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$Pd(OAc)_2$-Catalyzed Alkoxylation of Arylnitriles via sp^2 C−H Bond Activation Using Cyano as the Directing Group

Wu Li[†] and Peipei Sun*[,†,‡,§]

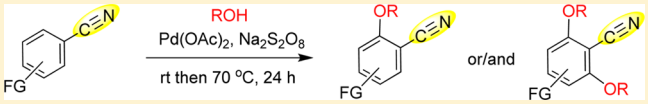
[†]Jiangsu Key Laboratory of Biofunctional Materials, College of Chemistry and Materials Science, Nanjing Normal University, Nanjing, 210097, China

[‡]Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China

[§]Key Laboratory of Applied Photochemistry, Nanjing Normal University, Nanjing, 210097, China

Supporting Information

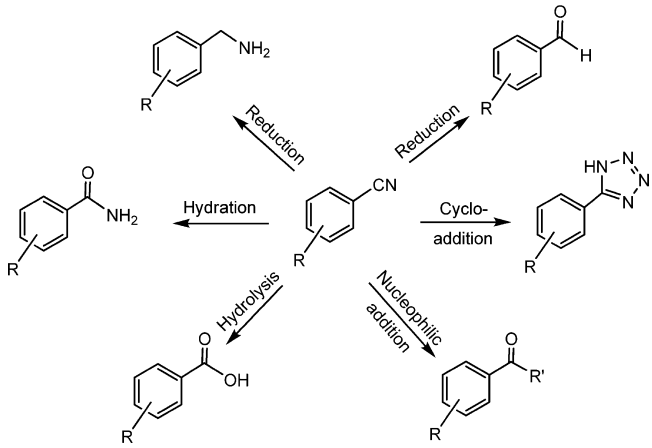
ABSTRACT: A $Pd(OAc)_2$-catalyzed *ortho*-alkoxylation of arylnitrile was described. Using cyano as a directing group, the aromatic C−H bond can be functionalized efficiently to generate *ortho*-alkoxylated arylnitrile derivatives with moderate yields. The optimal reaction conditions were identified after examining various factors such as oxidant, solvent, and reaction temperature. The method was compatible to the arylnitriles with either electron-withdrawing or electron-donating groups.



As a highly efficient and atom-economical way to construct carbon−carbon and carbon−heteroatom bonds, transition-metal-catalyzed C−H activation has received extensive attention in recent years.[1] Directing group assisted activation of *ortho* aromatic C−H bonds has met with remarkable success. The strongly coordinating groups such as acylamino,[2a,b] pyridyl,[2c] oxazolyl,[2d] and oximido[2e] used for palladium-catalyzed C−H bond functionalization have been widely studied. 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 will be a powerful approach for developing synthetically versatile reactions.[3] Some weakly coordinating directing groups (e.g., COOH,[4a] $CONHC_6F_5$,[4b] OH,[4c,d] and carbonyl[4e]) have been used in 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, amide, amines, aldehydes, tetrazoles, and ketones,[5] but the C−H functionalization using cyano as a directing group has not received sufficient attention. Recently, we reported the first example of palladium-catalyzed cyano group directed C−H functionalization to synthesize biphenyl-2-carbonitrile derivatives by the reaction of aryl nitriles with aryl halides.[6] A pioneering work of *meta*-selective C−H activation based on the weak coordinating between Pd(II) and cyano group was reported very recently by Yu.[7] We believe expanding the cyano group directed C−H functionalization should be significant in the synthesis of nitriles and related compounds on the basis of the coordination properties and the importance in organic synthesis of this group.

Transition-metal-catalyzed formation of C−O bond is quite difficult compared to the formation of C−C or C−N bonds because of the electronegativity of the elements as well as the metal−ligand bond strength.[8] On the other hand, an immense number of ether-containing chemicals are produced for the pharmaceutical, bulk, and fine chemical industries.[9] Therefore, developing novel methodologies for C−O bond formations is still of interest and a challenging task, and the development of C−O bond formation reactions has greatly accelerated in recent years.[10] Despite the success of C−H oxygenation methods, C−H alkoxylation reactions remain scarce. A few research groups reported the directed *ortho*-alkoxylation of the $C(sp^2)$−H bonds of arenes.[11] Our ongoing interest in finding new organic transformations through C−H bond activation prompted us to explore the utilization of the cyano as a

Scheme 1. Transformation of Aromatic Nitrile



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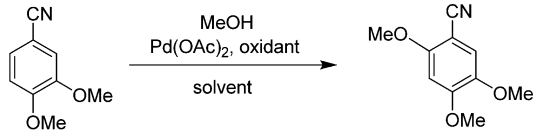
directing group for selective C−H functionalization reaction. Herein, we describe an efficient method for the synthesis of alkyl aryl ethers via a Pd-catalyzed, cyano-directed alkoxylation of C(sp^2)−H bonds at the aromatic ring using alcohols as alkoxylation reagents.

Our investigation started from the reaction of 3,4-dimethoxybenzonitrile (**1a**) with anhydrous methanol in the presence of $Pd(OAc)_2$ and an oxidant. We were delighted to observe the formation of the desired methoxylated product 2,4,5-trimethoxybenzonitrile (**3a**). Encouraged by this initial finding, we commenced a systematic screening to the reaction conditions to increase the yield of this alkoxylation reaction (Table 1). Without palladium catalyst, the reaction did not take

Table 1. Optimization of the Reaction Conditions[a]



1a **3a**

entry	catalyst	solvent	oxidant (equiv)	yield[b] (%)
1	$Pd(OAc)_2$	methanol	$Na_2S_2O_8$ (5.0)	70
2	$Pd(OAc)_2$	methanol	$Na_2S_2O_8$ (5.0)	38[c]
3	$Pd(TFA)_2$	methanol	$Na_2S_2O_8$ (5.0)	42
4	$PdCl_2(CH_3CN)_2$	methanol	$Na_2S_2O_8$ (5.0)	trace
5	$Pd(acac)_2$	methanol	$Na_2S_2O_8$ (5.0)	15
6	$PdCl_2(PPh_3)_2$	methanol	$Na_2S_2O_8$ (5.0)	trace
7	$Pd(OAc)_2$	methanol	$K_2S_2O_8$ (5.0)	58
8	$Pd(OAc)_2$	methanol	O_2	12
9	$Pd(OAc)_2$	methanol	$PhI(OAc)_2$ (5.0)	trace
10	$Pd(OAc)_2$	methanol	$MeCOOOBu^t$ (5.0)	35
11	$Pd(OAc)_2$	methanol	Ag_2O (5.0)	0
12	$Pd(OAc)_2$	methanol	$Na_2S_2O_8$ (4.0)	52
13	$Pd(OAc)_2$	methanol	$Na_2S_2O_8$ (6.0)	68
14	$Pd(OAc)_2$	methanol	$Na_2S_2O_8$ (5.0)	42[d]
15	$Pd(OAc)_2$	methanol/dioxane (1:1, 3 mL)	$Na_2S_2O_8$ (5.0)	60
16	$Pd(OAc)_2$	methanol/DCE (1:1, 3 mL)	$Na_2S_2O_8$ (5.0)	57
17	$Pd(OAc)_2$	methanol/MeCN (1:1, 3 mL)	$Na_2S_2O_8$ (5.0)	trace
18	$Pd(OAc)_2$	methanol/DMSO (1:1, 3 mL)	$Na_2S_2O_8$ (5.0)	trace
19	$Pd(OAc)_2$	methanol/NMP (1:1, 3 mL)	$Na_2S_2O_8$ (5.0)	trace

[a]Unless otherwise specified, all of the reactions were carried out with **1a** (1.0 mmol), Pd catalyst (0.1 mmol), and $Na_2S_2O_8$ (5.0 mmol) in MeOH (3 mL) at room temperature for 8 h, and then the temperature was raised to 70 °C for 16 h. [b]Isolated yields. [c]$Pd(OAc)_2$ (0.05 mmol) was used. [d]The reactions were carried out at 70 °C for 24 h.

place entirely. $Pd(OAc)_2$ was evidently catalytic active to the reaction, and an appropriate amount of the catalyst was 10 mol %. Decreasing the amount of $Pd(OAc)_2$ to 5 mol % could result in a decrease of the yield (entry 2). Other palladium species such as $Pd(TFA)_2$, $PdCl_2(CH_3CN)_2$, $Pd(acac)_2$, and $PdCl_2(PPh_3)_2$ were substantially less effective (entries 3−6). It was found that the nature of oxidants played a critical role on the reaction efficiency. Thus, oxidants such as $K_2S_2O_8$, $Na_2S_2O_8$, $PhI(OAc)_2$, O_2, $MeCOOOBu^t$, and Ag_2O were examined, and among these, $Na_2S_2O_8$ proved to be the most efficient oxidant for this reaction (entries 1 and 7−11). Other oxidants were less effective, and no desired product was observed when $PhI(OAc)_2$ or Ag_2O was employed. The appropriate amount of $Na_2S_2O_8$ was 5 equiv. Decreasing the amount of $Na_2S_2O_8$ resulted in a reduction of the yield, while increasing the amount of this oxidant to 6 equiv did not result in an increase of the yield (entries 12 and 13). Methanol was used as both reactant and solvent in this reaction. Some solvents such as dioxane, DCE, CH_3CN, DMSO, and NMP to be used as the cosolvent were tested in order to improve the yield of the reaction (entries 15−19, respectively). Unfortunately, the presence of these cosolvents did not promote the reaction, and even inhibited this transformation, and the reason for this action was not clear. Notably, this ether-forming reaction required careful temperature regulation (with a gradual ramp from room temperature to 70 °C). The higher reaction temperature at the beginning of the reaction led to the formation of palladium black and lowered the yield (entry 14).

Using the optimized reaction conditions, we then explored the substrate scope of this cyano-directed alkoxylation reaction. The results are summarized in Table 2. While methanol and ethanol were used as alkoxylation reagents, for most of the arylnitriles we employed, the reaction gave moderate yields. It seems that dialkoxylation on the two *ortho*-positions of the cyano group took place more readily than the monoalkoxylation. For example, in entries 2, 3, and 7, only dimethoxylation products were obtained. In entries 4−6, the yields of dimethoxylation products were higher than that of monomethoxylation products. But for the ethoxylation of 4-methoxybenzonitrile, no diethoxylation product was found (entry 17). It is worth noting that for the *meta*-substituted arylnitriles, the alkoxylation did not occur between cyano and the *meta*-substituent because of steric effects (entries 1, 13, 14, 18, 19, 20, and 22). Another interesting result was that the alkoxylation of 1-naphthonitrile took place on the 8-position instead of the 2-position (entries 11 and 21). It was maybe because that the ring strain in the cyclopalladated intermediate formed with the carbon atom on 8-position was weaker than that formed with the carbon atom on 2-position. That is to say, a more stable cyclopalladated intermediate could be generated on the 8-position.

It also can be seen that the action of the electronic effect of the substituent on arylnitriles to the reaction was not obvious. In the presence of an electron-withdrawing group such as nitro, halogen, or ester or electron-donating group such as methoxyl and methyl, the reaction could take place normally to give the desired alkoxylation products. Moreover, the tolerance of the reaction to these chemically active groups ensures that they can be further transformed into other different functionalities. Unfortunately, almost no alkoxylation product was isolated as a secondary alcohol such as 2-propanol was used under these reaction conditions (entry 23).

The detailed mechanism for this Pd-catalyzed, $Na_2S_2O_8$-mediated C−H alkoxylation reaction has not been firmly established. On the basis of the experimental results and the related transition-metal-catalyzed C−H activation reactions, a possible mechanism is proposed to account for the present C−O bond formation reaction (Scheme 2). First, the coordination of cyano in arylnitrile to $Pd(OAc)_2$ formed a cyclopalladated intermediate **A** in which the cyano group coordinated with palladium using its π-electrons between carbon and nitrogen. In fact, the directed C−H functionalization reactions through π-type coordinating groups recently have been shown to be

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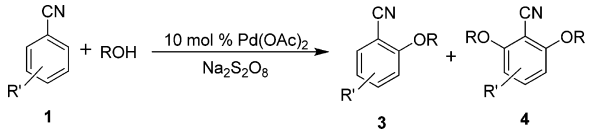
Table 2. Pd-Catalyzed Direct *Ortho*-Alkoxylation of Arylnitrile[a]



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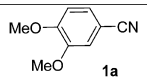
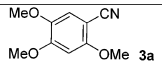
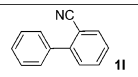
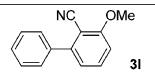
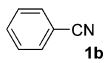
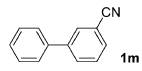
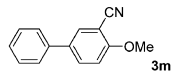
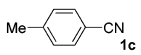
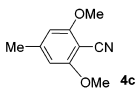
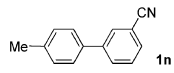
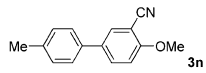
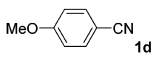
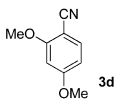
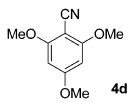
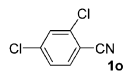
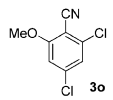
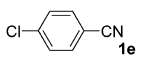
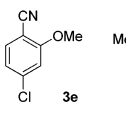
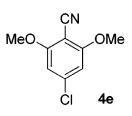
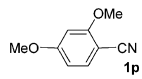
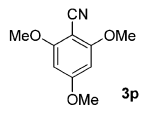
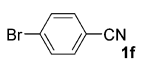
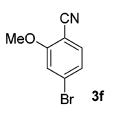
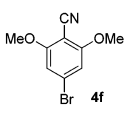
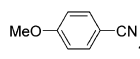
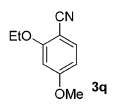
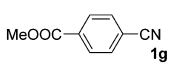
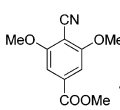
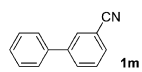
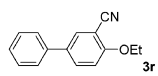
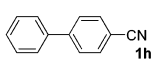
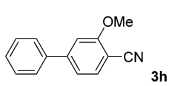
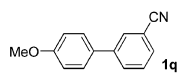
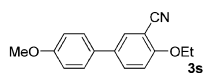
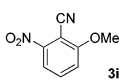
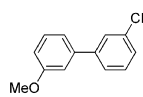
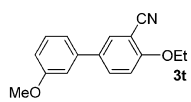
1	 1a	MeOH	 3a	70	12	 1l	MeOH	 3l	52
2	 1b	MeOH	 4b	68	13	 1m	MeOH	 3m	53
3	 1c	MeOH	 4c	60	14	 1n	MeOH	 3n	42
4	 1d	MeOH	 3d  4d	79 (22/57)	15	 1o	MeOH	 3o	51
5	 1e	MeOH	 3e  4e	70 (28/42)	16	 1p	MeOH	 3p	50
6	 1f	MeOH	 3f  4f	78 (20/58)	17	 1d	EtOH	 3q	48
7	 1g	MeOH	 4g	45	18	 1m	EtOH	 3r	54
8	 1h	MeOH	 3h	43	19	 1q	EtOH	 3s	47
9	 1i	MeOH	 3i	62	20	 1r	EtOH	 3t	53
10	1j	MeOH	3j	47	21	1k	EtOH	3u	56
11	1k	MeOH	3k	60	22	1a	EtOH	3v	59
					23	1a	^{i}PrOH	3w	trace

[a]All of the reactions were carried out using arylnitrile **1** (1.0 mmol), $Pd(OAc)_2$ (0.1 mmol), and $Na_2S_2O_8$ (5.0 mmol) in MeOH or EtOH (3 mL) at rt for 8 h, and then the temperature was raised to 70 °C for 16 h. [b]Isolated yields.

possible.[6,12] Next, acetate presumably participated in aromatic proton abstraction to generate an aryl palladium intermediate **B**, followed by an oxidation of the Pd^{II} intermediate **B** to the Pd^{IV} intermediate **C** by $Na_2S_2O_8$ in the presence of methanol.[6,11c,13] Then, a reductive alkoxylation from **C** regenerated the Pd^{II} catalyst and produces the observed methoxylated product **3**. The dimethoxylated product **4** could be produced by repeating these processes.

In summary, we have developed an efficient method for direct alkoxylation of arenes via Pd-catalyzed cyano group directed sp^2 C–H bond activation. Inexpensive, safe, and environmentally benign $Na_2S_2O_8$ was found to be a particularly effective oxidant in these transformations and exhibited functional group tolerance. Various aromatic nitriles with either electron-donating or electron-withdrawing groups could be alkoxylated directly and efficiently. To the best of our knowledge, the present work is the first example of transition metal-catalyzed C–O bond formation using cyano as the directing group.

EXPERIMENTAL SECTION

General Methods. All reactions were run in oven-dried flasks under nitrogen. Alcohols were dried using general method; other

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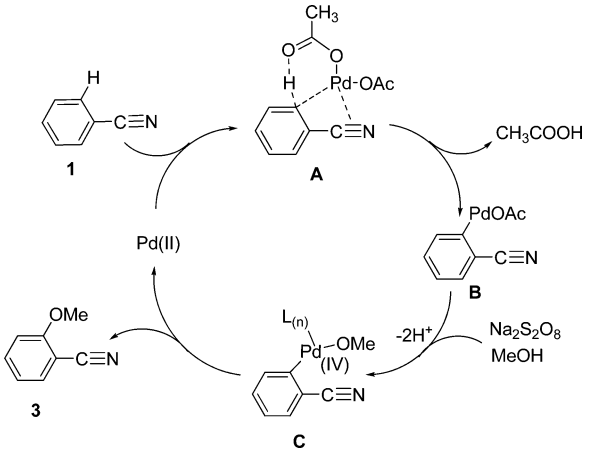
Scheme 2. Proposed Mechanism for the Pd-Catalyzed Alkoxylation Reaction



reagents were commercially available and were used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ [using $(CH_3)_4Si$ (for ^{1}H, δ = 0.00; for ^{13}C, δ = 77.00) as internal standard]. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, m = multiplet. Melting points are uncorrected. For the HRMS measurements, Q-TOF was used.

General Experimental Procedures and Characterizations. A sealed tube (15 mL) initially fitted with a septum containing $Pd(OAc)_2$ (0.1 mmol) and $Na_2S_2O_8$ (5.0 mmol) was evacuated and purged with nitrogen gas three times. MeOH (3 mL) and arylnitrile (1.0 mmol) were added to the system, and the reaction mixture was stirred at rt for 8 h and then stirred at 70 °C for another 16 h. The mixture was extracted with dichloromethane then washed and dried. The solution was concentrated by vacuum and separated on a silica gel column using hexane/EtOAc as eluent to give the corresponding pure *ortho*-alkoxylated arylnitrile derivatives.

*2,4,5-Trimethoxybenzonitrile (**3a**).* Yield: 70% (135 mg). Pale yellow solid. Mp: 102−103 °C (lit.[14] mp 105−106 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.97 (s, 1H), 6.51 (s, 1H), 3.95 (s, 3H), 3.92 (s, 3H), 3.85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.6, 154.1, 143.0, 117.0, 114.7, 96.4, 91.5, 56.6, 56.5, 56.2.

*2,6-Dimethoxybenzonitrile (**4b**).* Yield: 68% (111 mg). White solid. Mp: 117−118 °C (lit.[15] mp 118 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43 (t, J = 8.4 Hz, 1H), 6.55 (d, J = 8.4 Hz, 2H), 3.93 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 134.8, 114.2, 103.4, 91.2, 56.2.

*2,6-Dimethoxy-4-methylbenzonitrile (**4c**).* Yield: 60% (106 mg). White solid. Mp: 138−139 °C (lit.[16] mp 138−139 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.37 (s, 2H), 3.90 (s, 6H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.4, 146.3, 114.5, 104.4, 88.5, 56.1, 22.9.

*2,4-Dimethoxybenzonitrile (**3d**).* Yield: 22% (36 mg). Pale yellow solid. Mp: 88−89 °C (lit.[14] mp 90−91 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.45 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 6.8 Hz, 1H), 6.45 (s, 1H), 3.90 (s, 3H), 3,85 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.6, 162.8, 134.9, 117.0, 105.8, 98.9, 93.9, 55.7, 55.5.

*2,4,6-Trimethoxybenzonitrile (**4d**).* Yield: 57% (110 mg). White solid. Mp: 134−136 °C (lit.[14] mp 137−138 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.08 (s, 2H), 3.90 (s, 6H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.3, 163.8, 114.6, 90.4, 84.2, 56.1, 55.7.

*4-Chloro-2-methoxybenzonitrile (**3e**).* Yield: 28% (47 mg). White solid. Mp: 95−97 °C (lit.[17] mp 95−97 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.49 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 7.00 (s, 1H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.7, 140.7, 134.4, 121.3, 115.7, 112.3, 100.5, 56.4.

*4-Chloro-2,6-dimethoxybenzonitrile (**4e**).* Yield: 42% (83 mg). White solid. Mp: 145−147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.58 (s, 2H), 3.92 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.8, 141.1, 132.8, 113.3, 104.7, 56.5. HRMS (ESI): calcd for $C_9H_8ClNO_2$[H] 198.0322, found 198.0341.

*4-Bromo-2-methoxybenzonitrile (**3f**).* Yield: 20% (42 mg). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.42 (d, J = 8.0 Hz, 1H), 7.17 (d, J = 8.0 Hz, 1H), 7.15 (s, 1H), 3.95 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 134.4, 128.9, 124.2, 115.7, 115.3, 100.9, 56.4. HRMS (ESI): calcd for C_8H_6BrNO[Na] 233.9530, found 233.9518.

*4-Bromo-2,6-dimethoxybenzonitrile (**4f**).* Yield: 58% (140 mg). White solid. Mp: 151−153 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.75 (s, 2H), 3.93 (s, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.7, 129.2, 113.4, 107.7, 90.7, 56.6. HRMS (ESI): calcd for $C_9H_8BrNO_2$[H] 241.9817, found 241.9825.

*Methyl 4-Cyano-3,5-dimethoxybenzoate (**4g**).* Yield: 45% (99 mg). White solid. Mp: 125−127 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.64 (s, 2H), 3.97 (s, 3H), 3.96 (s, 3H), 3.91 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.2, 166.2, 134.4, 131.4, 121.2, 112.8, 56.2, 52.5. HRMS (ESI): calcd for $C_{11}H_{11}NO_4$[Na] 244.0586, found 244.0609.

*5-Methoxylbiphenyl-4-carbonitrile (**3h**).* Yield: 43% (90 mg). White solid. Mp: 83−85 °C (lit.[18] mp 86.5−87.5 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.59−7.65 (m, 3H), 7.45−7.50 (m, 3H), 7.22 (d, J = 6.4 H z, 1H), 7.15 (s, 1H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.5, 147.8, 139.6, 134.0, 129.1, 128.8, 127.3, 119.8, 118.0, 110.0, 100.4, 56.1.

*2-Methoxy-6-nitrobenzonitrile (**3i**).* Yield: 62% (110 mg). White solid. Mp: 174−176 °C (lit.[19] mp 174−177 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.86 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 4.07 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 163.0, 134.1, 134.0, 116.9, 116.6, 111.7, 97.4, 57.2.

*2-Methoxy-6-methylbenzonitrile (**3j**).* Yield: 47% (69 mg). White solid. Mp: 61−63 °C (lit.[20] mp 61−63 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.39 (t, J = 8.0 Hz, 1H), 6.87 (d, J = 8.0 H z, 1H), 6.78 (d, J = 7.6 Hz, 1H), 3.92 (s, 3H), 2.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 161.6, 143.9, 133.5, 122.1, 115.7, 108.2, 102.3, 56.0, 20.5.

*8-Methoxy-1-naphthonitrile (**3k**).* Yield: 60% (110 mg). Pale yellow solid. Mp: 65−67 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.00 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 7.2 Hz, 1H), 7.47−7.53 (m, 3H), 6.97 (m, 1H), 4.07 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.8, 135.0, 134.7, 132.9, 127.6, 125.4, 123.9, 121.0, 120.2, 106.9, 106.7, 55.7. HRMS (ESI): calcd for $C_{12}H_9NO$[Na] 206.0582, found 206.0599.

*3-Methoxylbiphenyl-2-carbonitrile (**3l**).* Yield: 52% (108 mg). White solid. Mp: 81−83 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.56−7.60 (m, 3H), 7.43−7.51 (m, 3H), 7.07 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.2, 137.3, 138.1, 133.7, 128.8, 128.7, 128.6, 122.0, 116.0, 109.6, 101.0, 56.3. HRMS (ESI): calcd for $C_{14}H_{11}NO$[Na] 232.0738, found 232.0741.

*4-Methoxylbiphenyl-3-carbonitrile (**3m**).* Yield: 53% (111 mg). White solid. Mp: 95−97 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76−7.78 (m, 2H), 7.51 (d, J = 8.0 Hz, 2H), 7.44−7.48 (m, 2H), 7.36 (m, 1H), 7.05 (d, J = 8.0 Hz, 1H), 3.99 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6, 138.7, 134.3, 133.0, 132.1, 129.0, 127.7, 126.7, 116.5, 111.7, 102.2, 56.2. HRMS (ESI): calcd for $C_{14}H_{11}NO$[Na] 232.0738, found 232.0731.

*4-Methoxy-4′-methylbiphenyl-3-carbonitrile (**3n**).* Yield: 42% (94 mg). White solid. Mp: 98−100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74−7.77 (m, 2H), 7.41 (d, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H, 7.03 (d, J = 8.0 Hz, 1H), 4.00 (s, 3H), 2.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.3, 137.6, 135.8, 134.2, 132.7, 131.9, 129.7, 126.5, 116.5, 111.7, 102.2, 56.2, 22.7. HRMS (ESI): calcd for $C_{15}H_{13}NO$[Na] 246.0895, found 246.0898.

*2,4-Dichloro-6-methoxybenzonitrile (**3o**).* Yield: 51% (102 mg). White solid. Mp: 99−100 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.12 (s, 1H), 6.90 (s, 1H), 3.97 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 162.6, 140.5, 138.7, 122.1, 112.9, 110.6, 102.2, 56.9. HRMS (ESI): calcd for $C_8H_5Cl_2NO$[Na] 223.9646, found 223.9665.

*2,4,6-Trimethoxybenzonitrile (**3p**).* Yield: 50% (96 mg). White solid. Mp: 134−136 °C (lit.[14] mp 137−138 °C). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.08 (s, 2H), 3.90 (s, 6H), 3.87 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.3, 163.8, 114.6, 90.4, 84.2, 56.1, 55.7.

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*2-Ethoxy-4-methoxybenzonitrile (**3q**).* Yield: 48% (85 mg). Colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47 (d, J = 8.4 Hz, 1H), 6.50 (d, J = 6.8 Hz, 1H), 6.45 (s, 1H), 4.10 (q, J = 6.8 Hz, 2H), 3.86 (s, 3H), 1.47 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 164.5, 162.2, 135.0, 117.1, 105.6, 99.2, 94.2, 64.6, 56.7, 14.5. HRMS (ESI): calcd for $C_{10}H_{11}NO_2$[Na] 200.0687, found 200.0704.

*4-Ethoxybiphenyl-3-carbonitrile (**3r**).* Yield: 54% (120 mg). White solid. Mp: 107−108 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73−7.78 (m, 2H), 7.51 (t, J = 8.8 Hz, 2H), 7.44 (t, J = 8.0 Hz, 2H), 7.36 (t, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 4.19 (q, J = 7.2 Hz, 2H), 1.51 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.0, 138.7, 134.0, 132.9, 132.1, 129.0, 127.6, 126.6, 116.5, 112.6, 102.5, 64.9, 14.6. HRMS (ESI): calcd for $C_{15}H_{13}NO$[Na] 246.0895, found 246.0917.

*4-Ethoxy-4′-methoxylbiphenyl-3-carbonitrile (**3s**).* Yield: 47% (119 mg). White solid. Mp: 103−105 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.67−7.73 (m, 2H), 7.43 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 8.0 Hz, 3H), 4.17 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 1.50 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.5, 159.4, 133.8, 132.4, 131.6, 131.3, 127.7, 116.6, 114.4, 112.4, 102.4, 64.9, 55.4, 14.6. HRMS (ESI): calcd for $C_{16}H_{15}NO_2$[Na] 276.1000, found 276.1003.

*4-Ethoxy-3′-methoxylbiphenyl-3-carbonitrile (**3t**).* Yield: 53% (134 mg). White solid. Mp: 68−70 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.71−7.78 (m, 2H), 7.35 (t, J = 8.0 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 7.01 (t, J = 8.0 Hz, 2H), 6.91 (m, 1H), 4.18 (q, J = 8.0 Hz, 2H), 3.88 (s, 3H), 1.51 (t, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.1, 160.0, 140.2, 133.9, 132.9, 132.2, 130.1, 119.1, 116.5, 112.9, 112.5, 112.4, 102.4, 64.9, 55.4, 14.6. HRMS (ESI): calcd for $C_{16}H_{15}NO_2$[H] 254.1181, found 254.1191.

*8-Ethoxy-1-naphthonitrile (**3u**).* Yield: 56% (110 mg). White solid. Mp: 73−75 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.80 (d, J = 8.0 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.46−7.52 (m, 3H), 6.96 (d, J = 8.0 Hz, 1H), 4.28 (q, J = 8.0 Hz, 2H), 1.65 (t, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 154.1, 135.0, 134.8, 132.9, 127.6, 125.2, 123.7, 120.7, 120.1, 107.4, 107.0, 65.0, 14.3. HRMS (ESI): calcd for $C_{13}H_{11}NO$[Na] 220.0738, found 220.0736.

*2-Ethoxy-4,5-dimethoxybenzonitrile (**3v**).* Yield: 59% (122 mg). Pale orange solid. Mp: 109−110 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.91 (s, 1H), 6.47 (s, 1H), 4.08 (q, J = 6.8 Hz, 2H), 3.91 (s, 3H), 3.81 (s, 3H), 1.41 (t, J = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 157.0, 154.0, 143.0, 117.1, 114.5, 97.5, 91.6, 65.4, 56.5, 56.1, 14.7. HRMS (ESI): calcd for $C_{11}H_{13}NO_3$[Na] 230.0793, found 230.0800.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H NMR and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: sunpeipei@njnu.edu.cn.

Notes

The authors declare no competing financial interest.

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