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CuI-Catalyzed Domino Process to 2,3-Disubstituted Benzofurans from 1-Bromo-2-Iodobenzenes and β-Keto Esters

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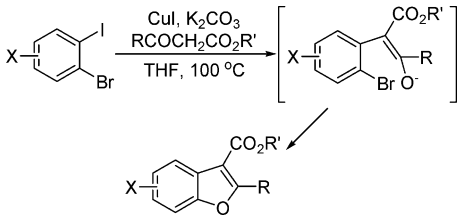

CuI-catalyzed coupling of 1-bromo-2-iodobenzenes with β-keto esters in THF at 100 °C leads to 2,3-disubstituted benzofurans. This domino transformation involves an intermolecular C−C bond formation and a subsequent intramolecular C−O bond formation process. Benzofurans with different substituents at the 5- and 6-position are accessible by employing the corresponding 1-bromo-2-iodobenzenes.

Introduction

The benzofuran moiety is abundant in both natural and artificial molecules possessing potent biological activities. Representative examples include amiodarone,[1] a clinically used drug for controlling intractable cardiac arrhythmias, and compounds **2**[2] and **3**,[3] two inhibitors of receptor kinases that are promising candidates for the treatment of disorders related to vasculogenesis or angiogenesis (see Figure 1). Consequently, great efforts have been devoted to the development of general methods for the assembly of substituted benzofurans.[4−6]

Recently, we discovered that the L-proline assisted, CuI-catalyzed coupling of β-keto esters with aryl halides can be carried out under relatively mild conditions.[7a] Extension of this work led to a convenient synthesis of 3-acyloxindols.[8] Benzofurans can be elaborated from α-(2-halobenzyl)ketones via a metal-catalyzed intramolecular cyclization.[5,6] On the basis of our previous results we decided to develop a domino process leading to benzofurans through coupling of 1-bromo-2-iodobenzenes with β-keto esters and subsequent intramolecular C−O bond formation.[6] The results of our investigations are disclosed herein.

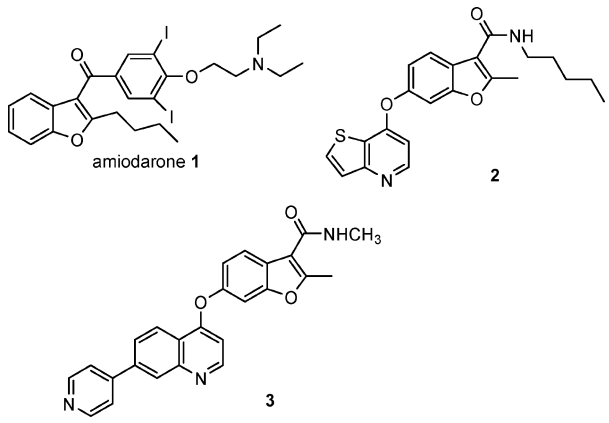

FIGURE 1. Structures of some biologically important benzofuran embodied molecules.

Results and Discussion

The initial experiment was conducted by heating a mixture of 1-bromo-2-iodobenzene (**4a**), ethyl acetoacetate (**5a**) CuI,

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(1) (a) Singh, S. N.; Fletcher, R. D.; Fisher, S. G.; Singh, B. N.; Lewis, H. D.; Deedwania, P. C.; Massie, B. M.; Colling, C.; Layyeri, D. *N. Eng. J. Med.* **1995**, *333*, 77. (b) Kálai, T.; Várbió, G.; Bognár, Z.; Pálfi, A.; Hantó, K.; Bognár, B.; Ösz, E.; Sümegi, B.; Hideg, K. *Bioorg. Med. Chem.* **2005**, *13*, 2629.

(2) Romines, W. H.; Kania, R. S.; Lou, J.; Collins, M. R.; Cripps, S. J.; He, M.; Zhou, R.; Palmer, C. L.; Deal, J. G. WO2003106462, 2003.

(3) Hong, Y.; Kania, R. S. U.S. Patent 5,137,395, 2005.

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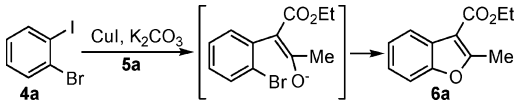
TABLE 1. Synthesis of Benzofuran 6a from 4a and 5a[a]

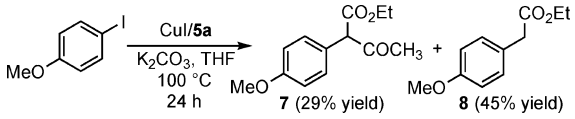


entry	ligand	solvent	temp (°C)	yield (%)[b]
1	L-proline	DMSO	40	0[c]
2	L-proline	THF	70	9
3	no	THF	70	28
4	no	THF	100	83
5	no	dioxane	100	57
6	no	DMSO	100	19
7	no	toluene	100	25
8[d]	no	THF	70	<3

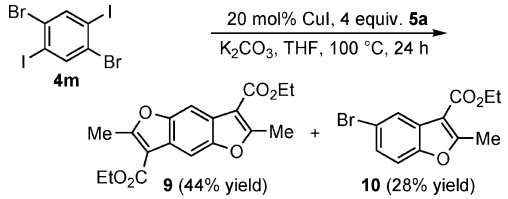
[a] Reaction conditions: **4a** (0.5 mmol), **5a** (1.0 mmol), CuI (50 μmol), ligand (0.1 mmol), K_2CO_3 (1.5 mmol), solvent (1.5 mL). [b] Isolated yield. [c] **4a** was recovered in 88% yield. [d] Cs_2CO_3 was used as a base.

L-proline and K_2CO_3 in DMSO at 40 °C (Table 1, entry 1). Surprisingly, these standard conditions[7a] for coupling aryl iodides and activated methylene compounds did not furnish any coupling products, and **4a** was recovered in 88% yield. After several attempts, it was found that by changing the solvent to THF and carrying out the reaction at 70 °C the desired benzofuran **6a** can be isolated in 9% yield (entry 2). Interestingly, removal of L-proline from the reaction system gave a better result (entry 3), indicating that this ligand does not benefit the current coupling reaction. The best result was observed when the reaction temperature was increased to 100 °C (entry 4). Using other solvents such as dioxane, DMSO, and toluene under the same conditions led to **6a** in low yields (entries 5−7), demonstrating that the cascade process is highly dependent upon the nature of the solvent. In addition, switching the base to Cs_2CO_3 also gave a poor result mainly because of the formation of some unidentified side products (entry 8). It is noteworthy that, under these optimized conditions, the reaction of 4-iodoanisole with **5a** resulted in 74% conversion, providing the coupling product **7** in 29% yield and its deacylation product **8** in 45% yield (Scheme 1).[9] This result indicates that the intramolecular cyclization of the cascade process aids the initial intermolecular coupling.

SCHEME 1



SCHEME 2



We then explored the scope and limits of our newly developed domino process using various 1-bromo-2-iodobenzenes and β-keto esters; the results are summarized in Table 2. From 5-methyl-1-bromo-2-iodobenzene (**4b**) benzofuran **6b** was isolated, and its structure was confirmed by X-ray analysis (see Supporting Information). This result clearly illustrates that intermolecular coupling takes place at the aryl iodide moiety, for **6b** was obtained exclusively (entry 1). The electronic nature of the substituents on the aromatic ring of **4** has little influence on the reaction process, since good yields were observed with both electron-rich and electron-deficient 1-bromo-2-iodobenzenes (entries 1−5). Free hydroxyl groups seem to interfere with the reaction process; this was indicated by the fact that **4g** resulted in a low yield, while its silyl ether **4h** delivered **6h** in 75% yield (entries 7 and 8). Furthermore, 4-substituted and 4,5-disubstituted 1-bromo-2-iodobenzenes furnished the corresponding benzofurans in reasonable yield (entries 9−11), demonstrating that variations at the 5,6 position of the benzofurans are compatible with the present method. The relatively low yield obtained from 4-nitro-1-bromo-2-iodobenzene **(4k**), might be due to the instability of the nitro group under the reaction conditions (entry 11).

From benzyl ester **5b**, benzofuran **6m** was isolated in 71% yield (entry 12). Two olefin and benzene embodied β-keto esters **5c** and **5d** also reacted well, delivering the corresponding products in good yields (entries 13−15). However, γ-*i*-propyl-substituted ester **5e** only gave a moderate yield (entry 16), while γ-phenyl ester **5f** was found to be unreactive (entry 17). This drawback may result from the steric hindrance at the γ-position of the β-keto ester.

When 1,4-dibromo-2,5-diiodobenzene (**4m**)[10] was applied, bisbenzofuran **9** was isolated in 44% yield, together with the dehalogenation product **10** (Scheme 2). This result demonstrates the potential usefulness of this process for the assembly of more complex benzofurans.

(4) For recent and selected examples, see: (a) Zhao, B.; Lu, X. *Org. Lett*. **2006**, *8*, 5987. (b) Bellur, E.; Langer, P. *J. Org. Chem*. **2005**, *70*, 7686. (c) Miyata, O.; Takeda, N.; Naito, T. *Org. Lett*. **2004**, *6*, 1761. (d) Zhang, H.; Ferreira, E. M.; Stoltz, B. M. *Angew. Chem., Int. Ed*. **2004**, *45*, 6235. (e) Cruz, M. C.; Tamariz, J. *Tetrahedron Lett.* **2004**, *45*, 2377. (f) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907. (g) Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem*. **2003**, *68*, 387. (h) Kraus, G. A.; Kim, I. *Org. Lett*. **2003**, *5*, 1191. (i) Kao, C.; Chern, J. *J. Org. Chem*. **2002**, *67*, 6772. (j) Kraus, G. A.; Zhang, N.; Verkade, J. G.; Nagarajan, M.; Kisanga, P. B. *Org. Lett.* **2000**, *2*, 2409. (k) Nan, Y.; Miao, H.; Yang, Z. *Org. Lett*. **2000**, *2*, 297.

(5) (a) Carril, M.; SanMartin, R.; Tellitu, I.; Domínguez, E. *Org. Lett*. **2006**, *8*, 1467. (b) Fang, Y.; Li, C. *J. Org. Chem*. **2006**, *71*, 6427. (c) Chen, C.; Dormer, P. G. *J. Org. Chem*. **2005**, *70*, 6964. (d) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Org. Lett*. **2004**, *6*, 4755.

(6) Pd-catalyzed benzofuran formation via coupling of some special ketones and *o*-dihalobenzenes has been reported, see: (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 2345. (b) Churruca, F.; SanMartin, R.; Tellitu, I.; Domínguez, E.; *Eur. J. Org. Chem.* **2005**, 2481. (c) Willis, M. C.; Taylor, D.; Gillmore, A. T. *Tetrahedron* **2006**, *62*, 11513.

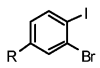
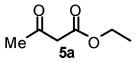
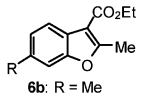
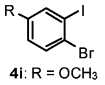
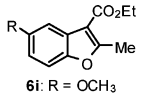
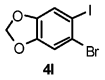
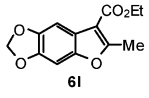
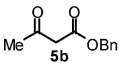
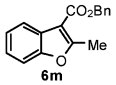
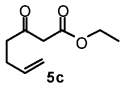
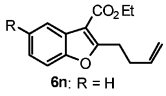
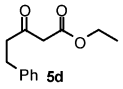
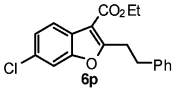
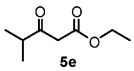
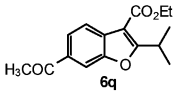
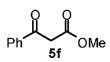
(7) (a) Xie, X.; Cai, G.; Ma, D. *Org. Lett*. **2005**, *7*, 4693. (b) Xie, X.; Chen Y.; Ma, D. *J. Am. Chem. Soc*. **2006**, *128*, 16050. For related studies from other groups, see: (c) Hennessy, E. J.; Buchwald, S. L. *Org. Lett*. **2002**, *4*, 269. (d) Cristau, H.-J.; Cellier, P. P.; Spindler, J.-F.; Taillefer, M. *Chem. Eur. J*. **2004**, *10*, 5607. (e) Jiang, Y.; Wu, N.; Wu, H.; He, M. *Synlett* **2005**, 2703. (f) Pei, L.; Qian, W. *Synlett* **2006**, 1719.

(8) Lu, B.; Ma, D. *Org. Lett*. **2006**, *8*, 6115.

(9) Similar conversion was reported by Parkinson and coworkers. See: Zeevaart, J. G.; Parkinson, C. J.; Koning, C. B. *Tetrahedron Lett.* **2007**, *48*, 3289.

(10) Hart, H.; Harada, H.; Du, C.-J. F. *J. Org. Chem*. **1985**, *50*, 3104.

TABLE 2. Synthesis of Substituted Benzofurans via a CuI-catalyzed Cascade Coupling Process of 1-Bromo-2-iodobenzenes with β-Keto Esters[a]

entry	iodide	β-keto ester	time (h)	product	yield (%)[b]
1	 **4b**: R = Me	 **5a**	24	 **6b**: R = Me	88
2	**4c**: R = Cl	**5a**	24	**6c**: R = Cl	75
3	**4d**: R = CF_3	**5a**	26	**6d**: R = CF_3	82
4	**4e**: R = $COCH_3$	**5a**	30	**6e**: R = $COCH_3$	78
5	**4f**: R = CO_2CH_3	**5a**	26	**6f**: R = CO_2CH_3	79
6	**4g**: R = CH_2OH	**5a**	26	**6g**: R = CH_2OH	32
7	**4h**: R = CH_2OTBS	**5a**	26	**6h**: R = CH_2OTBS	75
8	 **4i**: R = OCH_3	**5a**	26	 **6i**: R = OCH_3	78
9	**4j**: R = F	**5a**	24	**6j**: R = F	80
10	**4k**: R = NO_2	**5a**	30	**6k**: R = NO_2	52
11	 **4l**	**5a**	26	 **6l**	70
12	**4a**	 **5b**	26	 **6m**	71
13	**4a**	 **5c**	24	 **6n**: R = H	75
14	**4i**	**5c**	26	**6o**: R = OCH_3	74
15	**4c**	 **5d**	26	 **6p**	78
16	**4e**	 **5e**	26	 **6q**	48
17	**4a**	 **5f**	24	-	-[c]

[a] Reaction conditions: 1-bromo-2-iodobenzenes (**4**) (0.5 mmol), β-keto ester **5** (1.0 mmol), CuI (50 μmol), K_2CO_3 (1.5 mmol), THF (1.5 mL), 100 °C. [b] Isolated yield. [c] **4a** was recovered in about 90% yield.

Conclusion

In conclusion, we have developed a CuI-catalyzed domino process[11] for the assembly of 2,3-disubstituted benzofurans from 1-bromo-2-iodobenzenes and β-keto esters. A number of functional groups are tolerated by our reaction conditions, including vinyl, chloro, fluoro, nitro, carboxylate, ketone, and silyl ether groups. Thus, our process represents a versatile access to substituted benzofurans and a useful tool for the synthesis of biologically active molecules.

Experimental Section

General Procedure for Copper-Catalyzed Domino Process to Benzofuran. An oven-dried Schlenk tube was charged with CuI (10 mg, 0.05 mmol), potassium carbonate (207 mg, 1.5 mmol),

and 1-bromo-2-iodobenzenes (0.5 mmol). The tube was evacuated and backfilled with argon (three times), and then ethyl acetoacetate (130 mg, 1 mmol) and 1.5 mL of THF were added. The reaction mixture in this sealed tube was stirred at 100 °C until the starting aryl iodide was consumed. The cooled solution was partitioned between ethyl acetate (40 mL) and saturated brine (10 mL). The organic layer was isolated, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuum. The residue thus obtained was purified by silica gel chromatography to give the product.

Ethyl 2-methylbenzofuran-3-carboxylate (6a): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (m, 1H), 7.42 (m, 1H), 7.28 (m, 2H), 4.41 (q, J = 7.2 Hz, 2H), 2.77 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.6, 153.6, 126.3, 124.3, 123.7, 121.8, 110.8, 109.1, 60.3, 14.4 (2C); MS (EI) m/z 204 (M^+), 175 (81), 159 (77), 103 (57), 77 (100), 51 (43); HRMS calcd for $C_{12}H_{12}O_3$ (M^+) 204.0786, found 204.0779.

Ethyl 2,6-dimethylbenzofuran-3-carboxylate (6b): Mp: 65−67 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, J = 7.8 Hz, 1H), 7.23 (s, 1H), 7.11 (d, J = 7.8 Hz, 1H), 4.40 (q, J = 6.9 Hz, 2H), 2.75 (s, 3H), 2.46 (s, 3H), 1.44 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.0, 154.0, 134.5, 125.1, 123.7, 121.2, 110.0, 109.0, 60.2, 21.6, 14.4, 14.3; MS (EI) m/z 218 (M^+), 189 (100), 171 (60), 145 (30), 115 (50), 91 (32); HRMS (EI) calcd for $C_{13}H_{14}O_3$ (M^+) 218.0943, found 218.0944.

Ethyl 6-chloro-2-methylbenzofuran-3-carboxylate (6c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 1H), 7.42 (s, 1H), 7.26 (d, J = 8.1 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.75 (s, 3H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 164.0, 153.6, 130.1, 125.0, 124.4, 122.3, 111.3, 109.1, 60.4, 14.4 (2C) ; MS (EI) m/z 238 (M^+), 209 (100), 193 (47), 175 (19), 164 (17), 102 (25); HRMS calcd for $C_{12}H_{11}O_3Cl$(M^+) 238.0397, found 238.0395.

Ethyl 2-methyl-6-(trifluoromethyl)benzofuran-3-carboxylate (6d): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 1H), 7.69 (s, 1H), 7.55 (d, J = 8.4 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 2.80 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 163.8, 152.7, 129.4, 126.7 (q, J = 33.8 Hz), 125.7, 122.2, 120.7 (q, J = 3.8 Hz), 109.3, 108.3 (q, J = 4.2 Hz), 60.6, 14.6, 14.4; MS (EI) m/z 272 (M^+), 243 (60), 227 (100), 199 (20), 151 (41), 102 (12); HRMS (EI) calcd for $C_{13}H_{11}O_3F_3$ (M^+) 272.0660, found 272.0665.

Ethyl 6-acetyl-2-methylbenzofuran-3-carboxylate (6e): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.93 (d, J = 8.1 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 2.82 (s, 3H), 2.67 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 166.8, 163.9, 153.4, 133.8, 130.8, 124.2, 121.5, 111.0, 109.5, 60.6, 26.8, 14.7, 14.4; MS (EI) m/z 246 (M^+), 231 (100), 217 (7), 203 (45), 157 (14), 43 (27); HRMS calcd for $C_{14}H_{14}O_4$ (M^+) 246.0892, found 246.0892.

Ethyl 6-(methoxycarbonyl)-2-methylbenzofuran-3-carboxylate (6f): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 8.00 (m, 2H), 4.43 (q, J = 6.9 Hz, 2H), 3.95 (s, 3H), 2.81 (s, 3H), 1.46 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 166.4, 163.9, 153.1, 130.6, 126.4, 125.2, 121.4, 112.4, 109.4, 60.5, 52.2, 14.7, 14.4; MS (EI) m/z 262 (M^+), 233 (87), 217 (62), 203 (68), 188 (7), 157 (23); HRMS calcd for $C_{14}H_{14}O_5$ (M^+) 262.0841, found 262.0846.

Ethyl 6-(hydroxymethyl)-2-methylbenzofuran-3-carboxylate (6g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87 (d, J = 7.8 Hz, 1H), 7.42 (s, 1H), 7.25 (d, J = 7.8 Hz, 1H), 4.76 (s, 2H), 4.39 (q, J = 5.7 Hz, 2H), 2.74 (s, 3H), 1.44 (t, J = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 163.9, 153.8, 137.7, 125.7, 122.8, 121.6, 110.4, 109.3, 65.3, 60.3, 14.4, 14.3; MS (EI) m/z 234 (M^+), 205 (75), 189 (56), 177 (20), 159 (20), 105 (28); HRMS calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892, found 234.0893.

Ethyl 6-((*tert*-butyldimethylsilyloxy)methyl)-2-methylbenzofuran-3- carboxylate (6h): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.8 Hz, 1H), 7.45 (s, 1H), 7.22 (d, J = 7.8 Hz, 1H), 4.85 (s, 2H), 4.41 (q, J = 7.5 Hz, 2H), 2.77 (s, 3H), 1.46 (t, J = 7.5 Hz, 3H), 0.97 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 163.5, 153.9, 138.5, 125.1, 121.9, 121.3, 109.0, 108.4, 64.9, 60.2, 26.0, 18.4, 14.4 (2C), −5.20; MS (EI) m/z 348 (M^+), 303 (7), 291 (49), 263 (4), 217 (100), 189 (15); HRMS calcd for $C_{19}H_{28}O_4Si$ (M^+) 348.1757, found 348.1757.

Ethyl 2-methyl-5-nitrobenzofuran-3-carboxylate (6i): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 7.52 (d, J = 9.0 Hz, 1H), 4.47 (q, J = 7.2 Hz, 2H), 2.83 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 156.2, 145.0, 126.9, 120.3, 118.4, 118.3, 111.2, 111.0, 60.9, 14.5, 14.4; MS (EI) m/z 249 (M^+), 221 (80), 204 (100), 188 (7), 174 (24), 157 (56); HRMS calcd for $C_{12}H_{11}NO_5$ (M^+) 249.0637, found 249.0633.

Ethyl 5-methoxy-2-methylbenzofuran-3-carboxylate (6j): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.31 (d, J = 9.0 Hz, 1H), 6.87 (d, J = 9.0 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 2.75 (s, 3H), 3.87 (s, 3H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5, 164.2, 156.7, 148.5, 127.1, 112.8, 111.2, 109.1, 104.4, 60.2, 55.9, 14.6, 14.4; MS (EI) m/z 234 (M^+), 205 (90), 189 (45), 174 (10), 160(14), 63 (19); HRMS calcd for $C_{13}H_{14}O_4$ (M^+) 234.0892, found 234.0890.

Ethyl 5-fluoro-2-methylbenzofuran-3-carboxylate (6k): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, J = 6.3, 2.4 Hz, 1H), 7.35 (dd, J = 6.3, 3.9 Hz, 1H), 6.99 (m, 1H), 4.41 (q, J = 6.9 Hz, 2H), 2.76 (s, 3H), 1.45 (t, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 164.1, 159.8 (d, J = 189.9 Hz), 149.8, 127.3 (d, J = 9.0 Hz), 111.9 (d, J = 21.0 Hz), 111.4 (d, J = 7.7 Hz), 109.4 (d, J = 2.4 Hz), 107.7 (d, J = 21.0 Hz), 60.4, 14.5, 14.4; MS (EI) m/z 222 (M^+), 193 (100), 177 (100), 165 (6), 149 (24), 120 (12); HRMS calcd for $C_{12}H_{11}O_3F$ (M^+) 222.0692, found 222.0687.

Compound 6l: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (s, 1H), 6.91 (s, 1H), 5.99 (s, 2H), 4.38 (q, J = 7.2 Hz, 2H), 2.71(s, 3H), 1.43 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 162.6, 148.6, 145.9, 145.2, 119.7, 109.4, 101.4, 100.6, 93.1, 60.2, 14.4 (2C); MS (EI) m/z 248 (M^+), 219 (100), 203 (18), 174 (16), 101 (15), 53 (19); HRMS calcd for $C_{13}H_{12}O_5$ (M^+) 248.0685, found 248.0675.

Benzyl 2-methylbenzofuran-3-carboxylate (6m): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (m, 1H), 7.50−7.28 (m, 6H), 7.26 (m, 2H), 5.41 (s, 2H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.3, 164.0, 153.6, 136.2, 128.7, 128.5, 128.2, 126.2, 124.3, 123.8, 121.8, 110.8, 108.9, 66.1, 14.5; MS (EI) m/z 266 (M^+), 248 (11), 175 (40), 159 (42), 91 (100), 77 (13); HRMS calcd for $C_{17}H_{14}O_3$ (M^+) 266.0943, found 266.0945.

Ethyl 2-(but-3-enyl)benzofuran-3-carboxylate (6n): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (m, 1H), 7.44 (m, 1H), 7.29 (m, 2H), 5.89 (m, 1H), 5.09 (m, 1H), 5.00 (m, 1H), 4.41 (q, J = 7.2 Hz, 2H), 3.29 (t, J = 7.5 Hz, 2H), 2.56 (m, 2H), 1.47 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 164.3, 153.7, 128.8, 126.2, 124.4, 123.7, 121.9, 115.7, 110.9, 109.0, 60.3, 31.8, 27.8, 14.4; MS (EI) m/z 244 (M^+), 215 (8), 203 (34), 175 (100), 91 (53), 55 (36); HRMS calcd for $C_{15}H_{16}O_3$ (M^+) 244.1099, found 244.1105.

Ethyl 2-(but-3-enyl)-5-methoxybenzofuran-3-carboxylate (6o): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (d, J = 2.7 Hz, 1H), 7.33 (d, J = 9.3 Hz, 1H), 6.89 (dd, J = 9.0, 2.7 Hz, 1H), 5.89 (m, 1H), 5.09 (m, 1H), 5.01 (m, 1H), 4.42 (q, J = 7.2 Hz, 2H), 3.87 (s, 3H), 3.27 (t, J = 7.6 Hz, 2H), 2.55 (m, 2H), 1.45 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 164.4, 156.7, 148.6, 136.9, 127.0, 115.6, 113.0, 111.3, 109.0, 104.5, 60.2, 55.9, 31.9, 28.0,

(11) For recent examples of Cu-catalyzed domino processes, see: (a) Zou, B.; Yuan, Q.; Ma, D. *Angew. Chem., Int. Ed*. **2007**, *46*, 2598. (b) Martin, R.; Rodríguez, R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (c) Miyamoto, H.; Okawa, Y.; Nakazaki, A.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 2274. (d) Altenhoff, G.; Glorius, F. *Adv. Synth. Catal*. **2004**, *346*, 1661. (e) Nordmann, G.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 4978. (f) Zanon, J.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2003**, *125*, 2890.

14.4; MS (EI) *m*/*z* 274 (M^+), 245 (4), 233 (92), 205 (100), 189 (19), 91 (28); HRMS calcd for $C_{16}H_{18}O_4$ (M^+) 274.1205, found 274.1201.

Ethyl 6-chloro-2-phenethylbenzofuran-3-carboxylate (6p): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (d, J = 8.7 Hz , 1H), 7.43 (m, 1H), 7.27−7.19 (m, 6H), 4.37 (q, J = 7.2 Hz, 2H), 3.45 (m, 2H), 3.05 (m, 2H), 1.41 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 163.8, 153.6, 140.4, 130.3, 128.5 ,128.3, 126.3, 124.9, 124.5, 122.5, 111.5, 109.0, 60.5, 34.0, 30.2, 14.4; MS (EI) *m*/*z* 328 (M^+), 282 (40), 237 (50), 209 (78), 193 (9), 91(100); HRMS (EI) calcd for $C_{19}H_{17}O_3Cl$ (M^+) 328.0866, found 328.0864.

Methyl 6-acetyl-2-isopropylbenzofuran-3-carboxylate (6q): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.08 (s, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.95 (m, 1H), 4.05 (m, 1H), 3.97 (s, 3H), 2.67 (s, 3H), 1.39 (d, J = 6.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 174.7, 164.3, 153.3, 133.8, 130.7, 124.1, 121.8, 111.3, 107.3, 51.6, 27.8, 26.8, 20.5; MS (EI) *m*/*z* 260 (M^+), 245 (55), 229 (7), 185 (21), 171 (23), 115 (12); HRMS calcd for $C_{15}H_{16}O_4$ (M^+) 260.1049, found 260.1050.

Compound 9: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 2H), 4.43 (q, J = 6.9 Hz, 4H), 2.80 (s, 6H), 1.47 (t, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 164.4, 151.2, 123.9, 109.1, 102.8, 60.3, 14.7, 14.5; MS (EI) *m*/*z* 330 (M^+), 301 (67), 285 (20), 273 (50), 256 (15), 149 (11); HRMS calcd for $C_{18}H_{18}O_6$ (M^+) 330.1103, found 330.1104.

Ethyl 5-bromo-2-methylbenzofuran-3-carboxylate (10): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.35 (m, 1H), 7.27 (m, 1H), 4.42 (q, J = 5.4 Hz, 2H), 2.76 (s, 3H), 1.45 (t, J = 5.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 163.9, 152.3, 128.2, 127.2, 124.5, 117.1, 112.2, 108.8, 60.5, 14.4 (2×C); MS (EI) *m*/*z* 284 (M^+, ^{81}Br), 282 (M^+, ^{79}Br), 255 (83), 253 (82), 175 (64), 157 (29), 102 (52); HRMS (EI): calcd for (M^+, ^{79}Br) $C_{12}H_{11}O_3Br$ 281.9892, found 281.9895.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all new products; X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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