XH_2O$ (13.5 mg, 0.045 mmol), 2-hydroxypyridine (4.3 mg, 0.045 mmol), $(Me_3Si)_2$ (62 µL, 0.3mmol) and $CH_3CN$ (1 mL) were added into the tube. The reaction was then heated up to 150 °C for 24 h under an oxygen atmosphere. Then the reaction was cooled down to room temperature. $Cu(TFA)_2 \cdot XH_2O$ (13.5 mg, 0.045 mmol) and 2-hydroxypyridine (4.3 mg, 0.045 mmol) were added again. The reaction was heated up to 150 °C for 36 h again. After completion, the reaction mixture was cooled to room temperature, diluted with ethyl acetate and quenched with saturated aqueous $Na_2S$. The aqueous phase was extracted with ethyl acetate (3×10 mL). The combined organic phase was dried with anhydrous magnesium sulfate. After concentration, the purification by flash chromatography gave the corresponding N-Ar-phthalimide derivatives **4**.

## Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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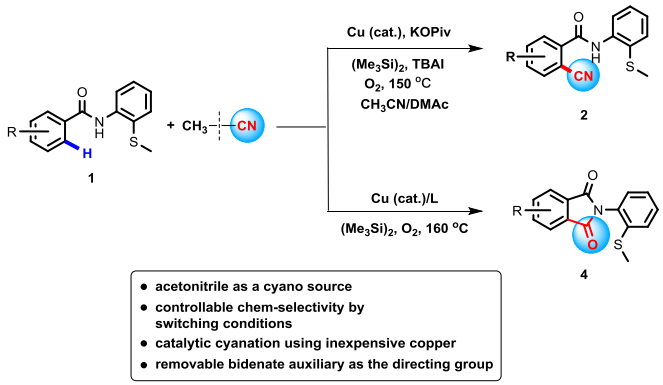
**Copper-mediated Cyanation of Aryl C(sp2)–H Bond with Removable Bidenate Auxiliary Using Acetonitrile as the Cyano Source**




**Zhengwei Yu, Saisai Zhang and Zengming Shen***