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Decarboxylative Halogenation and Cyanation of Electron-Deficient Aryl Carboxylic Acids via Cu Mediator as Well as Electron-Rich Ones through Pd Catalyst under Aerobic Conditions

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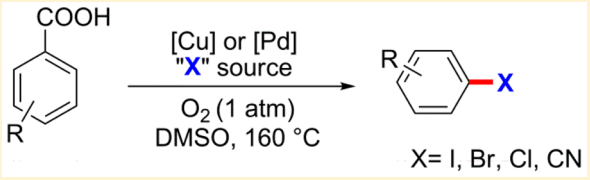
Supporting Information

ABSTRACT: Simple strategies for decarboxylative functionalizations of electron-deficient benzoic acids via using Cu(I) as promoter and electron-rich ones by employing Pd(II) as catalyst under aerobic conditions have been established, which lead to smooth synthesis of aryl halides (−I, Br, and Cl) through the decarboxylative functionalization of benzoic acids with readily available halogen sources CuX (X = I, Br, Cl), and easy preparation of benzonitriles from decarboxylative cyanation of aryl carboxylic acids with nontoxic and low-cost $K_4Fe(CN)_6$ under an oxygen atmosphere for the first time.



1. INTRODUCTION

Transition-metal-mediated transformations of functional groups are hot research topics to generate C−X (X = heteroatom) and C−C bonds in the organic community; as a result, many methods have been made to create new C−X and C−C bonds.[1] Owing to the attractive features of low toxicity, low cost, high stability, and easy availability, carboxylic acids represent as valuable starting materials in synthetic organic chemistry. Under transition-metal catalysis, the decarboxylative reaction only takes place at a neighboring position to the carboxyl group with high regioselectivity and releases innocuous carbon dioxide as sole byproduct. Hence, carboxylic acids and transition-metal-catalyzed decarboxylative reactions have displayed promising strategies to create C−X and C−C bonds during the past decade.[2] In this field, Myers,[3] Goossen,[4] and Forgione[5] have done some seminal studies to generate new C−C bonds through transition-metal-catalyzed decarboxylative coupling of (hetero)aromatic carboxylic acids with alkenes and aryl halides, respectively. These pioneering works have shown that traditional electrophilic aryl halides and nucleophilic organometallic reagents can be replaced by distinctly attractive carboxylic acid substrates.

Because of the fundamental importance of transition-metal-catalyzed decarboxylative coupling in synthetic organic chemistry, great progress has been made to create C−C, C−O, C−P, and C−S bonds via decarboxylation of carboxylic acids with various coupling partners including olefins[3,6] aryl halides,[4,5,7] alkynes,[8] arenes,[9] organoboron compounds,[10] trifluoromethylating agents,[11] silicate esters,[12] *H*-phosphine oxides,[13] trifluoromethylthiolating reagents,[14] thiols, and disulfides.[15] Although the carbon−halogen bond could be used for later stage installing other functional groups,[16] however, the old-established[17] or improved Hunsdiecker reaction[18] through direct halodecarboxylation of carboxylic acids suffered from limitations with regard to mere aliphatic carboxylic acid substrates and harsh reaction conditions.

Aryl halides are more widely employed as versatile coupling partners in transition-metal-catalyzed coupling reactions to construct complex molecules.[19] In this context, Gandelman reported conversion of aromatic carboxylic acids into aryl iodides by using 1,3-diiodo-5,5-dimethylhydantoin (DIH) as halogen source in 1,2-dichloroethane,[20] nevertheless, the high cost and moisture sensitivity of DIH, high toxicity of the solvent, aryl bromides and chlorides could not be achieved from this method resulted in neither a practical nor economical procedure to prepare aryl halides. Wu disclosed Ag-catalyzed decarboxylative halogenations (−Br and Cl) of electron-deficient arene carboxylic acids with the use of stoichiometric strong base KOH;[21] however, aryl iodides could not be prepared through this method, and the method suffered from limitations with regard to the exclusion of electron-rich aryl and heteroaryl carboxylic acids from the reaction. Larrosa also developed noble stoichiometric Au/Ag bimetallic mediated decarboxylation of limited substrate scope of electron-deficient aryl carboxylic acids, followed by addition of NBS or NIS to afford the corresponding haloarenes;[22] unfortunately, there were only three electron-deficient aryl carboxylic acid substrates that furnished decarboxylative bromination and iodination rather than chlorodecarboxylation products. Liu revealed a method for Pd/Ag-catalyzed bromo- and chlorodecarboxylation of electron-rich arene carboxylic acids;[23] nevertheless, it is neither an economical nor practical procedure for high loadings of Ag_2CO_3 and limited electron-rich aryl carboxylic acids substrates as well as low yields in the transformations.

In contrast to well-documented formation of a C−C bond via decarboxylative coupling of carboxylic acids with various *C*-

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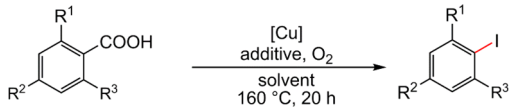
Table 1. Selected Screening Results for Iododecarboxylation of Arene Carboxylic Acids 1 and 17 under Aerobic Conditions[a]



1 (R^1 = NO_2, R^2 = Cl, R^3 = H)
17 (R^1 = R^3 = OMe, R^2 = H)

1a
17a

entry	substrate	[Pd] (equiv)	[Cu] (equiv)	additive (equiv)	solvent	isolated yield (%)[b]
1[c]	**1**		CuI (2)		DMSO	**1a** (40)
2	**1**		CuI (2)		DMSO	**1a** (74)
3[d]	**1**		CuI (2)		DMSO	**1a** (16)
4	**1**		CuI (2)		DMF	**1a** (20)
5	**1**		CuI (2)		5% DMF−DMSO	**1a** (39)
6	**1**		CuI (2)	KOAc (1)	DMSO	**1a** (54)
7	**1**		CuI (2)	KO^{t}Bu (1)	DMSO	**1a** (52)
8	**1**		CuI (1.2)		DMSO	**1a** (72)
9[e]	**1**		**CuI (1.2)**		**DMSO**	**1a (87)**
10[f]	**1**		CuI (1.2)		DMSO	**1a** (86)
11	**1**		CuI (0.3)	LiI (1)	DMSO	**1a** (<5)
12	**1**		CuI (0.3)	KI (1)	DMSO	**1a** (<5)
13	**1**		CuI (0.3)	NH_4I (1)	DMSO	**1a** (<5)
14	**1**		Cu_2O (0.15)	KI (1)	DMSO	**1a** (26)
15	**17**		CuI (1.2)		DMSO	**17a** (0)
16	**17**	$PdCl_2$ (0.1)	CuI (1.2)		DMSO	**17a** (88)
17	**17**	**$Pd(OAc)_2$ (0.1)**	**CuI (1.2)**		**DMSO**	**17a (95)**
18	**17**	$Pd(OAc)_2$ (0.05)	CuI (1.2)		DMSO	**17a** (82)

[a]Conditions: acid (0.2 mmol), solvent (2 mL), O_2 (1 atm), 20 h. [b]Average of two runs. [c]Reaction performed under an air atmosphere. [d]Reaction conducted at 140 °C. [e]Reaction run for 30 h. [f]Reaction run for 40 h.

containing reagents,[4−12] transition-metal-catalyzed decarboxylative functionalization of carboxylic acids into nitriles has been almost untouched. The only one example of conversion of arene carboxylic acids into aryl nitriles was made by Taran by using cyanohydrin as cyanide source with Pd/Ag as promoter;[24] in view of the requirement for high loadings of silver salt and the cost of cyanohydrin, there is still significant room for improvement of the decarboxylative cyanation reaction. Although Song observed a Cu-catalyzed decarboxylation at sp^3-hybridized carbon atoms of phenylacetic acids to form benzonitriles via employing urea as cyanide source, however, no benzonitriles were generated in the case of sp^2-hybridized benzoic acids.[25] $K_4Fe(CN)_6$ is a nontoxic food additive, which could serve as a green cyanide source for transition-metal-catalyzed cyanation of aryl halides.[26] Nevertheless, to date, no practical method for decarboxylative cyanation has been explored between benzoic acids and that green cyanide source.

Consequently, it is highly desirable to develop a simple, green, and practical method to synthesize aryl halides (−I, Br, and Cl) and nitriles via decarboxylative functionalization of readily accessible aromatic carboxylic acids. From the standpoint of sustainable chemistry, there is an increasing demand for the use of molecular oxygen as the terminal oxidant in oxidative transformation. In this regard, despite that remarkable advances have been made in transition-metal-catalyzed oxidative C−H halogenation[27] and cyanation,[28] to the best of our knowledge, only few reports on the use of dioxygen in the halodecarboxylation transformation[21] and decarboxylative cyanation[25] have been reported. In view of the significance of aryl halides and nitriles, and our continuing research pursuit in the functionalization of aromatic carboxylic acids, very recently, we have established the synthesis of aryl methyl thioethers and biaryls through Pd/Cu-catalyzed decarboxylation of benzoic acids with DMSO and Cu-catalyzed decarboxylative homocoupling of benzoic acids, respectively.[29] Herein, we first reveal a range of benzoic acids including electron-sufficient and electron-deficient aromatic as well as heteroaromatic carboxylic acids that directly underwent decarboxylative halogenation and cyanation with good functional group tolerance under aerobic conditions, namely, iododecarboxylation of electron-deficient *ortho*-nitrobenzoic acids and heteroaromatic carboxylic acids in the presence of 1.2 equiv of CuI as both mediator and iodine source, decarboxylative bromination and chlorination of electron-deficient *ortho*-nitrobenzoic acids and heteroaromatic carboxylic acids with the employment of CuI (0.3 equiv) as promoter and CuX (X = Br, Cl) (1.2 equiv) as halogen source, and decarboxylative cyanation of electron-deficient *ortho*-nitrobenzoic acids and heteroaromatic carboxylic acids with the employment of CuI (1 equiv) as promoter and nontoxic $K_4Fe(CN)_6$ (0.2 equiv) as cyanide source, while decarboxylative functionalization of electron-sufficient benzoic acids to synthesize aryl halides and nitriles was observed with the assistance of 10 mol % $Pd(OAc)_2$ as catalyst under otherwise equal conditions.

2. RESULTS AND DISCUSSION

We initially tested iododecarboxylation toward different aryl carboxylic acids substrates, as shown in Table 1. In the beginning, the reaction of electron-deficient 4-chloro-2-nitrobenzoic acid **1** in the presence of CuI (2 equiv) in DMSO at 160 °C under an air atmosphere furnished desired 4-chloro-1-iodo-2-nitrobenzene **1a** in 40% yield (entry 1, Table 1). Gratifyingly, the reaction conducted under 1 atm of dioxygen proceeded more efficiently than under an air atmosphere (entry 2). However, studies showed that lowering the temperature to

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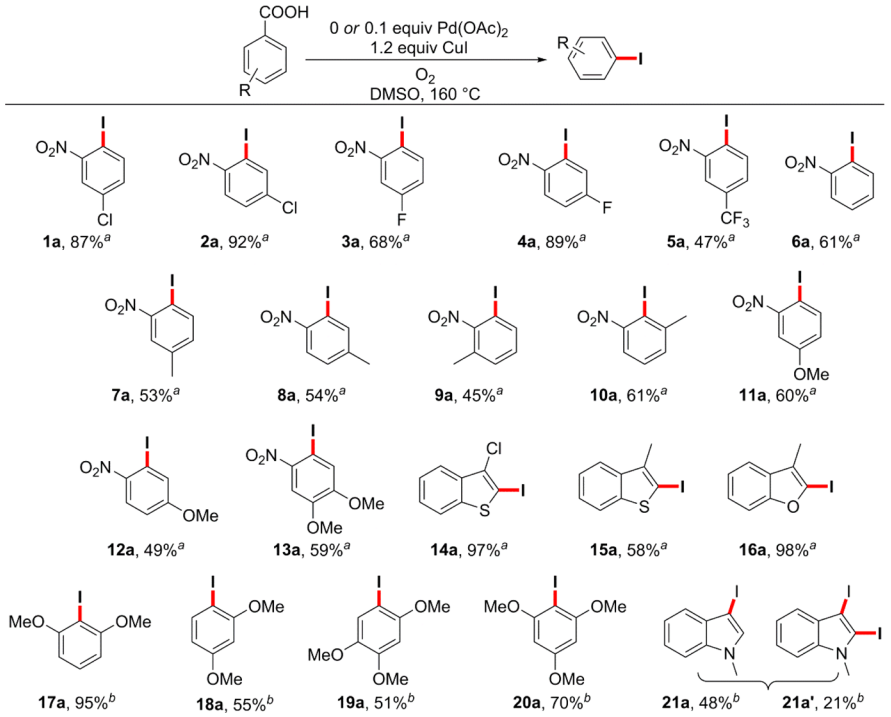
Scheme 1. Decarboxylative Iodination of Electron-Deficient Aryl and Heteroaromatic Carboxylic Acids via CuI as Well as Electron-Rich Benzoic Acids through $Pd(OAc)_2$ under Aerobic Conditions



[a]Acid (0.2 mmol), CuI (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 30 h. [b]Acid (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), CuI (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 20 h.

140 °C dramatically reduced the reaction conversion (entry 3). A brief survey of the solvents including single and mixed solvents under aerobic conditions illustrated that inferior yields were detected than that in DMSO (entries 4 and 5). Subsequently, it is found that the base has no beneficial effect on the transformation (entries 6 and 7). Notably, decreasing the loading of CuI to 1.2 equiv did not affect the efficiency (72%) (entry 8). The reaction time extended to 30 h readily gave final product **1a** in synthetically useful levels (87% yield), and a comparable yield was obtained when the reaction was run for prolonged 40 h (entries 9 and 10). Unfortunately, useless yields were obtained when other iodide compounds as iodine source were employed with catalytic Cu(I), regardless of the presence or absence of a nitrogen ligand in the reaction system (entries 11−14).

Applying the optimized conditions of decarboxylative iodination of electron-deficient carboxylic acid **1a** to an electron-rich aryl carboxylic acid, unfortunately, no desired product **17a** was detected for the iododecarboxylation of 2,6-dimethoxybenzoic acid **17** (entry 15). Under otherwise identical conditions, much to our surprise, the yield of **17a** was remarkably improved in the presence of 0.1 equiv of Pd catalyst, especially in the case of the introduction of $Pd(OAc)_2$ (entries 16 and 17). Study also showed that a lower loading of palladium led to slightly lower conversion (entry 18). Finally, the synthesis of aryl iodide in DMSO in the presence of CuI (1.2 equiv) for 30 h under aerobic conditions was chosen as the optimal reaction conditions (entry 9) for the iododecarboxylation of electron-deficient aryl carboxylic acid, while the reaction in the presence of the combination of $Pd(OAc)_2$ (0.1 equiv) and CuI (1.2 equiv) in DMSO for 20 h under aerobic conditions was defined as the optimized reaction conditions (entry 17) for the decarboxylative iodination of electron-rich aryl carboxylic acid.

With the optimized reaction conditions in hand, we next examined the scope of substituted benzoic acids in this iododecarboxylation process (Scheme 1). Under aerobic conditions, similarly to our recent observation,[29] this Cu-mediated decarboxylative iodination of electron-deficient aryl carboxylic acids was shown to be effective for a range of *ortho*-nitrobenzoic acids (**1**−**13**) as well as *S*- and *O*-containing heteroaromatic carboxylic acids (**14**−**16**), whereas iododecarboxylation of a variety of *ortho*-methoxylbenzoic acids (**17**−**20**) and *N*-methylindole-3-carboxylic acid (**21**) resulted from the contribution of the $Pd(OAc)_2$/CuI bimetallic system. *ortho*-Nitrobenzoic acid **6** was an effective substrate to afford 61% yield in the presence of 1.2 equiv of CuI, which was also the divide between electron-withdrawing (chloro, fluoro, and trifluoromethyl) and electron-donating groups (methoxy and methyl) on the aromatic ring of the 2-nitrobenzoic acid substrate. Furthermore, it is found that the electronic nature of the substituent on the *ortho*-nitrobenzoic acid substrate had an influence on the transformation; namely, 2-nitrobenzoic acids bearing electron-withdrawing groups (**1**−**4**) furnished the corresponding products in satisfactory to excellent yields, except in the case of 2-nitro-4-(trifluoromethyl)benzoic acid **5**, whereas 2-nitrobenzoic acids tolerated electron-donating groups (**7**−**13**) that provided the desired products in moderate to good yields. Compared with its isomer 5-fluoro-2-nitrobenzoic acid **4**, 4-fluoro-2-nitrobenzoic acid **3** was a less effective substrate. Likewise, a similar observation was consistent with good conversion for substrates of 2,6-dimethoxylbenzoic acid **17** and 2,4,6-trimethoxylbenzoic acid **20**, but modest yields were observed for the substrates of their

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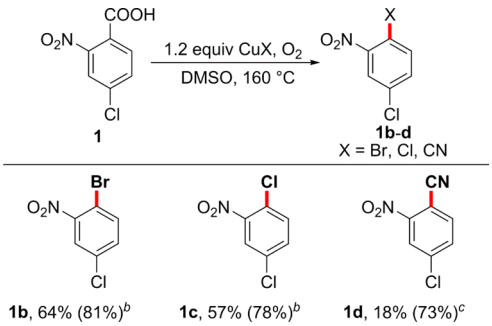
isomer 2,4-dimethoxylbenzoic acid **18** and 2,4,5-trimethoxylbenzoic acid **19**. Pleasingly, an amount of 1.2 equiv of CuI with 1 atm of O_2 gave good yields for *S*- and *O*-containing heterocyclic carboxylic acids (**14**−**16**), regardless of the presence of an electron-donating or electron-withdrawing substituent on the position *ortho* to the carboxyl group. Besides the desired C3-decarboxylative iodination product, *N*-methylindole-3-carboxylic acid (**21**) also afforded another 2,3-diiodinated *N*-methylindole product, namely, the iododecarboxylation along with heterocyclic ring C2-iodination.

The preliminarily successful iododecarboxylation reactions evoked us to test whether the use of other analogous copper salts CuX (X = Br, Cl, CN) could be equally effective under aerobic conditions, thereby introducing a similar functional group onto the aryl ring, followed by decarboxylation. As represented in Scheme 2, the bromo- and chlorodecarboxylation of 4-chloro-2-nitrobenzoic acid **1** were achieved in moderate yields (64% and 57%) at the outset via utilizing corresponding stoichiometric amounts of copper(I) halide without any Pd or Ag additive. In contrast, attractive decarboxylative cyanation was observed in a troublesome yield (18%) by employing stoichiometric amounts of CuCN under aerobic conditions. Consequently, there was still a need for improvement of the original decarboxylative functionalization results. Further investigations revealed that, by employing CuI (0.3 equiv) as additional catalyst on the basis of original conditions, good yields (81% and 78%) of bromo- and chlorodecarboxylation were obtained with corresponding copper(I) halide (1.2 equiv) as halogen source, and drastically increased yield (73%) of decarboxylative cyanation was observed with $K_4Fe(CN)_6$ (0.2 equiv) as cyanide source. However, increasing the loadings of $K_4Fe(CN)_6$ had a detrimental effect on the efficiency of decarboxylative cyanation reaction, which could be the result of transition-metal copper poisoned by excess of cyanide ions from the Fe(II) center.

Scheme 2. Decarboxylative Bromination, Chlorination, and Cyanation of 4-Chloro-2-nitrobenzoic Acid 1 with Corresponding Functional Group under Aerobic Conditions[a]



[a]Conditions: **1** (0.2 mmol), CuX (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 30 h. [b]**1** (0.2 mmol), CuI (0.3 equiv), CuX (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 30 h. [c]**1** (0.2 mmol), CuI (1 equiv), $K_4Fe(CN)_6$ (0.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 10 h.

Thereafter, these impressive results inspired us to evaluate the possible substrate scope of this decarboxylative halogenation (halogen = Br, Cl) and cyanation protocol with respect to aromatic carboxylic acids. As clearly shown in Scheme 3, it is also found that the combination of CuI/CuX (X = Br, Cl) and CuI/$K_4Fe(CN)_6$ worked well for various *ortho*-nitrobenzoic acids (**2**−**13**) bearing different substituents including electron-withdrawing (chloro, fluoro, and trifluoromethyl) and electron-donating groups (methoxy and methyl) as well as other classes of *S*- and *O*-containing heteroaromatic carboxylic acids (**14**−**16**), while smooth decarboxylative functionalization of *ortho*-methoxylbenzoic acids (**17**−**20**) was conveniently realized with the assistance of $Pd(OAc)_2$ catalyst under otherwise equal conditions as well.

3. CONCLUSIONS

In summary, we have established simple, general, and flexible methods for synthesis of valuable aryl iodides, bromides, chlorides, and nitriles from easily available aryl carboxylic acids. In the case of electron-deficient *ortho*-nitrobenzoic acids and heteroaromatic carboxylic acids, the protocols employed CuI and CuI/CuX (X = Br, Cl) as well as CuI/$K_4Fe(CN)_6$, respectively, providing target products under aerobic conditions, whereas decarboxylative functionalization of electron-rich *ortho*-methoxylbenzoic acids was observed with the assistance of $Pd(OAc)_2$ as catalyst under otherwise equal conditions. Compared to previously reported methods,[20−24] there are several distinguishing features in our protocols: extensive substrate scope including electron-sufficient and electron-deficient benzoic acids as well as heteroaromatic carboxylic acids with good functional group tolerance, a simple reaction system to afford aryl halide and nitrile products in good yields with readily available halogen and cyanide sources, and green and cheap dioxygen as sole terminal oxidant in the reaction. To the best of our knowledge, no general method for the assembly of functional groups (−I, Br, Cl, CN) on aromatic rings has been reported before now, so our simple and general methods will attract much attention in academic and industrial fields.

4. EXPERIMENTAL SECTION

4.1. General Information. The reagents used for experiments were commercially available and used as received unless otherwise noted. DMSO was distilled from CaH_2 under reduced pressure and stored under nitrogen. All reactions were performed under dioxygen with the strict exclusion of moisture via using Schlenk techniques. Column chromatography was performed on silica gel 300−400 mesh. The yields reported are the isolated yields and the average of two runs. ^1H, ^{13}C, and ^{19}F NMR spectra were recorded at 400, 100, and 377 MHz with $CDCl_3$ as solvent, respectively. All coupling constants (*J* values) were reported in hertz (Hz). HRMS was performed in electron impact (EI) mode, and TOF was used for HRMS measurements. Melting points (mp) were uncorrected and measured on micro melting point apparatus with samples in open capillary tubes.

4.2. Synthesis of *o*-Nitroiodobenzenes. *Synthesis of 4-Chloro-1-iodo-2-nitrobenzene (**1a**, Scheme 1).*[30] An oven-dried Schlenk tube equipped with a stir bar was charged with 4-chloro-2-nitrobenzoic acid (40.3 mg, 0.2 mmol) and CuI (45.7 mg, 0.24 mmol, 1.2 equiv). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, DMSO (2 mL) was added via syringe. The rubber septum was replaced with a Teflon screwcap under dioxygen flow, and the Schlenk tube was pressurized to 1 atm. With stirring, the reaction mixtures were heated at 160 °C for the indicated amount of time (unless otherwise specified), and then cooled down to room temperature. The resultant mixture was filtered through a short plug of silica gel and then concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (1% ether in hexane) to afford 49.4 mg (87%) of the product as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, J = 8.5 Hz, 1 H), 7.84 (d, J = 2.0 Hz, 1 H), 7.28−7.25 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 135.3, 133.6, 125.7, 83.6.

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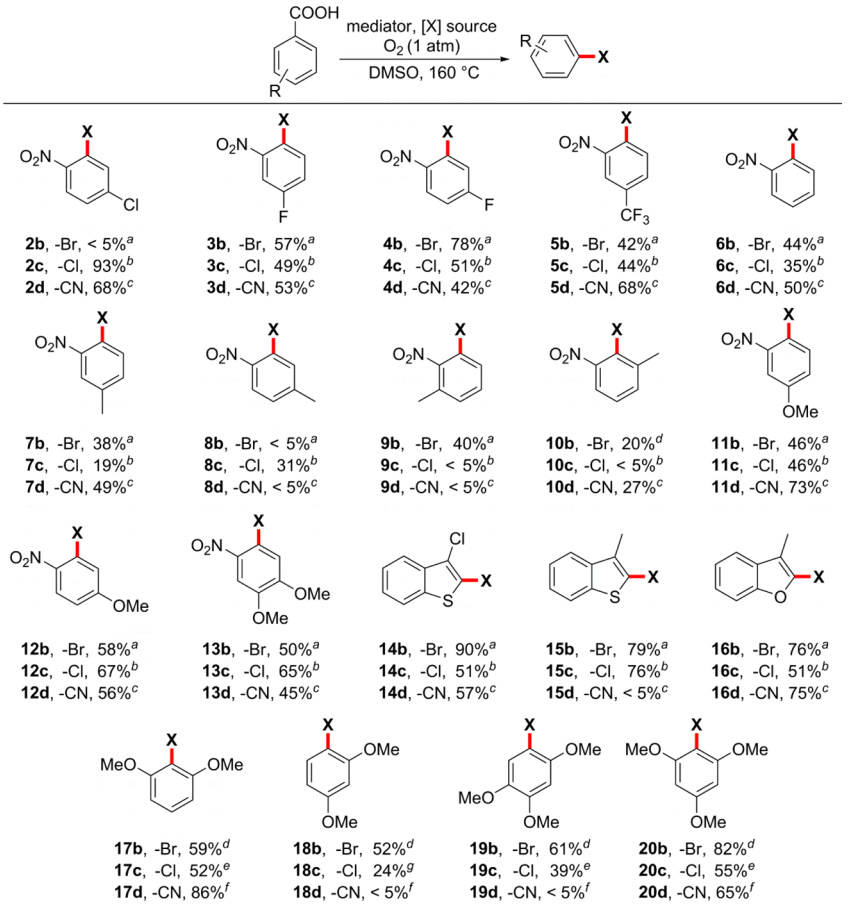
Scheme 3. Decarboxylative Bromination, Chlorination, and Cyanation of Electron-Deficient Aryl and Heteroaromatic Carboxylic Acids via Cu Mediator as Well as Electron-Rich Benzoic Acids through Pd Catalyst with Corresponding Functional Group under Aerobic Conditions



[a]Acid (0.2 mmol), CuI (0.3 equiv), CuBr (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 30 h. [b]Acid (0.2 mmol), CuI (0.3 equiv), CuCl (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 30 h. [c]Acid (0.2 mmol), CuI (1 equiv), $K_4Fe(CN)_6$ (0.2 equiv), 10 h. [d]Acid (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), CuI (0.3 equiv), CuBr (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 20 h. [e]Acid (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), CuI (0.3 equiv), CuCl (1.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 20 h. [f]Acid (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), CuI (1 equiv), $K_4Fe(CN)_6$ (0.2 equiv), DMSO (2 mL), O_2 (1 atm), 160 °C, 20 h. [g]Acid (0.2 mmol), $Pd(OAc)_2$ (0.1 equiv), CuI (0.3 equiv), CuCl (1.2 equiv), DMF (2 mL), O_2 (1 atm), 160 °C, 20 h.

The same procedure as that for 4-chloro-1-iodo-2-nitrobenzene **1a** was used to synthesize the other *o*-nitroiodobenzenes.

As same as the above procedure, $Pd(OAc)_2$ (0.01 equiv) was added as additional catalyst to prepare *o*-methoxyiodobenzenes.

*4-Chloro-2-iodo-1-nitrobenzene (**2a**).*[31] Eluent: 1% ether in hexane. Yellow solid, yield 52.2 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05 (d, J = 2.1 Hz, 1 H), 7.84 (d, J = 8.7 Hz, 1 H), 7.47 (dd, J = 2.1, 8.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 139.3, 129.2, 126.3, 87.0.

*4-Fluoro-1-iodo-2-nitrobenzene (**3a**).*[32] Eluent: 1% ether in hexane. Yellow liquid, yield 36.3 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (q, J = 4.0 Hz, 1 H), 7.64 (dd, J = 2.8, 8.0 Hz, 1 H), 7.07 (ddd, J = 2.8, 7.5, 8.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.5, 161.0, 143.1 (d, J = 7.4 Hz), 121.2 (d, J = 21.2 Hz), 113.7 (d, J = 26.3 Hz), 79.7 (m). ^{19}F NMR (377 MHz, $CDCl_3$): δ −109.6 to −109.7 (m, 1 F).

*4-Fluoro-2-iodo-1-nitrobenzene (**4a**).*[33] Eluent: 1% ether in hexane. Yellow liquid, yield 47.5 mg (89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96 (q, J = 8.0 Hz, 1 H), 7.77 (dd, J = 2.4, 7.6 Hz, 1 H), 7.20 (ddd, J = 2.3, 7.3 9.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.7, 162.1, 129.1 (d, J = 26.3 Hz), 127.4 (d, J = 9.7 Hz), 116.3, 116.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −103.8 (dd, J = 7.2, 12.6 Hz, 1 F).

*1-Iodo-2-nitro-4-(trifluoromethyl)benzene (**5a**).*[30] Eluent: 1% ether in hexane. Yellow solid, yield 29.8 mg (47%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.22 (d, J = 8.3 Hz, 1 H), 8.11 (d, J = 1.2 Hz, 1 H), 7.51 (dd, J = 1.5, 8.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 129.6 (q, J = 3.4 Hz), 122.4 (q, J = 3.9 Hz), 90.9 (d, J = 0.8 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ −63.3 (s, 3 F).

*1-Iodo-2-nitrobenzene (**6a**).*[34] Eluent: 1% ether in hexane. Yellow liquid, yield 30.4 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (dd, J = 1.0, 7.9 Hz, 1 H), 7.85 (dd, J = 1.3, 8.1 Hz, 1 H), 7.51−7.47 (m, 1 H), 7.28−7.24 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.9, 133.4, 129.0, 125.4, 110.0.

*1-Iodo-4-methyl-2-nitrobenzene (**7a**).*[30] Eluent: 1% ether in hexane. Yellow solid, yield 27.9 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.1 Hz, 1 H), 7.67 (s, 1 H), 7.08 (d, J = 8.0 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 139.9, 134.4, 126.0, 82.0, 20.8.

*2-Iodo-4-methyl-1-nitrobenzene (**8a**).* Eluent: 1% ether in hexane. Yellow oil, yield 28.4 mg (54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (s, 1 H), 7.80 (d, J = 8.3 Hz, 1 H), 7.25 (s, 1 H), 2.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.9, 142.4, 129.6, 1255, 86.5, 20.9. HRMS: m/z (EI-TOF) calculated [M]: 262.9443, found: 262.9447.

*1-Iodo-3-methyl-2-nitrobenzene (**9a**).* Eluent: 1% ether in hexane. Yellow solid, mp 120−121 °C, yield 23.7 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (d, J = 1.5 Hz, 1 H), 7.80 (dd, J = 1.5, 8.1 Hz, 1

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H), 7.08 (d, J = 8.1 Hz, 1 H), 2.54 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.8, 134.2, 133.2, 89.7, 20.1. HRMS: m/z (EI-TOF) calculated [M]: 262.9443, found: 262.9444.

*2-Iodo-1-methyl-3-nitrobenzene (**10a**).* Eluent: 1% ether in hexane. Yellow solid, mp 56−58 °C, yield 32.1 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, J = 7.7 Hz, 1 H), 7.36−7.31 (m, 1 H), 2.58 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.2, 132.3, 128.6, 121.8, 110.0, 92.4, 29.7. HRMS: m/z (EI-TOF) calculated [M]: 262.9443, found: 262.9441.

*1-Iodo-4-methoxy-2-nitrobenzene (**11a**).* Eluent: 3% ether in hexane. Yellow solid, mp 61−62 °C, yield 33.5 mg (60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J = 8.8 Hz, 1H), 7.41 (d, J = 2.9 Hz, 1H), 6.86 (dd, J = 2.9, 8.7 Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 142.1, 120.5, 110.9, 74.5, 56.0. HRMS: m/z (EI-TOF) calculated [M]: 278.9392, found: 278.9394.

*2-Iodo-4-methoxy-1-nitrobenzene (**12a**).* Eluent: 3% ether in hexane. Yellow solid, mp 65−67 °C, yield 27.3 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 9.1 Hz, 1 H), 7.53 (d, J = 2.6 Hz, 1 H), 6.94 (dd, J = 2.5, 9.1 Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.5, 127.5, 127.1, 114.2, 88.2, 56.1. HRMS: m/z (EI-TOF) calculated [M]: 278.9392, found: 278.9391.

*1-Iodo-4,5-dimethoxy-2-nitrobenzene (**13a**).* Eluent: 10% ether in hexane. Yellow solid, mp 86−88 °C, yield 36.5 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (s, 1 H), 7.39 (s, 1 H), 3.96 (s, 3 H), 3.93 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.7, 149.0, 123.1, 109.0, 56.7, 56.4. HRMS: m/z (EI-TOF) calculated [M]: 308.9498, found: 308.9496.

*3-Chloro-2-iodobenzo[b]thiophene (**14a**).* Eluent: 1% ether in hexane. Yellow solid, mp 95−97 °C, yield 57.1 mg (97%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (dd, J = 8.0, 20.0 Hz, 2 H), 7.44−7.32 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.1, 135.8, 128.6, 125.4, 125.2, 122.0, 121.8, 78.7. HRMS: m/z (EI-TOF) calculated [M]: 293.8767, found: 293.8771.

*2-Iodo-3-methylbenzo[b]thiophene (**15a**).* Eluent: 1% ether in hexane. Yellow solid, mp 62−64 °C, yield 31.8 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (dd, J = 7.2, 32.5 Hz, 2 H), 7.36−7.27 (m, 2 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.5, 138.5, 137.2, 124.3, 124.2, 121.6, 121.5, 79.9, 16.1. HRMS: m/z (EI-TOF) calculated [M]: 273.9313, found: 273.9316.

*2-Iodo-3-methylbenzofuran (**16a**).* Eluent: 1% ether in hexane. Colorless oil, yield 50.6 mg (98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48−7.41 (m, 2 H), 7.24−7.20 (m, 2 H), 2.22 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 128.9, 124.1, 123.0, 122.6, 118.5, 110.8, 97.4, 10.4. HRMS: m/z (EI-TOF) calculated [M]: 257.9542, found: 257.9539.

*2-Iodo-1,3-dimethoxybenzene (**17a**).*[35] Eluent: 1% ether in hexane. White solid, yield 50.2 mg (95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24 (t, J = 8.3 Hz, 1 H), 6.49 (d, J = 8.3 Hz, 2 H), 3.87 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 129.9, 104.1, 56.6.

*1-Iodo-2,4-dimethoxybenzene (**18a**).*[36] Eluent: 1% ether in hexane. White solid, yield 29.0 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 8.6 Hz, 1 H), 6.43 (d, J = 2.4 Hz, 1 H), 6.32 (dd, J = 2.3, 8.6 Hz, 1 H), 3.85 (s, 3 H), 3.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.4, 158.8, 139.2, 116.2, 107.0, 99.2, 74.8, 56.2, 55.5.

*1-Iodo-2,4,5-trimethoxybenzene (**19a**).* Eluent: 10% ether in hexane. White solid, mp 75−76 °C, yield 30.0 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.20 (s, 1 H), 6.51 (s, 1 H), 3.89 (s, 3 H), 3.85 (s, 3 H), 3.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.0, 150.2, 144.2, 121.8, 97.7, 72.9, 57.3, 56.7, 56.1. HRMS: m/z (EI-TOF) calculated [M]: 293.9753, found: 293.9751.

*2-Iodo-1,3,5-trimethoxybenzene (**20a**).*[37] Eluent: 10% ether in hexane. White solid, yield 41.2 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.14 (s, 2 H), 3.86 (s, 6 H), 3.83 (s, 3 H). 13C NMR (100 MHz, $CDCl_3$): δ 162.1, 159.8, 91.2, 66.7, 56.5, 55.5.

*3-Iodo-1-methyl-1H-indole (**21a**).* Eluent: 1% ether in hexane. Yellow solid, yield 24.7 mg (48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, J = 7.7 Hz, 1 H), 7.30−7.24 (m, 2 H), 7.21−7.17 (m, 1 H), 7.12 (s, 1 H), 3.78 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.8, 132.7, 130.4, 122.6, 121.1, 120.2, 109.4, 54.7, 33.1. HRMS: m/z (EI-TOF) calculated [M]: 256.9702, found: 256.9703.

*2,3-Diiodo-1-methyl-1H-indole (**21a′**).* Eluent: 30% ether in hexane. Yellow solid, mp 135−137 °C, yield 9.7 mg (21%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62−7.58 (m, J = 8.2 Hz, 2 H), 7.12 (t, J = 7.5 Hz, 1 H), 6.89 (d, J = 7.7 Hz, 1 H), 3.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 183.3, 158.2, 151.4, 138.4, 125.3, 123.8, 117.4, 109.9, 26.2. HRMS: m/z (EI-TOF) calculated [M]: 382.8668, found: 382.8673.

4.3. Synthesis of *o*-Nitrohalobenzenes (Halo = Bromo, Chloro). *Synthesis of 1-Bromo-4-chloro-2-nitrobenzene (**1b**, Scheme 2).*[38] An oven-dried Schlenk tube equipped with a stir bar was charged with 4-chloro-2-nitrobenzoic acid (40.3 mg, 0.2 mmol), CuI (11.4 mg, 0.06 mmol, 0.3 equiv), and CuBr (34.4 mg, 0.24 mmol, 1.2 equiv). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, DMSO (2 mL) was added via syringe. The rubber septum was replaced with a Teflon screwcap under dioxygen flow, and the Schlenk tube was pressurized to 1 atm. With stirring, the reaction mixtures were heated at 160 °C for the indicated amount of time (unless otherwise specified), and then cooled down to room temperature. The resultant mixture was filtered through a short plug of silica gel and then concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (1% ether in hexane) to afford 38.2 mg (81%) of the product as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (d, J = 2.1 Hz, 1 H), 7.69 (d, J = 8.6 Hz, 1 H), 7.42 (dd, J = 2.2, 8.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 133.3, 125.8, 112.6.

The same procedure as that for 1-bromo-4-chloro-2-nitrobenzene **1b** was used to synthesize the other *o*-nitrohalobenzenes (halo = bromo, chloro).

As same as the above procedure, $Pd(OAc)_2$ (0.01 equiv) was added as additional catalyst to prepare *o*-methoxyhalobenzenes (halo = bromo, chloro). The solvent of DMSO was replaced with DMF as solvent to synthesize 1-chloro-2,4-dimethoxybenzene (**18c**).

*1,4-Dichloro-2-nitrobenzene (**1c**).* Eluent: 1% ether in hexane. Yellow liquid, yield 29.9 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (s, 1 H), 7.50 (d, J = 0.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.3, 132.8, 125.7. HRMS: m/z (EI-TOF) calculated [M]: 190.9541, found: 190.9543.

*2,4-Dichloro-1-nitrobenzene (**2c**, Scheme 3).*[21] Eluent: 1% ether in hexane. Yellow liquid, yield 35.8 mg (93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J = 8.7 Hz, 1 H), 7.58 (d, J = 1.8 Hz, 1 H), 7.40 (dd, J = 1.7, 8.7 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 131.8, 127.9, 126.7.

*1-Bromo-4-fluoro-2-nitrobenzene (**3b**).*[39] Eluent: 1% ether in hexane. Yellow liquid, yield 25.1 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (q, J = 4.0 Hz, 1 H), 7.62 (dd, J = 2.6, 7.7 Hz, 1 H), 7.21 (td, J = 4.0, 8.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3 (d, J = 8.1 Hz), 120.9 (d, J = 22.2 Hz), 113.6 (d, J = 27.3 Hz), 109.2 (d, J = 3.0 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ −110.2 (dd, J = 7.4, 12.7 Hz, 1 F).

*1-Chloro-4-fluoro-2-nitrobenzene (**3c**).* Eluent: 1% ether in hexane. Yellow liquid, yield 17.2 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (dd, J = 2.2, 7.5 Hz, 1 H), 7.55 (q, J = 4.0 Hz, 1 H), 7.29 (dd, J = 2.3, 7.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.2 (d, J = 7.7 Hz), 120.8 (d, J = 22.2 Hz), 113.5 (d, J = 27.3 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ −110.7 to −110.6 (m, 1 F). HRMS: m/z (EI-TOF) calculated [M]: 174.9836, found: 174.9830.

*2-Bromo-4-fluoro-1-nitrobenzene (**4b**).*[39] Eluent: 1% ether in hexane. Yellow liquid, yield 34.3 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.50 (q, J = 4.0 Hz, 1 H), 8.24−8.20 (m, 1 H), 7.36−7.21 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 161.6, 129.6 (d, J = 2.2 Hz), 124.8 (d, J = 9.1 Hz), 117.0 (d, J = 25.3 Hz), 110.1 (d, J = 23.2 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ −96.0 to −96.1 (m, 1 F).

*2-Chloro-4-fluoro-1-nitrobenzene (**4c**).* Eluent: 1% ether in hexane. Yellow liquid, yield 17.9 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (dd, J = 6.1, 2.5 Hz, 1 H), 8.20−8.16 (m, 1 H), 7.32 (t, J = 8.5 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 126.7 (d, J = 1.5 Hz), 124.0 (d, J = 8.9 Hz), 117.2 (d, J = 23.2 Hz). ^{19}F NMR (377

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MHz, $CDCl_3$): δ −103.9 to −104.0 (m, 1 F). HRMS: *m*/*z* (EI-TOF) calculated [M]: 174.9836, found: 174.9833.

1-Bromo-2-nitro-4-(trifluoromethyl)benzene (**5b**). Eluent: 1% ether in hexane. Yellow liquid, yield 22.7 mg (42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (s, 1 H), 7.92 (d, *J* = 8.4 Hz, 1 H), 7.69 (d, *J* = 8.3 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.1, 129.6−129.5 (m), 123.8, 122.9−122.8 (m), 118.7, 110.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −63.1 (s, 1 F). HRMS: *m*/*z* (EI-TOF) calculated [M]: 268.9301, found: 268.9299.

1-Chloro-2-nitro-4-(trifluoromethyl)benzene (**5c**).[40] Eluent: 1% ether in hexane. Yellow liquid, yield 19.8 mg (44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (s, 1 H), 7.80−7.72 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.9, 129.7 (m), 123.0 (m), 110.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −63.0 (s, 3 F).

1-Bromo-2-nitrobenzene (**6b**).[21] Eluent: 1% ether in hexane. Yellow liquid, yield 17.8 mg (44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84 (dd, *J* = 1.8, 7.4 Hz, 1 H), 7.75 (dd, *J* = 1.5, 7.2 Hz, 1 H), 7.52−7.37 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 133.2, 128.2, 125.6, 114.4.

1-Chloro-2-nitrobenzene (**6c**).[21] Eluent: 1% ether in hexane. Yellow liquid, yield 11.0 mg (35%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86 (d, *J* = 8.0 Hz, 1 H), 7.56−7.50 (m, 2 H), 7.44−7.39 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 133.1, 131.8, 127.5, 127.0, 125.5.

1-Bromo-4-methyl-2-nitrobenzene (**7b**). Eluent: 1% ether in hexane. Yellow liquid, yield 16.4 mg (38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (s, 1 H), 7.59 (d, *J* = 8.2 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 2.39 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.0, 134.6, 134.1, 126.0, 110.9, 20.7. HRMS: *m*/*z* (EI-TOF) calculated [M]: 214.9580, found: 214.9582.

1-Chloro-4-methyl-2-nitrobenzene (**7c**). Eluent: 1% ether in hexane. Yellow liquid, yield 6.5 mg (19%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03 (s, 1 H), 7.94 (s, 1 H), 7.50 (s, 1 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.2, 122.2, 121.0, 21.2. HRMS: *m*/*z* (EI-TOF) calculated [M]: 171.0089, found: 171.0087.

2-Chloro-4-methyl-1-nitrobenzene (**8c**). Eluent: 1% ether in hexane. Yellow liquid, yield 10.6 mg (31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, *J* = 8.3 Hz, 1 H), 7.35 (s, 1 H), 7.19 (d, *J* = 8.2 Hz, 1 H), 2.42 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 132.2, 128.1, 127.1, 125.7, 21.1. HRMS: *m*/*z* (EI-TOF) calculated [M]: 171.0092, found: 171.0087.

1-Bromo-3-methyl-2-nitrobenzene (**9b**). Eluent: 1% ether in hexane. Yellow liquid, yield 17.3 mg (40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (s, 1 H), 7.62 (d, *J* = 8.2 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 1 H), 2.55 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.9, 134.1, 132.5, 127.5, 119.6, 20.1. HRMS: *m*/*z* (EI-TOF) calculated [M]: 214.9582, found: 214.9579.

2-Bromo-1-methyl-3-nitrobenzene (**10b**).[41] Eluent: 1% ether in hexane. Yellow liquid, yield 8.6 mg (20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52 (d, *J* = 7.9 Hz, 1 H), 7.43 (d, *J* = 7.4 Hz, 1 H), 7.33 (t, *J* = 7.8 Hz, 1 H), 2.52 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.3, 133.4, 127.5, 122.3, 115.8, 23.6.

1-Bromo-4-methoxy-2-nitrobenzene (**11b**).[42] Eluent: 1% ether in hexane. Yellow solid, yield 21.3 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, *J* = 8.9 Hz, 1 H), 7.35 (d, *J* = 2.8 Hz, 1 H), 6.98 (dd, *J* = 8.9, 2.9 Hz, 1 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 123.9, 123.0, 119.0, 107.7, 56.2.

1-Chloro-4-methoxy-2-nitrobenzene (**11c**).[42] Eluent: 1% ether in hexane. Yellow solid, yield 17.3 mg (46%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.9 Hz, 1 H), 7.39 (d, *J* = 2.8 Hz, 1 H), 7.06 (dd, *J* = 2.9, 8.9 Hz, 1 H), 3.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 132.4, 119.9, 118.2, 110.4, 56.1.

2-Bromo-4-methoxy-1-nitrobenzene (**12b**).[21] Eluent: 3% ether in hexane. Yellow solid, yield 26.9 mg (58%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97 (d, *J* = 9.1 Hz, 1 H), 7.21 (d, *J* = 2.3 Hz, 1 H), 6.91 (dd, *J* = 2.2, 9.1 Hz, 1 H), 3.89 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 128.0, 120.1, 116.8, 113.5, 56.2.

2-Chloro-4-methoxy-1-nitrobenzene (**12c**).[21] Eluent: 3% ether in hexane. Yellow solid, yield 21.0 mg (56%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, *J* = 9.4 Hz, 1 H), 7.00 (d, *J* = 2.2 Hz, 1 H), 6.86 (dd, *J* = 2.1, 9.1 Hz, 1 H), 3.88 (s, 3 H). ^{13}C NMR (100 MHz, CDCl3): δ 162.9, 129.6, 128.0, 116.8, 113.0, 56.2.

1-Bromo-4,5-dimethoxy-2-nitrobenzene (**13b**).[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1 H), 7.12 (s, 1 H), 3.96 (s, 3 H), 3.94(s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8, 116.5, 109.0, 107.5, 56.7, 56.5.

1-Chloro-4,5-dimethoxy-2-nitrobenzene (**13c**).[21] Eluent: 10% ether in hexane. Yellow solid, yield 28.3 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 1 H), 6.93 (s, 1 H), 3.95 (s, 3 H), 3.93 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.9, 147.6, 121.2, 113.4, 108.7, 56.7, 56.5.

2-Bromo-3-chlorobenzo[b]thiophene (**14b**). Eluent: 1% ether in hexane. White solid, mp 65−67 °C, yield 44.6 mg (90%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78−7.69 (m, 2 H), 7.50−7.33 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.0, 135.8, 125.7, 125.4, 123.3, 122.0, 121.8, 111.7. HRMS: *m*/*z* (EI-TOF) calculated [M]: 245.8906, found: 245.8907.

2,3-Dichlorobenzo[b]thiophene (**14c**). Eluent: 1% ether in hexane. Colorless oil, yield 20.7 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, *J* = 8.0 Hz, 1 H), 7.85 (d, *J* = 8.0 Hz, 1 H), 7.64−7.55 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 1345, 129.0, 126.4, 123.6, 122.9, 112.4, 105.5. HRMS: *m*/*z* (EI-TOF) calculated [M]: 201.9411, found: 201.9414.

2-Bromo-3-methylbenzo[b]thiophene (**15b**). Eluent: 1% ether in hexane. Yellow liquid, yield 35.9 mg (79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, *J* = 8.0 Hz, 1 H), 7.64 (d, *J* = 8.5 Hz, 1 H), 7.40−7.29 (m, 2 H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 138.9, 124.5, 124.4, 121.7, 121.6, 13.1. HRMS: *m*/*z* (EI-TOF) calculated [M]: 225.9452, found: 225.9455.

2-Chloro-3-methylbenzo[b]thiophene (**15c**). Eluent: 1% ether in hexane. Yellow liquid, yield 27.8 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32 (d, *J* = 9.3 Hz, 1 H), 7.32 (d, *J* = 2.7 Hz, 1 H), 7.21 (dd, *J* = 2.6, 9.3 Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.6, 127.9, 120.5, 118.2, 115.0, 110.1, 56.6. HRMS: *m*/*z* (EI-TOF) calculated [M]: 181.9957, found: 181.9950.

2-Bromo-3-methylbenzofuran (**16b**).[43] Eluent: 1% ether in hexane. Yellow liquid, yield 32.1 mg (76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−7.37 (m, 2 H), 7.27−7.22 (m, 2 H), 2.19 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.0, 129.3, 126.3, 124.1, 122.9, 118.7, 115.1, 110.8, 8.8.

2-Chloro-3-methylbenzofuran (**16c**).[44] Eluent: 1% ether in hexane. Yellow liquid, yield 17.0 mg (51%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.41 (m, 2 H), 7.24−7.21 (m, 2 H), 2.22 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 1289, 124.1, 123.1, 122.7, 118.5, 110.8, 97.4, 10.4.

2-Bromo-1,3-dimethoxybenzene (**17b**).[45] Eluent: 1% ether in hexane. White solid, yield 25.5 mg (59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25−7.19 (m, 1 H), 6.57−6.55 (m, 2 H), 3.88 (d, *J* = 0.9 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.1, 128.2, 104.7, 100.9, 56.4.

2-Chloro-1,3-dimethoxybenzene (**17c**).[46] Eluent: 1% ether in hexane. White solid, yield 18.0 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (t, *J* = 8.7 Hz, 1 H), 6.50 (d, *J* = 8.3 Hz, 2 H), 3.88 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5, 129.8, 110.0, 104.1, 56.6.

1-Bromo-2,4-dimethoxybenzene (**18b**).[47] Eluent: 1% ether in hexane. White solid, yield 22.6 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, *J* = 8.7 Hz, 1 H), 6.49 (d, *J* = 2.2 Hz, 1 H), 6.40 (dd, *J* = 2.0, 8.7 Hz, 1 H), 3.87 (s, 3 H), 3.80 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 156.5, 133.1, 105.8, 102.4, 99.9, 56.1, 55.6.

1-Chloro-2,4-dimethoxybenzene (**18c**).[48] Eluent: 10% ether in hexane. White solid, yield 8.3 mg (24%). ^{1}H NMR (400 MHz, $CDCl_3$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (d, *J* = 8.6 Hz, 1 H), 6.51 (dd, *J* = 1.8, 8.6 Hz, 1 H), 6.46 (d, *J* = 1.8 Hz, 1 H), 3.90 (s, 3 H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 105.7, 98.5, 55.9, 55.7.

1-Bromo-2,4,5-trimethoxybenzene (**19b**).[49] Eluent: 10% ether in hexane. White solid, yield 30.1 mg (61%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.02 (s, 1 H), 6.55 (s, 1 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 149.1, 143.8, 116.4, 101.0, 98.8, 57.2, 56.6, 56.2.

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*1-Chloro-2,4,5-trimethoxybenzene (**19c**).*[50] Eluent: 10% ether in hexane. White solid, yield 15.8 mg (39%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.89 (s, 1 H), 6.57 (s, 1 H), 3.88 (d, J = 3.8 Hz, 6 H), 3.83 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 148.4, 143.5, 113.8, 99.1, 57.2, 56.6, 56.3.

*2-Bromo-1,3,5-trimethoxybenzene (**20b**).*[51] Eluent: 10% ether in hexane. White solid, yield 40.5 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.16 (s, 2 H), 3.87 (s, 6 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.4, 157.4, 91.6, 56.3, 55.5.

*2-Chloro-1,3,5-trimethoxybenzene (**20c**).*[52] Eluent: 10% ether in hexane. White solid, yield 22.3 mg (55%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.18 (s, 2 H), 3.88 (s, 6 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.4, 156.5, 91.5, 56.3, 55.5.

4.4. Synthesis of *o*-Nitrobenzonitriles. *Synthesis of 4-Chloro-2-nitrobenzonitrile (**1d**, Scheme 2).* An oven-dried Schlenk tube equipped with a stir bar was charged with 4-chloro-2-nitrobenzoic acid (40.3 mg, 0.2 mmol), CuI (11.4 mg, 0.06 mmol, 0.3 equiv), and $K_4Fe(CN)_6$ (0.04 mmol, 0.2 equiv). The tube was fitted with a rubber septum, and then it was evacuated and refilled with dioxygen three times. Under dioxygen, DMSO (2 mL) was added via syringe. The rubber septum was replaced with a Teflon screwcap under dioxygen flow, and the Schlenk tube was pressurized to 1 atm. With stirring, the reaction mixtures were heated at 160 °C for the indicated amount of time (unless otherwise specified), and then cooled down to room temperature. The resultant mixture was filtered through a short plug of silica gel and then concentrated in vacuo. The residue was then purified by flash chromatography on silica gel (10% ether in hexane) to afford 26.7 mg (73%) of the product as a yellow solid, mp 105−106 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.34 (s, 1 H), 7.86−7.81 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.2, 134.5, 126.1, 110.0, 106.4. HRMS: m/z (EI-TOF) calculated [M]: 181.9883, found: 181.9885.

The same procedure as that for 4-chloro-2-nitrobenzonitrile **1d** was used to synthesize the other *o*-nitrobenzonitriles.

Basing on this procedure, $Pd(OAc)_2$ (0.01 equiv) was added as additional catalyst to prepare *o*-methoxybenzonitriles.

*5-Chloro-2-nitrobenzonitrile (**2d**, Scheme 3).* Eluent: 10% ether in hexane. Yellow solid, mp 95−96 °C, yield 24.8 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 8.9 Hz, 1 H), 7.89 (d, J = 1.9 Hz, 1 H), 7.79 (dd, J = 2.2, 8.9 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.4, 135.3, 133.9, 126.9, 113.8, 109.7. HRMS: m/z (EI-TOF) calculated [M]: 181.9883, found: 181.9885.

*4-Fluoro-2-nitrobenzonitrile (**3d**).* Eluent: 10% ether in hexane. Yellow solid, mp 76−78 °C, yield 17.6 mg (53%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (dd, J = 2.1, 7.9 Hz, 1 H), 7.97 (q, J = 4.0 Hz, 1 H), 7.59−7.54 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.6, 163.0, 137.5 (d, J = 9.1 Hz), 122.0 (d, J = 22.2 Hz), 114.1 (d, J = 27.3 Hz), 104.3 (d, J = 4.0 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ −97.8 to −97.7 (m, 1 F). HRMS: m/z (EI-TOF) calculated [M]: 166.0180, found: 166.0179.

*5-Fluoro-2-nitrobenzonitrile (**4d**).* Eluent: 10% ether in hexane. Yellow solid, mp 104−106 °C, yield 14.0 mg (42%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.41 (q, J = 4.0 Hz, 1 H), 7.62 (dd, J = 2.7, 7.3 Hz, 1 H), 7.55−7.50 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 163.5, 128.5 (d, J = 10.0 Hz), 122.8 (d, J = 26.3 Hz), 121.0 (d, J = 22.2 Hz), 113.8 (d, J = 2.1 Hz), 110.6 (d, J = 10.4 Hz). ^{19}F NMR (377 MHz, $CDCl_3$): δ −99.4 to −99.5 (m, 1 F). HRMS: m/z (EI-TOF) calculated [M]: 166.0179, found: 166.0173.

*2-Nitro-4-(trifluoromethyl)benzonitrile (**5d**).*[53] Eluent: 10% ether in hexane. Yellow solid, yield 29.4 mg (68%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.60 (s, 1 H), 8.14−8.04 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.6, 131.1−131.0 (m), 123.0−122.9 (m), 120.5, 113.8, 111.5. ^{19}F NMR (376 MHz, $CDCl_3$): δ −63.4 (s, 3 F).

*2-Nitrobenzonitrile (**6d**).* Eluent: 10% ether in hexane. Yellow solid, mp 109−111 °C, yield 14.8 mg (50%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35 (m, 1 H), 7.94 (m, 1 H), 7.84 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.7, 134.4, 133.7, 125.6, 115.0, 108.2. HRMS: m/z (EI-TOF) calculated [M]: 148.0273, found: 148.0272.

*4-Methyl-2-nitrobenzonitrile (**7d**).* Eluent: 10% ether in hexane. Yellow solid, mp 102−104 °C, yield 15.9 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1 H), 7.79 (d, J = 7.9 Hz, 1 H), 7.62 (d, J = 7.8 Hz, 1 H), 2.57 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 135.3, 134.9, 126.1, 115.2, 105.1, 21.8. HRMS: m/z (EI-TOF) calculated [M]: 162.0424, found: 162.0429.

*2-Methyl-6-nitrobenzonitrile (**10d**).*[54] Eluent: 10% ether in hexane. Yellow solid, yield 8.8 mg (27%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (dd, J = 2.5, 6.6 Hz, 1 H), 7.70−7.66 (m, 2 H), 2.70 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.7, 135.4, 132.6, 122.8, 113.6, 108.0, 21.0.

*4-Methoxy-2-nitrobenzonitrile (**11d**).*[55] Eluent: 20% ether in hexane. Yellow solid, yield 26 mg (73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81−7.78 (m, 2 H), 7.27 (dd, J = 2.5, 8.7 Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.2, 150.2, 136.7, 120.0, 115.4, 111.1, 99.4, 56.6.

*5-Methoxy-2-nitrobenzonitrile (**12d**).*[56] Eluent: 15% ether in hexane. Yellow solid, yield 23.9 mg (67%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, J = 9.3 Hz, 1 H), 7.32 (d, J = 2.6 Hz, 1 H), 7.21 (dd, J = 2.6, 9.3 Hz, 1 H), 3.97 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.7, 141.4, 128.0, 120.6, 118.2, 115.1, 110.0, 56.7.

*4,5-Dimethoxy-2-nitrobenzonitrile (**13d**).*[57] Eluent: 25% ether in hexane. Yellow solid, yield 18.7 mg (45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1 H), 7.21 (s, 1 H), 4.03 (d, J = 5.8 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 152.2, 115.4, 107.9, 100.9, 57.0, 56.9.

*3-Chlorobenzo[b]thiophene-2-carbonitrile (**14d**).* Eluent: 1% ether in hexane. White solid, mp 123−125 °C, yield 22.1 mg (57%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (d, J = 7.9 Hz, 1 H), 7.84 (d, J = 7.5 Hz, 1 H), 7.66−7.52 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1, 134.5, 129.0, 126.4, 123.6, 122.9, 112.4, 105.5. HRMS: m/z (EI-TOF) calculated [M]: 192.9753, found: 192.9756.

*3-Methylbenzofuran-2-carbonitrile (**16d**).* Eluent: 1% ether in hexane. Yellow solid, mp 71−72 °C, yield 23.6 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, J = 7.8 Hz, 1 H), 7.50 (d, J = 3.5 Hz, 2 H), 7.38−7.35 (m, 1 H), 2.46 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 155.4, 129.8, 128.4, 126.9, 125.0, 124.0, 120.9, 8.8. HRMS: m/z (EI-TOF) calculated [M]: 157.0528, found: 157.0522.

*2,6-Dimethoxybenzonitrile (**17d**).*[58] Eluent: 20% ether in hexane. White solid, yield 28.1 mg (86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (t, J = 8.5 Hz, 1 H), 6.55 (d, J = 8.5 Hz, 2 H), 3.90 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7, 134.8, 114.1, 103.5, 91.3, 56.2.

*2,4,6-Trimethoxybenzonitrile (**20d**).*[52] Eluent: 30% ether in hexane. White solid, yield 25.1 mg (65%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.06 (s, 2 H), 3.88 (s, 6H), 3.85 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 163.8, 114.6, 90.3, 56.1, 55.7.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02873.

Characterization of products (copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra) (PDF)

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Notes

The authors declare no competing financial interest.

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