JOC The Journal of Organic Chemistry

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Palladium-Catalyzed Highly Selective *ortho*-Halogenation (I, Br, Cl) of Arylnitriles via sp^2 C−H Bond Activation Using Cyano as Directing Group

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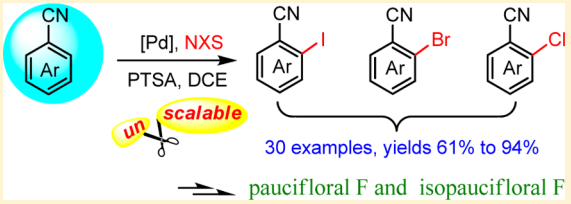
Supporting Information

ABSTRACT: A palladium-catalyzed *ortho*-halogenation (I, Br, Cl) of arylnitrile is described. The optimal reaction conditions were identified after examining various factors such as catalyst, additive, solvent, and reaction temperature. Using cyano as the directing group, the halogenation reaction gave good to excellent yields. The method is compatible to the arylnitriles with either electron-withdrawing or electron-donating groups. The reaction is available to the substrate in at least gram scale. The present method was successfully applied to the synthesis of the precursors of paucifloral F and isopaucifloral F.



Over the past decade, transition-metal-catalyzed C−H functionalization has emerged as a valuable and atom-economical strategy for organic synthesis. Of particular interest is the palladium-catalyzed chelation-directed sp^2 C−H activation, which provides various valuable products in a highly efficient way.[1] Utilizing substrates with weakly coordinating directing groups enables unprecedented breadth in the functionalization step, owing to the higher reactivity of the putative cyclopalladated intermediates, which is becoming a powerful approach for developing synthetically versatile reactions.[2] Thus, some weakly coordinating directing groups such as carboxyl,[3] hydroxyl,[4] and carbonyl[5] have been adopted in the cyclometalation in recent years. It is well-known that the cyano group is not only a coordinating functional group but also an important precursor for a multitude of transformations into various functional groups such as carboxylic acids, esters, amides, amines, aldehydes, tetrazoles, and ketones.[6] In our previous works, palladium-catalyzed cyano-directed sp^2 C−C and C−O bond formation reactions were studied.[7] We believe that expanding the cyano-directed C−H functionalization should be significant in the synthesis of polyfunctional nitriles and the related compounds.

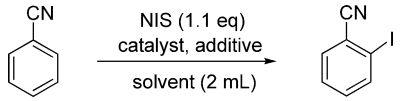
Though a plethora of carbon−carbon bond-formation reactions have been discovered by the transition-metal-catalyzed C−H functionalization, application of this strategy to create carbon−heteroatom bonds, in particular carbon−halogen bonds, is still underdeveloped. Aryl halides are extremely valuable starting materials for synthetic elaboration. For example, they are used as precursors for the synthesis of organometallic reagents and for nucleophilic substitution reactions.[8] In recent decades, aryl halides, especially aryl iodides and aryl bromides, have also found widespread utility as substrates to construct complex structures in organic syntheses via transition-metal-catalyzed coupling reactions (such as Suzuki coupling, Negishi coupling, Heck coupling, et al).[9] Consequently, efficient and selective methods to access this class of compounds are highly valuable. Several groups reported palladium-catalyzed sp^2 C−H halogenations directed by heteroaromatics or other electron-donating directing groups,[10] but direct iodination to the aromatic ring was still rare because of the highly oxidative addition activity of aryl iodides to transition metals. Also, some methods were unavailable to the electron-deficient substrates. To develop new method enabling the high-yielding and selective formation of valuable and versatile C−X (X = I, Br, Cl) bonds, compatible with a large scope of diverse arenes, is of prime synthetic value. Since the cyano is an electron-withdrawing (type II) group, the general electrophilic aromatic substitution to arylnitriles cannot give *ortho*-halogenated arylnitriles. The cyclometalation-based *ortho*-C−H activation will provide the possibility for the direct *ortho*-halogenation. In this work, we wish to report an efficient method for the synthesis of *o*-haloarylnitriles via a Pd-catalyzed, cyano-directed halogenation of aromatic C−H bond using NXS (X = I, Br, Cl) as halogenation reagents. As an important polyfunctional reagent, one of the products was further successfully used to synthesize a precursor of a natural compound.

The reaction of benzonitrile and *N*-iodosuccinimide (NIS) was initially selected to optimize the reaction conditions. Without catalyst, the reaction did not take place at all. $Pd(OAc)_2$ seemed to be the efficient catalyst for this transformation to give the only *ortho*-iodinated product, 2-iodo-benzonitrile, while other palladium species such as $Pd(TFA)_2$, $PdCl_2$, $Pd(acac)_2$, and $Pd(PPh_3)_4$ were substantially less effective (entries 7−10, Table 1). A 5 mol % catalyst

Received: December 20, 2012
Published: February 1, 2013

dx.doi.org/10.1021/jo302765g | J. Org. Chem. 2013, 78, 2786−2791

Table 1. Optimization of the *ortho*-Halogenation Reaction[a]



entry	catalyst	additive (equiv)	solvent	yield (%)[b]
1		PTSA (0.5)	DCE	0
2	$Pd(OAc)_2$	PTSA (0)	DCE	22
3	$Pd(OAc)_2$	PTSA (1)	DCE	80
4	$Pd(OAc)_2$	PTSA (0.5)	DCE	84
5[c]	$Pd(OAc)_2$	PTSA (0.5)	DCE	85
6[d]	$Pd(OAc)_2$	PTSA (0.5)	DCE	70
7	$Pd(TFA)_2$	PTSA (0.5)	DCE	56
8	$PdCl_2$	PTSA (0.5)	DCE	trace
9	$Pd(acac)_2$	PTSA (0.5)	DCE	trace
10	$Pd(PPh_3)_4$	PTSA (0.5)	DCE	trace
11	$Pd(OAc)_2$	PivOH (0.5)	DCE	58
12	$Pd(OAc)_2$	CF_3COOH (0.5)	DCE	63
13	$Pd(OAc)_2$	CH_3COOH (0.5)	DCE	32
14	$Pd(OAc)_2$	PTSA (0.5)	toluene	43
15	$Pd(OAc)_2$	PTSA (0.5)	dioxane	35
16	$Pd(OAc)_2$	PTSA (0.5)	DMF	55
17	$Pd(OAc)_2$	PTSA (0.5)	CH_3COOH	38
18	$Pd(OAc)_2$	PTSA (0.5)	CH_3CN	10
19[e]	$Pd(OAc)_2$	PTSA (0.5)	DCE	72

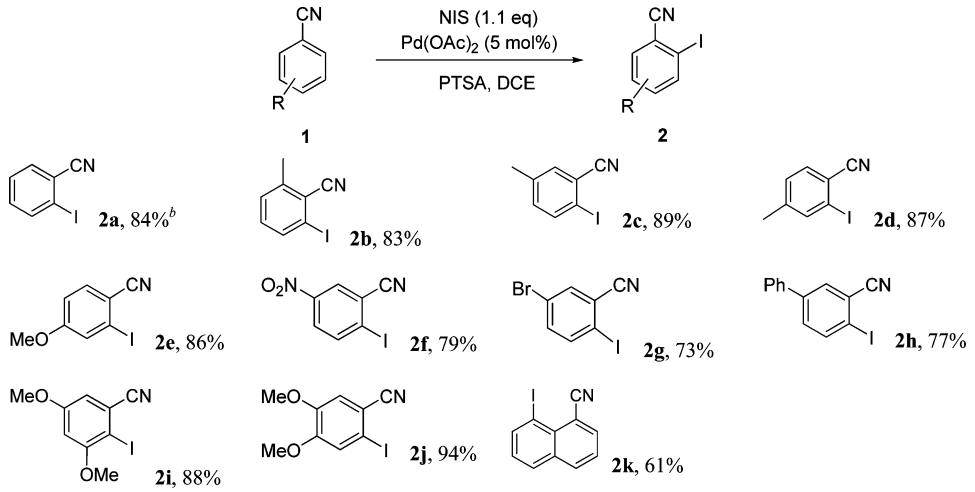
[a]Reaction conditions: unless otherwise specified, all reactions were carried out with benzonitrile (0.5 mmol), NIS (0.55 mmol), catalyst (5 mol %), and additive (0.5 equiv) in 2.0 mL of solvent under air atmosphere at 70 °C for 12 h. [b]Isolated yields. [c]10 mol % catalyst was used. [d]3 mol % catalyst was used. [e]The reaction performed at 50 °C.

loading gave a high yield of 84%. Increasing the amount of $Pd(OAc)_2$ to 10 mol % did not bring an evident improvement of the yield, while decreasing the catalyst to 3 mol % lowered the yield to 70% (entries 5, 6). An acidic additive was proved to be essential to this reaction. Some reagents such as *p*-toluenesulfonic acid (PTSA), PivOH, CF_3COOH, and CH_3COOH were tested in which PTSA gave the best result (entries 11−13). Another factor to influence this reaction was the solvent. In toluene, dioxane, DMF, CH_3COOH, and CH_3CN, the reaction gave poor to moderate yields (entries 14−18), while in DCE the highest yield was obtained (entry 4). At 70 °C, the reaction proceeded smoothly and finished in 12 h. Decreasing the temperature to 50 °C led to a lower yield of 72% (entry 19). Besides, I_2 was also tested as iodic source. However, a mixture with a low yield was obtained under above reaction conditions.

To test the scope of this *ortho*-iodination reaction, we explored variously substituted arylnitriles under the established reaction conditions (Table 2). For most of the substrates we employed, the reaction gave the corresponding products with high selectivity and good yields. It seemed that the substrates with different substitution patterns on the aryl ring had no evident effect on this transformation. For example, the reactions proceeded smoothly with similar yields when methyl, methoxyl, and nitro groups existed, respectively, on the substrates. The presence of a methyl group in the *ortho*-position of the cyano group did not bring decrease of the yield by "ortho-substituent effect", which generally existed in many palladium-catalyzed coupling reactions (**2b**). An interesting regioselectivity could be found in that when a *meta*-substituent existed at arylnitrile, the iodination did not take place between cyano and that substituent because of the steric hindrance. It is worth noting that in the presence of nitro, a strongly electron-withdrawing group, the reaction still gave a yield of 79% (**2f**). Moreover, with 1-naphthonitrile, an iodination product on the 8-position was obtained with moderate yield (**2k**) and no 2-position iodination product was found, which may be because a more stable cyclopalladated intermediate could be generated on 8-position. Several disubstituted benzonitrile derivatives were also tested, and high yields were achieved (**2i**, **2j**).

We next examined the bromination and chlorination of arylnitriles under the same reaction conditions (Table 3). Similar to the iodination described above, for the most of the substrates we used the reaction gave good yields. Good tolerances to the chemically active functional groups were also revealed. For example, the bromo and ester groups on arylnitriles remained after this palladium-catalyzed reaction (**3g**, **3m**, **4m**, **5m**, **3n**). It is worth noting that when 1.1 equiv of NXS was added to the reaction system, only monohalogenation reaction took place, but the presence of excess halogenation

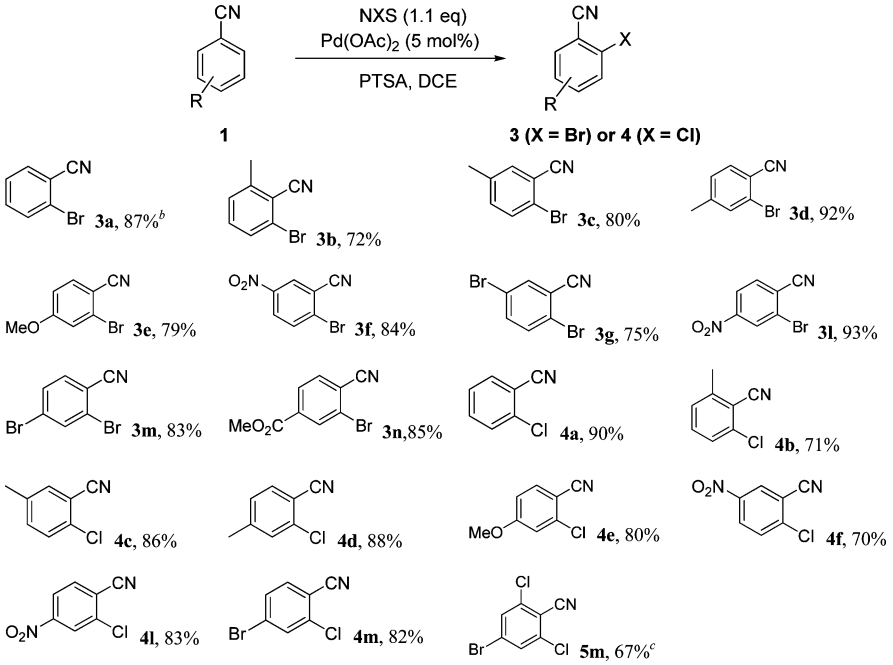
Table 2. *ortho*-Iodination of Arylnitriles[a]



[a]All reactions were carried out with arylnitrile (0.5 mmol), NIS (0.55 mmol), catalyst (5 mol %), and PTSA (0.5 equiv) in 2.0 mL of DCE under air atmosphere at 70 °C for 12 h. [b]Isolated yields.

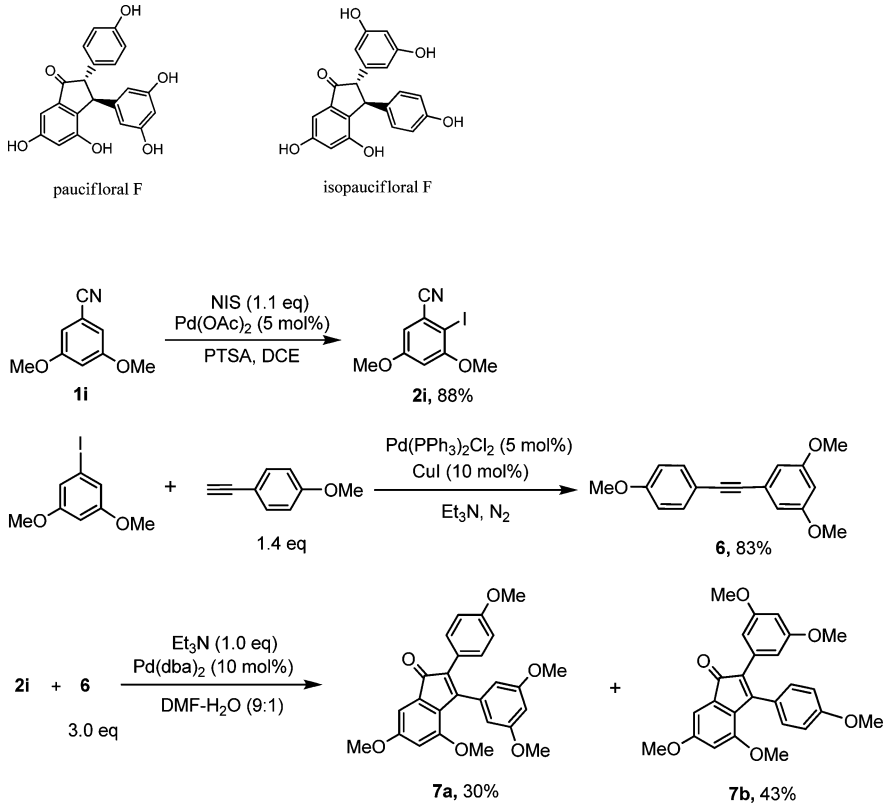
dx.doi.org/10.1021/jo302765g | J. Org. Chem. 2013, 78, 2786−2791

Table 3. *ortho*-Bromination and Chlorination of Arylnitriles[a]



[a]All reactions were carried out with arylnitrile (0.5 mmol), NXS (0.55 mmol, X = Br, Cl), catalyst (5 mol %), and PTSA (0.5 equiv) in 2.0 mL of DCE under air atmosphere at 70 °C for 12 h. [b]Isolated yields. [c]4-Bromobenzonitrile was used as reactant, and 2.5 equiv of NCS was added.

Scheme 1. Synthesis of Precursors of Paucifloral F and Isopaucifloral F



reagent could give a dihalogenation product with a moderate yield (**5m**).

Up to now, the application of transition-metal-catalyzed C–H functionalization in the syntheses of complex organic molecules has remained a formidable challenge to chemists. Reacting scale is a key restraining factor in the use of many methods in organic synthesis. In this context, expanding reacting weight exhibits particular interest, so we attempted to conduct the reaction on gram scale. Use 20 mmol (2.34 g) of 3-methylbenzonitrile as the reactant, under the established iodination reaction conditions, 3.78 g (yield 78%) of 2-iodo-5-methylbenzonitrile was obtained. Similarly, the bromination

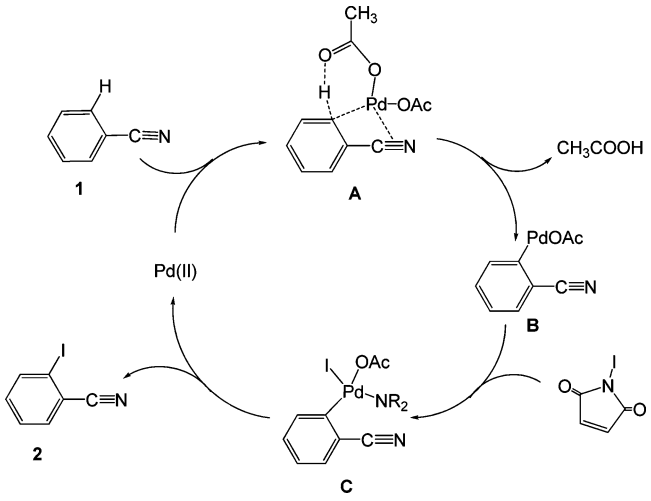
dx.doi.org/10.1021/jo302765g | J. Org. Chem. 2013, 78, 2786–2791

of 20 mmol (2.34 g) of 4-methylbenzonitrile gave 3.15 g (yield 81%) of 2-bromo-4-methylbenzonitrile. That is to say, decreases of less than 12% of the yields were revealed when the reaction proceeded on the gram scale, which demonstrates the possibility to use this method in general organic synthesis.

We next decided to use this convenient halogenation in the synthesis of the precursors of natural products paucifloral F and its regioisomer isopaucifloral F, both of them compounds with anticancer activity.[11] First, 3, 5-dimethoxybenzonitrile (**1i**) reacted with NIS to give *ortho*-iodinated product 2-iodo-3,5-dimethoxybenzonitrile (**2i**) with an isolated yield of 88% (Scheme 1). Catalyzed by $Pd(dba)_2$, the reaction of **2i** with compound **6**, which was obtained through a Sonogashira reaction, generated the products **7a** and **7b**,[12] which could be isolated easily by column chromatography and gave yields of 30% and 43%, respectively.

A possible mechanism was proposed to account for this palladium-catalyzed regioselective halogenation reaction (Scheme 2). First, the coordination of cyano in arylnitrile to

Scheme 2. Plausible Reaction Mechanism



$Pd(OAc)_2$ formed a cyclopalladated intermediate **A** in which the cyano group coordinated with palladium using its π-electrons between carbon and nitrogen. This was different from the n-electron coordination in some other coordinating group directed C–H bond activation, and the weak coordination property of this cyclopalladated intermediate might make it have higher reactivity. Acetate then presumably participated in aromatic proton abstraction to generate an aryl palladium intermediate **B**, followed by an oxidative addition of NXS to intermediate **B** to form intermediate **C**.[10b,c] The function of PTSA in this reaction system is presumably to protonate the carbonyl group of *N*-halosuccinimide (NXS) and make it a more effective X^+ source.[10l] The subsequent reductive elimination of **C** gave the *ortho*-halogenated product and regenerated the Pd^{II} catalyst.

In summary, a practical strategy for the *ortho*-halogenation of arylnitriles was developed by a simple palladium-catalyzed reaction with regioselectivities and high yields. It is applicable to iodination, bromination, and chlorination and allows the use of substrates with electron-withdrawing or electron-donating groups. Moreover, the reaction is available to at least the gram scale. As an example, it was successfully applied to the synthesis of the precursors of paucifloral F and isopaucifloral F. The established method is further expected to be used in the syntheses of many types of complex organic compounds and natural products.

EXPERIMENTAL SECTION

General. All reactions were run in a sealed tube with a Teflon-lined cap under air atmosphere. All reagents were commercially available and were used without purification. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ [using $(CH_3)_4Si$ (for ^1H, δ = 0.00; for ^{13}C, δ = 77.00) as internal standard]. The following abbreviations are used to designate the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Melting points are uncorrected. HRMS was obtained by ESI on TOF mass analyzer.

General Procedures for the Palladium-Catalyzed Halogenation of Arylnitriles. Arylnitrile (0.5 mmol), NXS (0.55 mmol), $Pd(OAc)_2$ (0.025 mmol), PTSA (0.25 mmol), and DCE (2.0 mL) were added into a 25-mL sealed tube with a Teflon-lined cap. The mixture was heated at 70 °C (oil bath temperature) for 12 h. After cooling to room temperature, the volatiles were removed under reduced pressure, and the residue was purified by a flash column chromatography on silica gel using EtOAc/hexane (1:5) as eluent to give the corresponding product.

Preparation of 1,3-Dimethoxy-5-((4-methoxyphenyl)-ethynyl)benzene (6). 3,5-Dimethoxyiodobenzene (264 mg, 1.0 mmol), $Pd(PPh_3)_2Cl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.1 mmol), and 4-methoxyphenylacetylene (185 mg, 1.4 mmol) were added into Et_3N (8 mL). The solution was stirred under N_2 at room temperature for 18 h. After purification by column chromatography, 1,3-dimethoxy-5-((4-methoxyphenyl)ethynyl)benzene (**6**) was obtained as a colorless oil in 83% yield.

Synthesis of Indenones (7a and 7b). 2-Iodo-3,5-dimethoxybenzonitrile (**2i**) (72 mg, 0.25 mmol), $Pd(dba)_2$ (14.4 mg, 0.025 mmol), Et_3N (25.3 mg, 0.25 mmol), and compound (**6**) (198 mg, 0.75 mmol) were added into a 9:1 DMF/water solution (5 mL). The reaction mixture was stirred at 130 °C for 24 h. After purification by column chromatography on silica gel (60, academic grade) using CH_2Cl_2/hexane (1:2) as eluent, indenone (**7a** and **7b**) were obtained as purple solids in 30% and 43% yields, respectively.

*2-Iodobenzonitrile (**2a**).* Yield 96 mg, 84%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.0 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.48 (t, J = 7.9 Hz, 1H), 7.28–7.33 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 134.3, 133.7, 128.3, 120.6, 119.3, 98.4.

*2-Iodo-6-methyl-benzonitrile (**2b**).* Yield 101 mg, 83%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.17 (t, J = 7.9 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7, 136.8, 133.3, 129.5, 120.9, 118.6, 98.8, 21.6.

*2-Iodo-5-methyl-benzonitrile (**2c**).* Yield 108 mg, 89%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 1H), 7.42 (s, 1H), 7.12 (d, J = 8.0 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 138.8, 134.9, 134.8, 120.4, 119.4, 94.2, 20.8.

*2-Iodo-4-methyl-benzonitrile (**2d**).* Yield 104 mg, 87%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 7.25 (d, J = 7.9 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.1, 140.1, 133.9, 129.2, 119.6, 117.1, 98.3, 21.4.

*2-Iodo-4-methoxybenzonitrile (**2e**).* Yield 113 mg, 86%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (s, 1H), 7.64 (d, J = 8.4 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 142.7, 134.1, 117.6, 110.7, 105.9, 86.0, 56.7.

*2-Iodo-5-nitrobenzonitrile (**2f**).* Yield 108 mg, 79%. ^1H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, J = 2.5 Hz,1H), 8.20 (d, J = 8.7 Hz, 1H), 8.12 (dd, J_1 = 2.5 Hz, J_2 = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 141.1, 128.7, 127.7, 122.4, 117.5, 106.9.

*2-Iodo-5-bromobenzonitrile (**2g**).* Yield 112 mg, 73%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1H), 7.74 (d, J = 2.4 Hz, 1H), 7.43 (dd, J_1 = 2.4, J_2 = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 137.0, 136.7, 122.4, 122.3, 118.0, 96.5.

*2-Iodo-5-phenylbenzonitrile (**2h**).* Yield 117 mg, 77%. Mp 63–64 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 1H), 7.83 (d, J = 2.3 Hz, 1H), 7.55 (dd, J_1 = 2.3 Hz, J_2 = 8.0 Hz, 2H), 7.45–7.52 (m,

dx.doi.org/10.1021/jo302765g | J. Org. Chem. 2013, 78, 2786–2791

4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 139.9, 137.9, 132.7, 132.3, 129.3, 128.8, 126.9, 121.2, 119.3, 96.5; HRMS (ESI) calcd for $C_{13}H_8IN[Na]$ 327.9599, found 327.9593.

*2-Iodo-3,5-dimethoxybenzonitrile (**2i**).* Yield 127 mg, 88%. Mp. 99−100 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.76 (d, J = 2.4 Hz, 1H), 6.57 (d, J = 2.4 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.9, 121.7, 119.4, 110.3, 103.2, 80.4, 56.8, 55.9; HRMS (ESI) calcd for $C_9H_8INO_2[Na]$ 311.9498, found 311.9529.

*2-Iodo-4,5-dimethoxybenzonitrile (**2j**).* Yield 136 mg, 94%. Mp 103−104 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.01 (s, 1H), 3.91 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.8, 149.2, 121.4, 119.8, 115.7, 112.0, 88.7, 56.5, 56.3; HRMS (ESI) calcd for $C_9H_8INO_2[Na]$ 311.9498, found 311.9455.

*8-Iodo-1-naphthonitrile (**2k**).* Yield 85 mg, 61%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.99−8.02 (m, 2H), 7.85 (d, J = 8.2 Hz, 1H), 7.48 (dd, J_1 = 8.0 Hz, J_2 = 8.0 Hz, 1H), 7.18 (t, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 138.8, 135.0, 134.6, 131.1, 130.4, 128.2, 125.3, 119.0, 112.5, 92.3.

*2-Bromobenzonitrile (**3a**).* Yield 79 mg, 87%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66−7.71 (m, 2H), 7.44−7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3, 134.0, 133.2, 127.7, 125.3, 117.1, 115.8.

*2-Bromo-6-methylbenzonitrile (**3b**).* Yield 71 mg, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, J = 7.9 Hz, 1H), 7.34 (t, J = 7.9 Hz, 1H), 7.27 (d, J = 8.0 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.8, 133.3, 130.3, 128.8, 125.5, 116.4, 116.2, 21.2.

*2-Bromo-5-methylbenzonitrile (**3c**).* Yield 78 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 8.2 Hz, 1H), 7.34 (d, J = 1.8 Hz, 1H), 7.26 (dd, J_1 = 8.2 Hz, J_2 = 1.8 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 135.0, 134.6, 132.9, 121.8, 117.3, 115.4, 20.7.

*2-Bromo-4-methylbenzonitrile (**3d**).* Yield 91 mg, 92%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.0 Hz, 1H), 7.52 (s, 1H), 7.22 (d, J = 8.0 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.4, 134.0, 133.8, 128.5, 125.1, 117.4, 116.1, 21.6.

*2-Bromo-4-methoxybenzonitrile (**3e**).* Yield 84 mg, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 1.9 Hz, 1H), 7.59 (dd, J_1 = 1.9 Hz, J_2 = 8.6 Hz, 1H), 6.95 (d, J = 8.6 Hz, 1H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 136.6, 133.2, 117.7, 112.3, 112.0, 105.2, 56.6.

*2-Bromo-5-nitrobenzonitrile (**3f**).* Yield 95 mg, 84%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, J = 2.6 Hz, 1H), 8.30 (dd, J_1 = 2.6 Hz, J_2 = 8.7 Hz, 1H), 7.94 (d, J = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 134.6, 132.6, 129.1, 128.2, 117.4, 115.3.

*2,4-Dibromobenzonitrile (**3m**).* Yield 108 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 1.6 Hz, 1H), 7.59 (dd, J_1 = 1.6 Hz, J_2 = 8.3 Hz, 1H), 7.53 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 134.9, 131.2, 128.3, 126.0, 116.5, 114.8.

*2-Bromo-4-nitrobenzonitrile (**3l**).* Yield 106 mg, 93%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 2.0 Hz, 1H), 8.29 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 135.2, 128.2, 126.5, 122.6, 121.6, 115.5.

*2,5-Dibromobenzonitrile (**3g**).* Yield 98 mg, 75%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 2.1 Hz, 1H), 7.56−7.61 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 136.7, 134.5, 124.1, 121.2, 117.6, 115.8.

*Methyl 3-Bromo-4-cyanobenzoate (**3n**).* Yield 102 mg, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 135.1, 134.3, 134.0, 128.4, 125.4, 119.6, 116.5, 53.0.

*2-Chlorobenzonitrile (**4a**).* Yield 62 mg, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (dd, J_1 = 1.4 Hz, J_2 = 8.0 Hz, 1H), 7.52−7.57 (m, 2H), 7.38−7.42 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.9, 134.0, 133.9, 130.1, 127.2, 116.0, 113.4.

*2-Chloro-6-methylbenzonitrile (**4b**).* Yield 54 mg, 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, J = 8.0 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.0 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.4, 136.9, 133.1, 128.3, 127.1, 115.2, 113.8, 20.9.

*2-Chloro-5-methylbenzonitrile (**4c**).* Yield 62 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.33−7.41 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.5, 134.8, 134.2, 132.5, 129.7, 116.1, 113.0, 20.6.

*2-Chloro-4-methylbenzonitrile (**4d**).* Yield 67 mg, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.9 Hz, 1H), 7.33 (s, 1H), 7.17 (d, J = 7.9 Hz, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 136.5, 133.7, 130.6, 128.1, 116.3, 110.2, 21.7.

*2-Chloro-4-methoxybenzonitrile (**4e**).* Yield 67 mg, 80%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 1.9 Hz, 1H), 7.57 (dd, J_1 = 1.9 Hz, J_2 = 8.6 Hz, 1H), 6.99 (d, J = 8.6 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 138.3, 135.0, 116.4, 115.6, 113.5, 105.0, 56.0.

*4-Bromo-2-chlorobenzonitrile (**4m**).* Yield 89 mg, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.55 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 134.6, 133.1, 130.8, 128.2, 115.3, 112.3.

*2-Chloro-4-nitrobenzonitrile (**4l**).* Yield 76 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 2.1 Hz, 1H), 8.26 (dd, J_1 = 2.1 Hz, J_2 = 8.5 Hz, 1H), 7.93 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 138.6, 135.0, 125.2, 122.1, 119.1, 114.2.

*2-Chloro-5-nitrobenzonitrile (**4f**).* Yield 64 mg, 70%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 2.6 Hz, 1H), 8.42 (dd, J_1 = 2.6 Hz, J_2 = 8.9 Hz, 1H), 7.77 (d, J = 8.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 143.6, 131.3, 129.0, 128.4, 114.9, 114.0.

*4-Bromo-2,6-dichlorobenzonitrile (**5m**).* Yield 84 mg, 67%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 131.3, 127.8, 113.5, 112.9.

*1,3-Dimethoxy-5-((4-methoxyphenyl)ethynyl)benzene (**6**).* Yield 222 mg, 83%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (d, J = 8.6 Hz, 2H), 6.90 (d, J = 8.6 Hz, 2H), 6.71 (d, J = 2.0 Hz, 2H), 6.47 (s, 1H), 3.84 (s, 3H), 3.82 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 159.7, 133.1, 124.9, 115.2, 114.0, 109.2, 101.6, 89.0, 88.1, 55.4, 55.3.

*Indenone (**7a**).* Yield 32 mg, 30%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 2.4 Hz, 1H), 6.77 (d, J = 8.8 Hz, 2H), 6.52 (d, J = 2.4 Hz, 2H), 6.46 (t, J = 2.4 Hz, 2H), 3.88 (s, 3H), 3.79 (s, 3H), 3.72 (s, 6H), 3.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.6, 162.5, 160.2, 158.7, 156.6, 154.7, 137.0, 134.1, 131.0, 130.6, 123.6, 122.7, 113.4, 106.6, 104.1, 102.8, 101.0, 55.9, 55.8, 55.4, 55.2.

*Indenone (**7b**).* Yield 46 mg, 43%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.46 (d, J = 1.8 Hz, 1H), 6.32−6.33 (m, 3H), 3.88 (s, 3H), 3.84 (s, 3H), 3.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.8, 162.8, 160.1, 159.9, 158.9, 155.0, 134.5, 133.2, 130.5, 130.4, 126.9, 122.1, 112.9, 107.9, 103.9, 102.6, 100.1, 55.9, 55.7, 55.2, 55.1.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR spectra for all products. 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.

■ ACKNOWLEDGMENTS

This work was supported by the National Natural Science Foundation of China (Project 21272117 and 20972068) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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