JOC*Note*

Facile Assembly of Fused Benzo[4,5]furo Heterocycles

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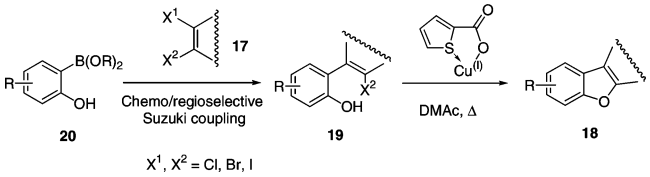


A concise synthesis of fused benzo[4,5]furo heterocycles **18** has been developed. Chemo/regioselective Suzuki coupling between 1,2-dihaloarene **17** and α-hydroxyphenylboronic acid or ester **20** gives biaryl phenol **19**, which then undergoes copper(I) thiophene-2-carboxylate (CuTC)-mediated intramolecular cyclization to afford **18** in good overall yield. This method has broad substrate scope and allows facile assembly of a wide variety of benzo[4,5]furo heterocycles.

Fused benzofuro heterocycles are common structural motifs in biologically active compounds and drug candidates (Figure 1). For example, Elbfluorene (**1**) and its derivatives are interesting leads as cyclin-dependent kinase (CDK) inhibitors.[1] Benzofurocoumarins such as **2** were found to inhibit the growth of several human cancer cell lines.[2] Benzofuropyrimidine **3** (MP-470, SuperGen Inc.)[3] is a novel multitarget tyrosine kinase inhibitor currently in Phase I clinical trials, while compound **4** and its analogues were found to be histamine H_4 modulators.[4]

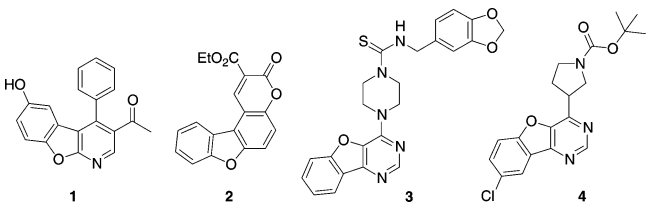
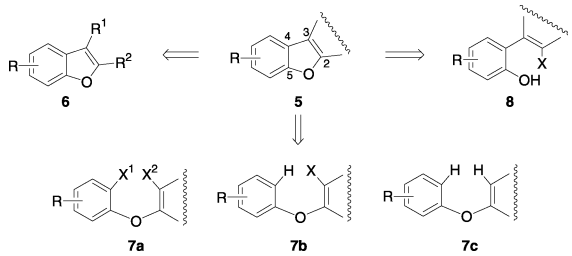


FIGURE 1. Biologically active benzo[4,5]furo heterocycles.

Numerous syntheses of benzo[4,5]furo heterocycle **5** have been reported. Most often, a benzofuran derivative **6** is prepared first, followed by the construction of the heterocyclic ring[5] (Scheme 1). This approach usually requires lengthy multistep synthesis. Alternatively, the retrosynthetic disconnection can be made at the C3−C4 bond of the central furan ring. This bond is often formed by the reductive dehalocoupling of diaryl ether **7a**,[6] dehydrohalogenation of **7b**,[7] or oxidative coupling of **7c**.[8] Finally, a more classical but less utilized route involves the intramolecular cyclization of biaryl phenol **8**.[9] This approach offers distinctly different synthetic opportunities but is often avoided owing to the harsh conditions usually required for the intramolecular cyclization and the lack of a general method for the preparation of biaryl phenol **8**.

SCHEME 1. Synthetic Approaches for Benzofuro Heterocycles 5



In our lead optimization studies, benzofuropyrimidine **9** was identified as a key intermediate. Initially, **9** was prepared from 2-cyanophenol **10** via a multistep sequence, in which the furan and pyrimidine rings were constructed sequentially (Scheme 2a). We envisioned that **9** might be synthesized via a more concise route (Scheme 2b). A regioselective Suzuki coupling between boronic acid **11** and 2,4,5,6-tetrachloropyrimidine (**12**) could

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(2) Oliveira, A. M. A. G.; Raposo, M. M. M.; Oliveira-Campos, A. M. F.; Machado, A. E. H.; Puapairoj, P.; Pedro, M.; Nascimento, M. S. J.; Portela, C.; Afonso, C.; Pinto, M. *Eur. J. Med. Chem.* **2006**, *41*, 367−372.

(3) Hurley, L. H.; Mahadevan, D.; Han, H.; Bearss, D. J.; Vankayalapati, H.; Bashyam, S.; Munoz, R. M.; Warner, S. L.; Della, C. K.; Von Hoff, D. D.; Grand, C. L. PCT Int. Appl. WO 2005/037825, 2005.

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(5) (a) Dixit, M.; Raghunandan, R.; Kumar, B.; Maulik, P. R.; Goel, A. *Tetrahedron* **2007**, *63*, 1610−1616. (b) Liebeskind, L. S.; Wang, J. *J. Org. Chem.* **1993**, *58*, 3550−3556. (c) Ando, Y.; Ando, K.; Yamaguchi, M.; Kunitomo, J.; Koida, M.; Fukuyama, R.; Nakamuta, H.; Yamashita, M.; Ohta, S.; Ohishi, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5849−5854. (d) Gerster, M.; Wicki, R. *Synthesis* **2004**, 249−254. (e) Isomura, K.; Noguchi, S.; Saruwatari, M.; Hatano, S.; Taniguchi, H. *Tetrahedron Lett.* **1980**, *21*, 3879−3882. (f) Degl'Innocenti, A.; Funicello, M.; Scafato, P.; Spagnolo, P. *Tetrahedron Lett.* **1997**, *38*, 2171−2174. (g) González-Gómez, J. C.; Uriarte, E. *Synlett* **2002**, 2095−2097. (h) Shafiee, A.; Behnam, E. *J. Heterocycl. Chem.* **1978**, *15*, 1459−1462. (i) Yamaguchi, S.; Tsuzuki, K.; Sannomiya, Y.; Oh-hira, Y.; Kawase, Y. *J. Heterocycl. Chem.* **1989**, *26*, 285−287. (j) Sargent, M. V.; Stransky, P. O. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1605−1610.

(6) Sanz, R.; Fernández, Y.; Castroviejo, M. P.; Pérez, A.; Fañanás, F. J. *J. Org. Chem.* **2006**, *71*, 6291−6294.

(7) (a) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347−355. (b) Zhang, Y.-M.; Razler, T.; Jackson, P. F. *Tetrahedron Lett.* **2002**, *43*, 8235−8239. (c) Ames, D. E.; Opalko, A. *Synthesis* **1983**, 234−235.

(8) (a) Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. *J. Org. Chem.* **1975**, *40*, 1365−1367. (b) De Lombaert, S.; Blanchard, L.; Stamford, L. B.; Tan, J.; Wallace, E. M.; Satoh, Y.; Fitt, J.; Hoyer, D.; Simonsbergen, D.; Moliterni, J.; Marcopoulos, N.; Savage, P.; Chou, M.; Trapani, A. J.; Jeng, A. Y. *J. Med. Chem.* **2000**, *43*, 488−504. (c) Zeller, K.-P.; Petersen, H. *Synthesis* **1975**, 532−533. Also see ref 5j.

(9) For the synthesis of dibenzofurans via this approach, see: (a) Kawaguchi, K.; Nakano, K.; Nozaki, K. *J. Org. Chem.* **2007**, *72*, 5119−5128. (b) Martínez, A.; Fernández, M.; Estévez, J. C.; Estévez, R. J.; Castedo, L. *Tetrahedron* **2005**, *61*, 1353−1362. (c) Litinas, K. E.; Nicolaides, D. N. *J. Chem. Soc., Perkin Trans. 1* **1985**, 429−435. For benzofuropyridines, see: (d) Yue, W. S.; Li, J. J. *Org. Lett.* **2002**, *4*, 2201−2203. (e) Abramovitch, R. A.; Inbasekaran, M. N.; Kato, S.; Radzikowska, T. A.; Tomasik, P. *J. Org. Chem.* **1983**, *48*, 690−695. (f) Parmentier, M.; Gros, P.; Fort, Y. *Tetrahedron* **2005**, *61*, 3261−3269. For benzofuropyrazines, see: (g) Coates, W. J.; McKillop, A. *J. Org. Chem.* **1990**, *55*, 5418−5420.

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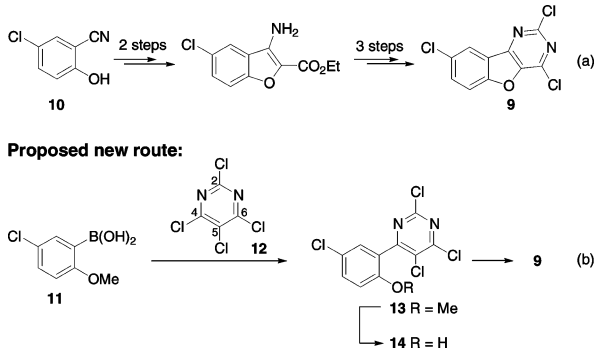
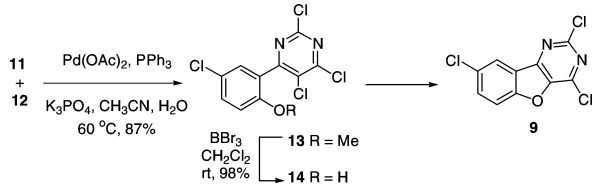
SCHEME 2. Syntheses of Benzofuropyrimidine 9



afford phenylpyrimidine **13**. After demethylation, intramolecular cyclization of biaryl phenol **14** should give benzofuropyrimidine **9**.

First, regioselective Suzuki coupling between **11** and **12** was studied. Similar reactions with 2,4-dihalo- and 2,4,5-trihalopyrimidines are known to occur preferentially at the C4-position, but C2-coupling is also often observed.[10] On the other hand, Suzuki reaction with tetrachloropyrimidine **12** has never been reported. Systematic screening of a Pd catalyst, ligand, base, and solvent was conducted. Under the optimized conditions [Pd(OAc)$_2$, PPh$_3$, and K$_3$PO$_4$ in CH$_3$CN/H$_2$O], the reaction gave phenylpyrimidine **13** in 87% yield and 7:1 regioselectivity (Table 1). The use of more active ligands, such as dppf or tricyclohexylphosphine, resulted in significantly lower regioselectivity (2:1 or less). The product **13** was then demethylated (BBr$_3$, CH$_2$Cl$_2$) to give biaryl phenol **14**.

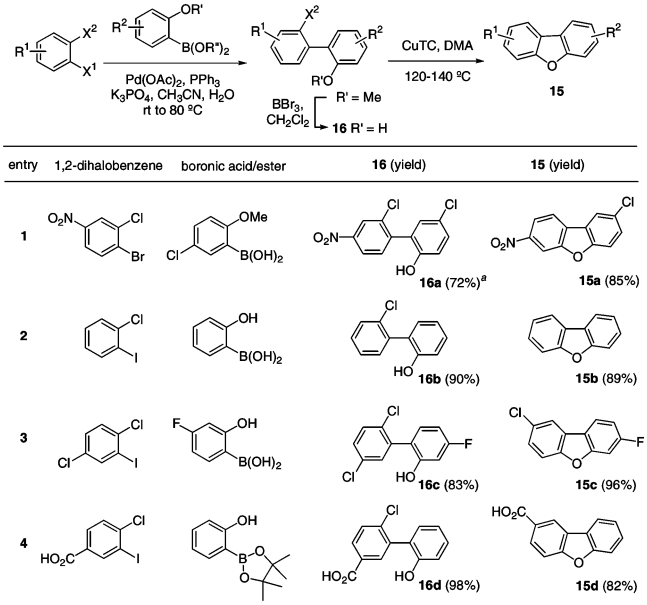
TABLE 1. Optimization of Cyclization Conditions



entry	reagent	solvent	T/t	result
1	K_2CO_3	acetone	rt, 90 min	decomposition
2	$^iPr_2NEt$	CH_2Cl_2	rt, overnight	decomposition
3	none	toluene	170 °C, 1 h	no reaction
4	HCl	THF	50 °C, 2 days	no reaction
5	BF_3Et_2O	CH_2Cl_2	100 °C, 20 min	no reaction
6	$Pd(OAc)_2/PPh_3$	toluene	140 °C, 20 min	no reaction
7	$CuCl_2$	DMAc	100 °C, 40 min	no reaction
8	CuCl	dioxane	100 °C, 20 min	no reaction
9	CuCl	DMAc	100 °C, 2 h	**9** (~70% by HPLC)
10	 (CuTC)	NMP	80 °C, 2 h	**9** (83%)

The intramolecular cyclization of **14** proved to be more difficult than expected. Although the desired intramolecular cyclization at the 5-chloro position should be favored entropically, far more reactive 2- and 6-chloro groups often interfere with the reaction. Thus, cyclization under basic conditions failed because **14** decomposes quickly even in the presence of weak bases (Table 1, entries 1 and 2). This instability also precludes the use of traditional Ullmann-type reactions in which a base is required. On the other hand, no reaction was observed under neutral or acidic conditions even at high temperature (entries 3−5). Several attempts to affect the cyclization with Pd or Ni catalysts were also unsuccessful (entry 6). Interestingly, CuCl promoted the cyclization quite well in polar solvents (entry 9). Upon further screening, commercially available copper(I) thiophene-2-carboxylate (CuTC)[11] was found to be the most active promoter for this transformation. The reaction can be carried out under neutral conditions in DMA or NMP to provide product **9** in good yield (entry 10).

TABLE 2. Preparation of Dibenzofuran Derivatives 15



[a] Isolated yield after Suzuki coupling and demethylation.

We then explored the scope of this concise route for the synthesis of other tricyclic benzofuro compounds. Under the same reaction conditions, dibenzofuran **15a** (Table 2, entry 1) can be prepared from the corresponding dihalobenzene and 2-methoxyphenylboronic acid. Furthermore, commercially available 2-*hydroxy*phenylboronic acids and esters are also excellent substrates for the halogen-selective Suzuki coupling under the same conditions (entries 2−4).[12] The reactions occur exclusively at the position with the most active halogen to give biaryl phenols **16b**−**d** directly, and O-deprotection is no longer necessary. Using this method, various substituted dibenzofurans **15b**−**d** were synthesized in two simple steps.

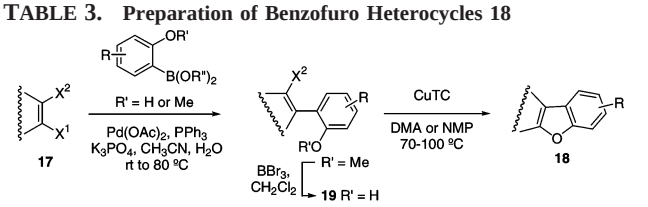
The scope of this method is not limited to the synthesis of benzofuropyrimidines and dibenzofurans. With the appropriate

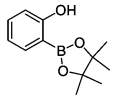
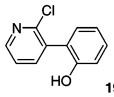
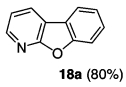
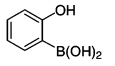
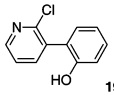
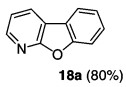
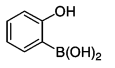
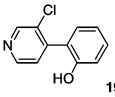
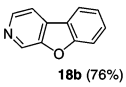
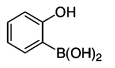
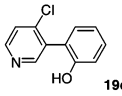
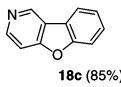
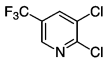
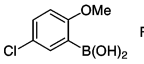
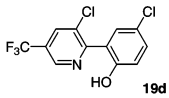
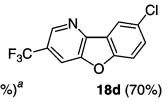
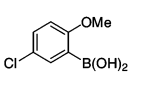
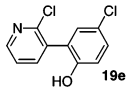
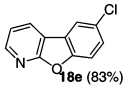
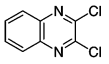
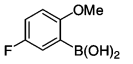
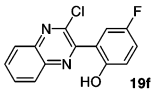
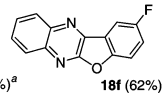
(10) (a) Ceide, S. C.; Montalban, A. G. *Tetrahedron Lett.* **2006**, *47*, 4415−4418. (b) Blackaby, W. P.; Atack, J. R.; Bromidge, F.; Castro, J. L.; Goodacre, S. C.; Hallett, D. J.; Lewis, R. T.; Marshall, G. R.; Pike, A.; Smith, A. J.; Street, L. J.; Tattersall, D. F. D.; Wafford, K. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1175−1179. (c) Peng, Z.-H.; Journet, M.; Humphrey, G. *Org. Lett.* **2006**, *8*, 395−398. (d) Delia, T. J.; Schomaker, J. M.; Kalinda, A. S. *J. Heterocycl. Chem.* **2006**, *43*, 127−130.

(11) CuTC promotes many coupling reactions very effectively and often demonstrates unique reactivities. See: (a) Zhang, S.; Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1997**, *62*, 2312−2313. (b) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (c) Innitzer, A. *Synlett* **2005**, 2405−2406 and references therein.

(12) For isolated literature examples of halogen-selective Suzuki couplings between 1,2-dihalobenzenes and α-hydroxyphenylboronic acid derivatives, see: (a) Buchwald, S. L.; Huang, X.; Zim, D. PCT Int. Appl. WO 2004/052939, 2004. (b) Buchwald, S. L.; Old, D. W.; Wolfe, J. P.; Palucki, M.; Kamikawa, K. U.S. Patent 6,307,087, 2001.

TABLE 3. Preparation of Benzofuro Heterocycles 18



entry	17	boronic acid/ester	19 (yield)	18 (yield)
1			 **19a** (63%)	 **18a** (80%)
2			 **19a** (78%)	 **18a** (80%)
3			 **19b** (62%)	 **18b** (76%)
4			 **19c** (83%)	 **18c** (85%)
5			 **19d** (72%)[a]	 **18d** (70%)
6			 **19e** (77%)[a]	 **18e** (83%)
7			 **19f** (64%)[a]	 **18f** (62%)

[a] Isolated yield after Suzuki coupling and demethylation.

choice of 1,2-dihalo heterocycles **17** as starting materials, a wide variety of other benzofuro heterocycles **18** can also be easily prepared in two or three steps (Table 3). There are three possible scenarios for the chemo- or regioselective Suzuki coupling reaction: If the two halogen atoms of 1,2-dihalo heterocycle **17** are different (Table 3, entries 1, 2, 4, and 6), the coupling occurs at the position with the most active halogen. If the halogen atoms are the same but their positions on the heterocycle are different, the reaction takes place selectively at the most active position (entries 3 and 5). If compound **17** is symmetrical and the two halogen atoms are completely identical, monocoupling is observed under the reaction conditions when stoichiometric or a slight excess of boronic acid is used (entry 7).[13]

For all the above scenarios, the Suzuki reaction conditions again proved to be very general, giving the desired product in good yield and excellent chemo- or regioselectivity. Unprotected 2-hydroxyphenylboronic acid derivatives are the preferred starting material since it provides biaryl phenol **19** directly. However, α-methoxyphenylboronic acids and other O-protected α-hydroxyphenylboronic acids are more widely available and often much less expensive. They are equally efficient in the selective Suzuki coupling reaction. The coupling products can then be deprotected to afford biaryl phenol **19** in good overall yields. In the subsequent intramolecular cyclization, CuTC promotes the transformation very effectively and allows most cyclizations with heterocyclic substrates to be carried out at 70−100 °C. The versatility of this concise route is illustrated by the facile synthesis of all four benzo[4,5]furopyridine isomers from the appropriate dihalopyridines in two or three steps and high overall yield (entries 2−5). To the best of our knowledge, this is the first reported synthesis of all four benzofuro[4,5]-pyridines via one common route.[9d]

One important advantage of this new method is the neutral and relatively mild conditions in the CuTC-mediated cyclization step. While the same transformation can sometimes also be accomplished under basic conditions, strong base and high temperature are often required. For instance, CuTC-mediated cyclizations of pyridyl phenols **19b** and **19c** were conducted at 100 °C in good yields (Table 3, entries 3 and 4), but the same cyclizations under basic conditions require NaO^{t}Bu in refluxing DMSO and the yields are moderate (57 and 34% for **19b** and **19c**, respectively).[9d] The current conditions also compare favorably to classical Ullmann-type biaryl ether formations.[14] Most importantly, base-sensitive substrates, such as phenylpyrimidine **14** (vide supra), are well tolerated under the neutral reaction conditions in the current synthesis.

Finally, from a practical standpoint, it is worth noting that all starting materials listed in Tables 1−3 are purchased from commercial vendors and used directly. Since many α-hydroxyphenylboronic acid derivatives and 1,2-dihaloarenes are commercially available, a wide variety of dibenzofurans, benzofuropyridines, benzofuropyrazines, as well as benzofuropyrimidines can be readily synthesized in two or three steps via this route. The general substrate scope and simple reaction conditions for both Suzuki coupling and intramolecular cyclization make this new method suitable for library preparations.

In conclusion, we have developed a concise synthesis for the facile assembly of fused benzo[4,5]furo heterocycles. The key reactions are chemo/regioselective Suzuki coupling and CuTC-mediated intramolecular cyclization under neutral and relatively mild conditions. This route has broad substrate scope and should be applicable for the preparation of many pharmacologically interesting molecules.

Experimental Section

General Procedure for the Suzuki Coupling between 1,2-Dihaloarene and 2-Hydroxyphenylboronic Acid/Ester. 1,2-Dihaloarene (1.0 equiv), boronic acid or ester (1.1−1.5 equiv), $Pd(OAc)_2$ (0.05 equiv), PPh_3 (0.1 equiv), and K_3PO_4 (2.5−3.5 equiv) were added to degassed acetonitrile/H_2O (3:1 v/v) solvents. The reaction mixture was stirred under a N_2 atmosphere at room temperature to 80 °C until the 1,2-dihaloarene substrate was completely consumed as indicated by HPLC or TLC. Acetonitrile was removed, and the crude product was extracted into dichloromethane. Pure product was obtained after silica gel flash column chromatography purification.

General Procedure for the CuTC-Mediated Cyclization. Biaryl phenol (1.0 equiv) and CuTC (1.1−1.3 equiv) were added to degassed DMA (*N*,*N*-dimethylacetamide) or NMP (*N*-methylpyrrolidone) solvent. The mixture was heated under a N_2 atmosphere at 70−140 °C until the reaction was complete as indicated by HPLC or TLC. The reaction mixture was partitioned between 0.1 M HCl/

(13) The Suzuki coupling between 2,3-dichloroquinoxaline and α-methoxyphenylboronic acid has been reported: Mao, L.; Sakurai, H.; Hirao, T. *Synthesis* **2004**, 2535−2539.

(14) Frlan, R.; Kikelj, D. *Synthesis* **2006**, 2271−2285 and references therein.

dichloromethane or 0.1 M NaOH/0.2 M EDTA (ethylenediamine tetraacetic acid)/dichloromethane.[15] Dichloromethane extract was washed with water several times to remove residual DMA or NMP. The crude residue was purified by silica gel flash column chromatography to afford the product.

Characterization Data for Representative Compounds. 2-Chloro-8-fluorodibenzofuran (15c): White crystalline solid; ^{1}H NMR (600 MHz, $CDCl_3$, δ) 7.83 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.6, 5.4 Hz, 1H), 7.45 (d, J = 8.7 Hz, 1H), 7.37 (dd, J = 8.7, 2.2 Hz, 1H), 7.26 (dd, J = 8.8, 2.2 Hz, 1H), 7.09 (td, J = 9.0, 2.3 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, δ) 162.7 (d, J_{C-F} = 246.5 Hz), 157.1 (d, J_{C-F} = 13.5 Hz), 155.1 (d, J_{C-F} = 2.2 Hz), 128.6, 126.7, 125.1, 121.4 (d, J_{C-F} = 10.4 Hz), 120.8, 119.6 (d, J_{C-F} = 2.1 Hz), 112.6, 111.2 (d, J_{C-F} = 24.0 Hz), 99.9 (d, J_{C-F} = 26.9 Hz); MS (EI+) calcd for $C_{12}H_6ClFO$ [$M^{\bullet+}$], 220.0; m/z found, 220.1. Anal. Calcd for $C_{12}H_6ClFO$: C, 65.33; H, 2.74; N, 0.00. Found: C, 65.14; H, 2.65; N, <0.05.

8-Chloro-3-trifluoromethylbenzo[4,5]furo[3,2-*b*]pyridine (18d): White crystalline solid; ^{1}H NMR (500 MHz, $CDCl_3$, δ) 8.95 (s, 1H), 8.27 (s, 1H), 8.10 (s, 1H), 7.65−7.61 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$, δ) 156.9, 149.1, 146.5, 142.6 (q, J_{C-F} = 4.1 Hz), 130.8, 130.1, 124.8 (q, J_{C-F} = 27.6 Hz), 123.7, 123.6 (q, J_{C-F} = 272.8 Hz), 121.7, 116.3 (q, J_{C-F} = 3.8 Hz), 113.7; HRMS (ESI+) calcd for $C_{12}H_6ClF_3NO$ [$M + H^+$], 272.0085; m/z found, 272.0077.

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Supporting Information Available: Detailed representative experimental procedures; characterization data and ^{1}H/^{13}C NMR spectra for all new compounds reported in Tables 1−3. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) It should be noted that if a routine aqueous extractive workup were employed, a heavy emulsion would often form due to the formation of insoluble Cu complex, which could result in product loss. The use of aqueous HCl or EDTA/NaOH solution, for non-basic and basic substrates, respectively, significantly alleviates and often eliminates this problem.