DOI: 10.1002/adsc.200900067

Copper-Catalyzed Stereoselective Hydroarylation of 3-Aryl-2-propynenitriles with Arylboronic Acids

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Received: February 1, 2009; Revised: April 15, 2009; Published online: June 2, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900067.

Abstract: The selective synthesis of 3,3-diarylacrylonitriles has been achieved by copper-catalyzed hydroarylation of 3-aryl-2-propynenitriles with arylboronic acids. The starting cyanoalkynes were efficiently prepared from the appropriate aromatic aldehydes and diethyl cyanomethylphosphonate in two steps. The hydroarylation of the obtained cyanoalkyne substrates proceeded in methanol at ambient temperature to produce 3,3-diarylacrylonitriles in good to high yields with excellent *syn* selectivity. The present method was successfully applied to the regiospecific synthesis of both stereoisomers of CC-5079, which was recently reported as a potent anticancer drug.

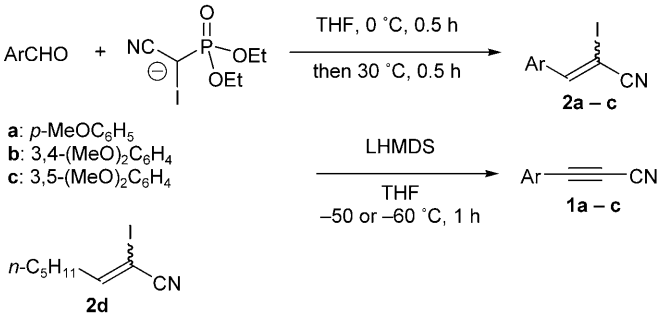
Keywords: alkynes; arylation; boron; copper; nitriles

3,3-Diarylacrylonitriles are potential building blocks for the synthesis of 3,3-diarylpropylamines,[1] which are important structural motifs widely found in synthetic drugs.[2] In addition, the biological activity of highly oxygenated 3,3-diarylacrylonitriles has gained renewed interest since the recent discovery of CC-5079.[3] CC-5079, which is an acrylonitrile possessing 3,4- and 3,5-dimethoxyphenyl rings on the 3 position, was reported to inhibit the growth of cancer cells by interrupting the microtubule assembly process. CC-5079 also inhibits the production of tumor necrosis factor-α, whose excessive production is assumed to cause the pathogenesis of cancers with inhibiting apoptosis. Although a mixture of stereoisomers of CC-5079 was tested for biological activity in the previous study, it was later reported that the biological activities of relevant 3,3-diarylacrylonitriles depend highly on their olefin geometry.[4] The results of these reports suggest that it is very important to develop a stereospecific method to obtain 3,3-diarylacrylonitriles to carry out further bioactivity screening of this class of compounds. In this communication, we present the results of our study on Cu-catalyzed stereoselective hydroarylation of 3-aryl-2-propynenitriles using arylboronic acids.

The stereoselective synthesis of acrylonitriles possessing different aryl rings on the 3 position has been accomplished by the following different processes: the Heck reaction of 3-arylacrylonitriles with aryl iodides,[5] the Suzuki–Miyaura coupling of 3-aryl-3-chloroacrylonitriles with arylboronic acids,[1d] and the Stille coupling of 3-aryl-3-(tributylstannyl)acrylonitriles with aryl iodides.[4] However, these precedents require expensive palladium catalysts, ligands, and/or additives. Therefore, it is beneficial to develop a new method involving an inexpensive non-precious metal catalyst. We have previously reported that the *syn*-hydroarylation of propiolates with arylboronic acids proceeds at ambient temperature without any additives in the presence of a catalytic amount of inexpensive copper salts in methanol.[6] If our Cu-catalyzed hydroarylation is applicable to 3-aryl-2-propynenitriles, the desired 3,3-diarylacrylonitriles can be obtained in a material-economic way. Although the related conjugate addition of cuprates to cyanoalkynes has been reported,[7] only symmetrical 3,3-diphenylacrylonitrile has been synthesized using this method.[7b] In addition, our method has a significant advantage over precedents in that it introduces aromatic rings bearing reactive functional groups, which can be used for further transformations.

Our investigations commenced with the development of a new method for the preparation of cyanoal-

kyne substrates **1a–c** from readily available arylaldehydes (Scheme 1). The literature precedents require the toxic cyanide nucleophile CuCN[8] or cyano elec-

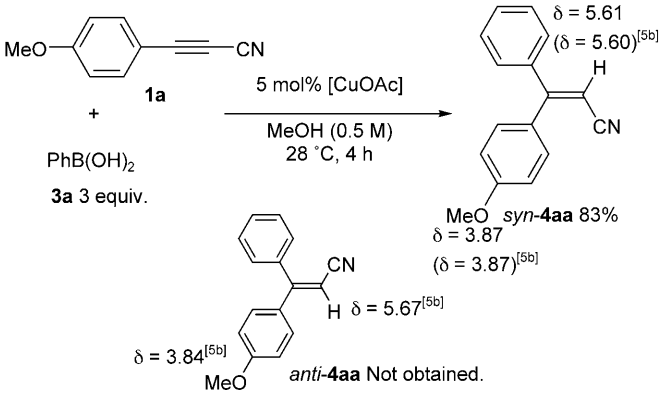


Scheme 1. Synthesis of 3-aryl-2-propynenitriles **1a–c**.

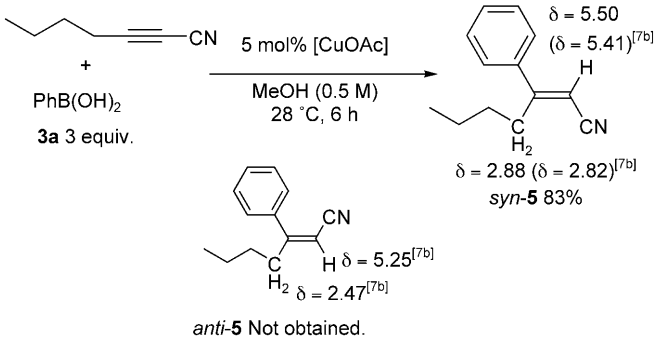
trophiles such as BrCN[9] or PhOCN.[10] Therefore, we used diethyl cyanomethylphosphonate as a less toxic nitrile precursor. According to a previous report,[11] *p*-methoxy-, 3,4-dimethoxy-, and 3,5-dimethoxy-substituted benzaldehydes were treated with an iodinated Horner–Emmons reagent *in situ* prepared from cyanomethylphosphonate in THF to yield 2-iodoacrylonitriles **2a–c** in 82%, 76%, and 72% yields, respectively. Then, **2a** was dehydroiodinated using 2 equivalents of lithium hexamethyldisilazide (LHMDS) in THF at −50 °C to obtain the desired alkyne **1a** in 87% yield. The use of LHMDS is quite essential to obtain a high yield of **1a**; the use of other bases such as sodium and potassium hexamethyldisilazides, LDA, *t*-BuOK, or DBU results in low yields or no reaction. Similarly, dehydroiodination of **2b** and **2c** with LHMDS at −50 °C (−60 °C for **2c**) furnished **1b** and **1c** in 92% and 91% yields, respectively. Under optimized conditions, an aliphatic cyanoalkyne was not obtained from the corresponding iodoacrylonitrile precursor **2d**.

We then examined the Cu-catalyzed reaction of **1a** with arylboronic acid **3a**. Under our previously optimized conditions, **1a** reacted with phenylboronic acid (**3a**, 3 equiv.) in the presence of 5 mol% CuOAc for 4 h to yield crude **4aa** with >98% *syn* selectivity (^{1}H NMR). Purification of the obtained compound by silica gel column chromatography afforded **4aa** in 83% yield as an exclusive *syn* isomer (Scheme 2). Diagnostic resonances of the vinyl and methoxy protons of **4aa** appeared as singlets at $\delta = 5.61$ and 3.87 ppm, respectively, which were in good agreement with those reported for the expected *Z* isomer as shown in parentheses.[5b] On the other hand, the corresponding resonances of *E* isomer were reported to appear at lower and higher fields, respectively ($\delta = 5.67$ and 3.84 ppm).[5b]

The Cu-catalyzed hydroarylation also effectively proceeded with an aliphatic cyanoalkyne (Scheme 3).



Scheme 2. Cu-Catalyzed hydroarylation of **1a** with **3a.**



Scheme 3. Cu-Catalyzed hydroarylation of 2-heptynenitrile with **3a**.

The reaction of 2-heptynenitrile with phenylboronic acid was carried out to obtain *syn*-**5** in 83% yield as a single stereoisomer. The *syn* selectivity was again confirmed by comparison of its ^{1}H NMR data with those reported previously.[7b] From these observations, we concluded that the Cu-catalyzed hydroarylation of cyanoalkynes also proceeds with excellent *syn* selectivity, as previously observed for alkynoates.[6]

In order to examine the influence of the substituents on arylboronic acids, boron reagents **3b–k** (Figure 1) were used for the reaction with **1a** (Table 1). Although higher catalyst loadings were required for the reaction of sterically demanding *o*- and *m*-isomers, tolylboronic acids **3b–d** afforded the desired products **4ab–ad** uneventfully in high yields with excellent *syn* selectivity (entries 1–3). It should be noted that our protocol well tolerates various functional groups such as halides, electron-withdrawing ester, nitro, and electron-donating methoxy groups (entries 4–9). In cases of arylboronic acids **3g**, **i**, **j**, the chromatographic purification was hampered due to the formation of several aromatic by-products from these reagents, although the ^{1}H NMR analysis of the crude mixture showed that hydroarylation products were formed in high yields. Therefore, **4ai** was separated with preparative TLC in 76% yield (entry 8).

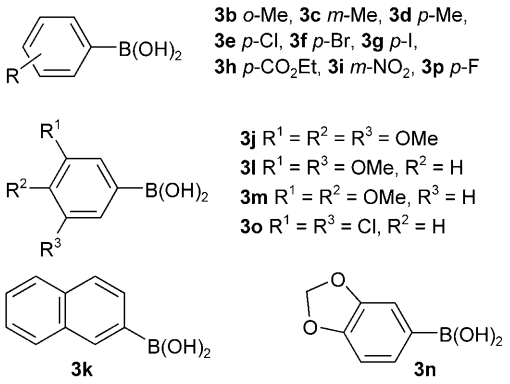


Figure 1. Arylboronic acids used in this study.

Because a decrease in stereoselectivity was observed for electron-rich **4ag** and **4aj** after PTLC, these products were purified by recrystallization (entries 6 and 9). In addition to these phenylboronic acid derivatives, 2-naphthylboronic acid **3k** produced the corresponding adduct **4ak** in 94% yield (entry 10).

Iodide **4ag** is of particular importance among the obtained products, because it is otherwise difficult to be synthesized using other methods and can be used for further transformations. In order to demonstrate its synthetic potential, the Ullmann coupling of **4ag** with indole was examined as shown in Scheme 4. The isolated **4ag** was subjected to Ullmann coupling with slightly excess amounts of indole according to the

Table 1. Hydroarylation of **1a** with **3b–k**.[a]

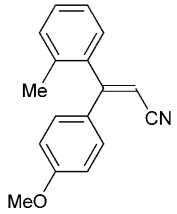
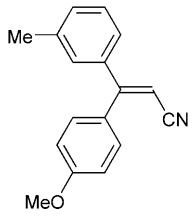
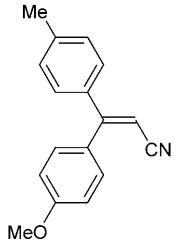
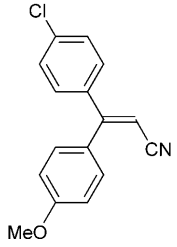
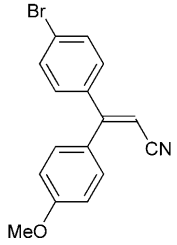
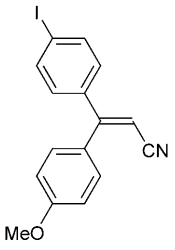
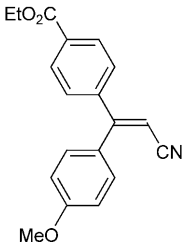
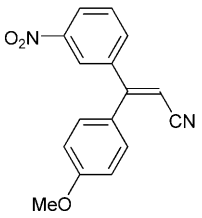
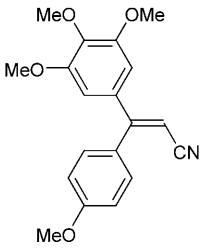
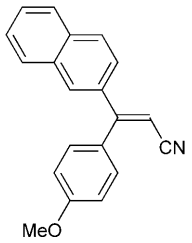
Entry	**3**	Cu [mol%]	Time [h]	**4**		Yield [%][b,c]
1	**3b**	10	12	**4ab**		80
2	**3c**	8	12	**4ac**		81
3	**3d**	5	12	**4ad**		85
4	**3e**	5	10	**4ae**		91
5	**3f**	8	8	**4af**		96

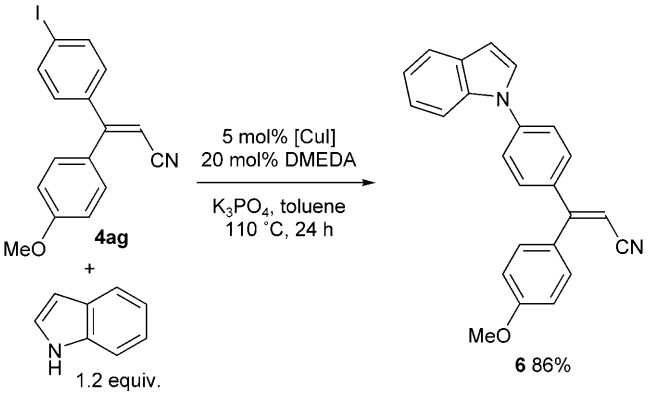
Table 1. (Continued)

Entry	**3**	Cu [mol%]	Time [h]	**4**		Yield [%][b,c]
6	**3g**	8	8	**4ag**		68 (93)[d]
7	**3h**	8	4	**4ah**		87
8	**3i**	8	8	**4ai**		76 (96)[d]
9	**3j**	5	4	**4aj**		72 (82)[d]
10	**3k**	5	24	**4ak**		94

[a] All reactions were carried out in MeOH (0.5 M) at 28 °C under argon.
[b] Isolated yields.
[c] Stereoselectivity of >99% was inferred from ^{1}H NMR and GC-MS analyses of isolated products.
[d] Yields in parentheses were estimated by ^{1}H NMR analysis of crude samples.

procedures reported by Buchwald and co-workers.[12] In the presence of 5 mol% CuI, 20 mol% *N*,*N*′-dimethylethylenediamine (DMEDA), and K_3PO_4, **4ag** and indole were refluxed in toluene for 24 h to obtain **6** in 86% yield. No erosion of olefin stereochemistry was observed for the isolated **6**.

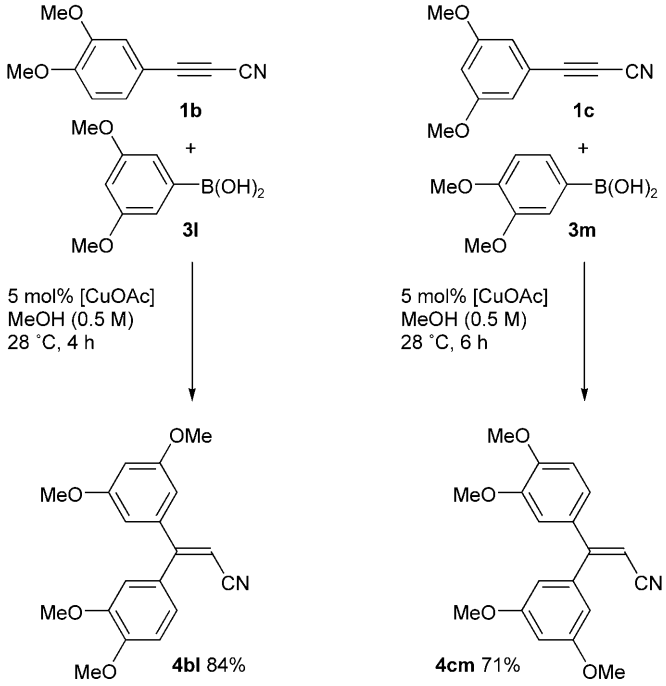
After the successful selective formation of highly oxygenated 3,3-diarylacrylonitrile **4aj**, which is the substitutional isomer of CC-5079, the stereospecific synthesis of the two stereoisomers of CC-5079 was carried out (Scheme 5). In the original report,[3b] CC-5079 was obtained as an *E*/*Z* mixture *via* the Horner–Emmons reaction of 3,4,3′,5′-tetramethoxybenzophenone with diethyl cyanomethylphophonate. In turn, the starting benzophenone was prepared from 3,5-dimethoxybenzonitrile and 4-bromoveratrole in a low yield of 26%. Our method involves the highly *syn*-selective Cu-catalyzed hydroarylation of readily available 3-aryl-2-propynenitriles and arylboronic acids, thereby enabling practical and stereospecific access to



Scheme 4. Cu-Catalyzed Ullmann coupling of **4ag** with indole.

the desired target molecules. In fact, the reaction of **1b** and **3l** was carried out under optimal conditions to obtain **4bl** in 84% yield as an exclusive stereoisomer. Similarly, the opposite stereoisomer **4cm** was synthesized in 71% yield by coupling **1c** with **3m**.

We finally synthesized several known derivatives relevant to CC-5079. In the previous studies, the 3,4-dimethoxyphenyl moiety was found to play a role in biological activities of this class of compounds.[3,4] Therefore, the coupling of **1b** with several commercially available arylboronic acids were carried out as



Scheme 5. Stereospecific synthesis of CC-5079.

summarized in Table 2. In the presence of 5 or 8 mol% CuOAc as a catalyst, **1b** was allowed to react with arylboronic acids **3d**, **k**, **n**–**p** in MeOH at 28 °C

Table 2. Coupling of **1b** with **3d**, **k**, **n**–**p**.[a]

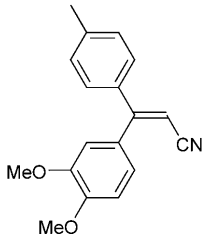
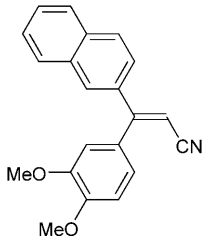
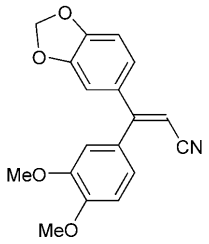
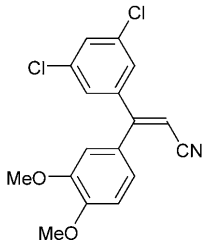
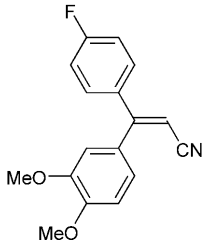
Entry	**3**	Cu [mol%]	Time [h]	**4**		Yield [%][b,c]
1	**3d**	5	12	**4bd**		84
2	**3k**	5	24	**4bk**		89
3	**3n**	8	6	**4bn**		90

Table 2. (Continued)

Entry	3	Cu [mol%]	Time [h]	4	Yield [%][b,c]
4	**3o**	8	8	**4bo** 	97
5	**3p**	5	10	**4bp** 	92

[a] All reactions were carried out in MeOH (0.5 M) at 28 °C under argon.
[b] Isolated yields.
[c] Stereoselectivity of >99% was inferred from ^{1}H NMR and GC-MS analyses of isolated products.

for 6–24 h to deliver the corresponding hydroarylation products in 84–97% yields. The perfect *syn* stereoselectivity was again observed for each case. These results successfully demonstrate the feasibility of the copper-catalyzed hydroarylation toward the stereoselective synthesis of pharmaceutically important 3,3-diarylacrylonitriles.

Experimental Section

Representative Procedures for Cu-Catalyzed Hydroarylation

To a solution of 3-(*p*-methoxyphenyl)-2-propynenitrile (**1a**) (78.58 mg, 0.50 mmol) and phenylboronic acid (**3a**) (182.88 mg, 1.50 mmol) in methanol (1.0 mL) was added CuOAc (3.08 mg, 0.025 mmol). The reaction mixture was degassed at −78 °C, and then stirred at 28 °C under an argon atmosphere for 4 h. After filtration through a pad of Celite® to remove insoluble materials, the filtrate was concentrated under vacuum. The residue was purified by silica gel flash column chromatography (hexane-AcOEt 50:1) to give **4aa** as a colorless oil; yield: 97.5 mg (83%).

Acknowledgements

This research was partially supported by the Ministry of Education, Science, Sports and Culture, Grant-in-Aid for Scientific Research (B) (20350045), Scientific Research on Priority Area "Chemistry on Concerto Catalysis" (20037018). We thank Prof. K. Tomooka (Kyushu University) for use of an NMR spectrometer and Profs. H. Suzuki and T. Ikariya (Tokyo Instituted of Technology) for use of mass spectrometers.

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