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Synthesis of Benzo[*b*]furans via CuI-Catalyzed Ring Closure

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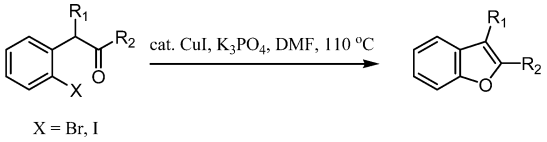
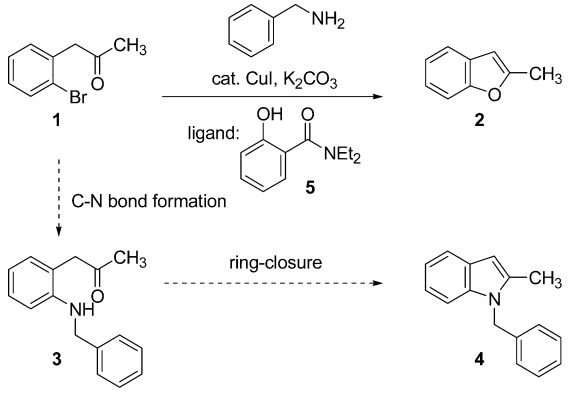


A wide variety of benzo[*b*]furans were synthesized efficiently via a CuI-catalyzed ring closure of 2-haloaromatic ketones. The methodology was tolerant to various functional groups, affording benzofurans in 72−99% yields.

Benzo[*b*]furans are of great synthetic interest because of their wide distribution in nature and useful biological activities.[1] The benzo[*b*]furan ring is often incorporated in pharmaceutical agents as a core structural motif, and as a result continues to attract extensive synthetic efforts.[2,3] Many reported synthetic approaches are based on the construction of furan rings from various arene derivatives via different bond formation.[3h] In contrast, very few examples of benzo[*b*]furan synthesis are based on the C_{7a}−O bond formation.[4−6] Grimshaw and Thompson reported three examples of 2-bromo deoxoybenzoins undergoing ring closure to give benzofurans in 65−70% yields using typical Ullmann coupling conditions.[5,6] The excessive use of activated bronze, harsh reaction conditions (160 °C in DMAC), and narrow substrate scope apparently limited the application of this method. Herein, we wish to report that this very ring closure can be effectively carried out with a catalytic amount of copper iodide under much milder conditions (100−110 °C in DMF). The catalytic process offers great advantages over the conventional methods in that a wide array of benzofurans can be readily synthesized in excellent yields.

SCHEME 1. Initial Research Goal



Our initial intention was to explore the synthesis of indole **4** from 2-bromophenylacetone (Scheme 1).[7] In particular, we carried out the amination of 2-bromophenylacetone with benzylamine under copper-catalyzed conditions.[8] We expected that amination followed by an intramolecular ring closure would smoothly afford indole **4**. Unexpectedly, the catalytic conditions afforded 2-methylbenzo[*b*]furan exclusively in 72% yield. We subsequently found that the CuI-catalyzed ring closure of 2-bromophenyl acetone proceeded smoothly to the methylbenzylfuran without use of ligand **5**. This unexpected result prompted us to investigate the potential for using this protocol for the construction of benzo[*b*]furans.

We optimized the catalytic process using 2-bromophenyl ketone **6** as a model compound and our results are

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(2) For recent reviews on the synthesis of benzo[*b*]furans, see: (a) Hou, X.-L.; Yang, Z.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2003**, *15*, 167−205. (b) Dell, C. P. *Sci. Synth.* **2001**, *10*, 11−86. McCallion, G. D. *Curr. Org. Chem.* **1999**, *3*, 67−76.

(3) For recent, selected examples on the synthesis of benzo[*b*]furans, see: (a) Kraus, G. A.; Kim, I. *Org. Lett*. **2003**, *5*, 1191−1192. (b) Kraus, G. A.; Zhang, N.; Verkade, J. G.; Nagarajan, M.; Kisanga, P. B. *Org. Lett*. **2000**, *2*, 2409−2410. (c) Hu, Y.; Yang, Z. *Org. Lett*. **2001**, *3*, 1387−1390. (d) Kao, C.-L.; Chern, J.-W. *J. Org. Chem.* **2002**, *67*, 6772−6787. (e) Wallez, V.; Durieux-Poissonnier, S.; Chavatte, P.; Boutin, J. A.; Audinot, V.; Nicolas, J.-P.; Bennejean, C.; Delagrange, P.; Renard, P.; Lesieur, D. *J. Med. Chem*. **2002**, *45*, 2788−2800. (f) Macleod, C.; McKiernan, G. J.; Guthrie, E. J.; Farrugia, L. J.; Hamprecht, D. W.; Macritchie, J.; Hartley, R. C. *J. Org. Chem.* **2003**, 68, 387−401. (g) Inoue, M.; Carson, M. W.; Frontier, A. J.; Danishefsky, S. J. *J. Am. Chem. Soc*. **2001**, *123*, 1878−1889. (h) Katritzky, A. R.; Ji, Y.; Fang, Y.; Prakash, I. *J. Org. Chem.* **2001**, *66*, 5613−5615. (i) Cruz, M. del C.; and Tamariz, J. *Tetrahedron Lett*, **2004**, *45*, *2377−2380.* (j) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, *907−910.* (k) Dupont R.; Cotelle, P. *Tetrahedron* **2001**, *57*, *5585−5589.* (l) Kao, C.-L.; Chern. J.-W. *Tetrahedron Lett.* **2001**, *42*, *1111−1113.* (m) Atsushi Sakai, A.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1999**, *40*, *4211−4214.* (n) Roshchin, A. I.; Kel'chevski, S. M.; Bumagin, N. A. *J. Organomet. Chem.* **1998**, *560*, *163−167.*

(4) Formation of dihydrobenzofuran by palladium-catalyzed ether formation was reported: (a) Palucki, M.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 10333−10334. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J Org. Chem.* **2002**, *67*, 5553−5566. (c) Kuwabe, S.-I.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202−12206.

(5) Grimshaw, J.; Thompson, N. *Chem. Commun.* **1987**, *240*.

(6) Conversion of 1,2-dibromoarene and acetophenones to benzo[*b*]-furan via in situ palladium-catalyzed arylation followed by ring closure was reported: (a) Terao, Y.; Satoh, T.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 2345−2350. (b) Veeramaneni, V. R.; Pal, M.; Yeleswarapu, K. R. *Tetrahedron* **2003**, *59*, 3283−3290. (c) Recently, a Pd-catalyzed intramolecular O-arylation of enolates was disclosed: Willis, M. C.; Taylor, D.; Gillmore A. T. *Org. Lett*. **2004**, *6*, 4755−57.

(7) For leading references in the synthesis of indole, see: (a) Balme, G.; Bouyssi, D.; Lomberget, T.; Monteiro, N. *Synthesis* **2003**, 2115−2134. (b) Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Pergamon: Oxford, UK, 2000. (c) Gribble, G. W. *J. Chem. Soc.*, *Perkin Trans. 1* **2000**, 1045−1075. (d) Pindur, U.; Adam, R. *J. Heterocycl. Chem.* **1988**, *25*, 1.

(8) Kwong, F. Y.; Buchwald, S. L. *Org. Lett*. **2003**, *5*, 793−796.

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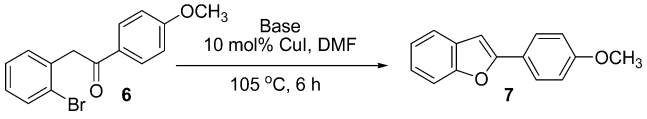
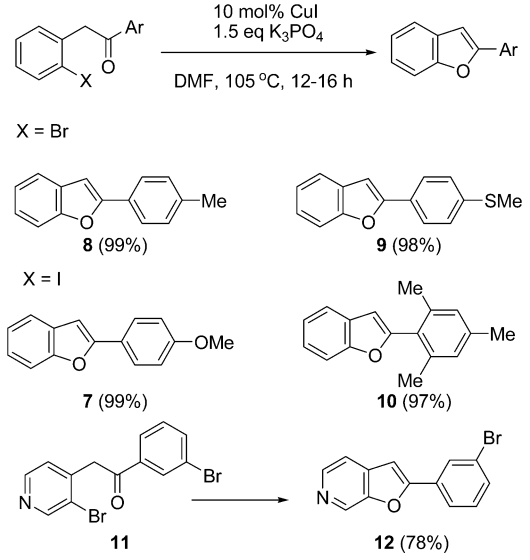
TABLE 1. Optimization of the Ring-Closure Conditions



entry	base	benzofuran **7**, %	ketone **6**, %
1	Na_2CO_3	17	60
2	K_2CO_3	81	19
3	Cs_2CO_3	89	3
4	K_3PO_4	93	4
5	DABCO	10	88

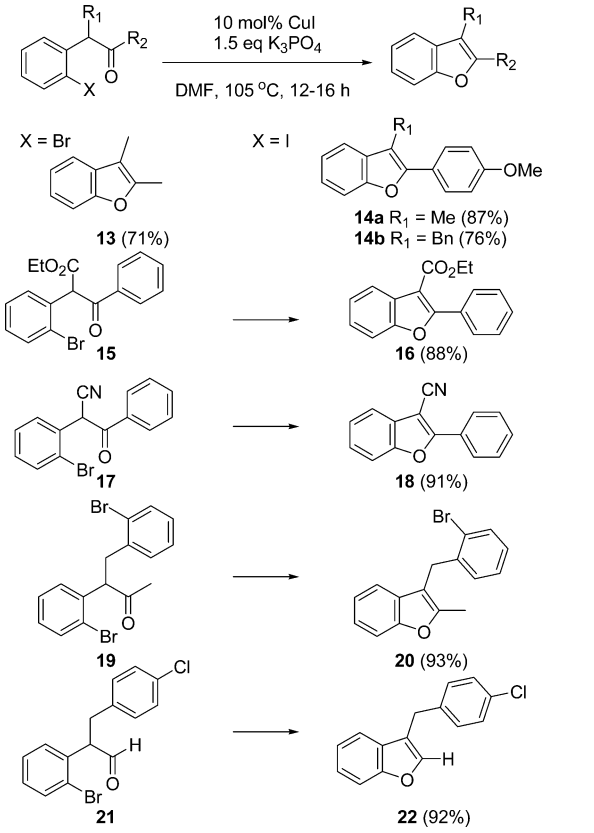
TABLE 2. Preparation of 2-Ar Benzofuran



summarized in Table 1. All the reactions were carried out by heating a mixture of substrate and base in DMF for 6 h, and the yield of the product was assayed by HPLC against a standard. Reactions proceeded smoothly when K_2CO_3, Cs_2CO_3, and K_3PO_4 were used as bases, giving product **7** in 81%, 81.5%, and 93.4% assayed yield, respectively. Bases such as Na_2CO_3, DABCO were ineffective for the transformation. On the basis of these results we chose the conditions in entry 4 (cat. CuI, K_3PO_4 in DMF) for the application of the method to the cyclization of the 2-haloketone substrates.[9]

We found that the optimized conditions worked extremely well with several 2-halo deoxoybenzoins, affording benzo[*b*]furans in excellent yields (Table 2).[10] For example, benzo[*b*]furans **7**, **8**, **9**, and **10** were all obtained quantitatively. The catalytic system was effective for both iodo and bromo ketones, but did not facilitate the ring closure of 2-chloro derivatives. The reaction was also applied to a heterocyclic substrate such as **11** to give pyridyl furan **12** in 78% yield. Isolation of benzo[*b*]furans

TABLE 3. Preparation of 2,3-Disubstituted Benzo[*b*]furans



was extremely straightforward: crystallization from the reaction mixture via addition of water afforded the product in excellent yield and purity.

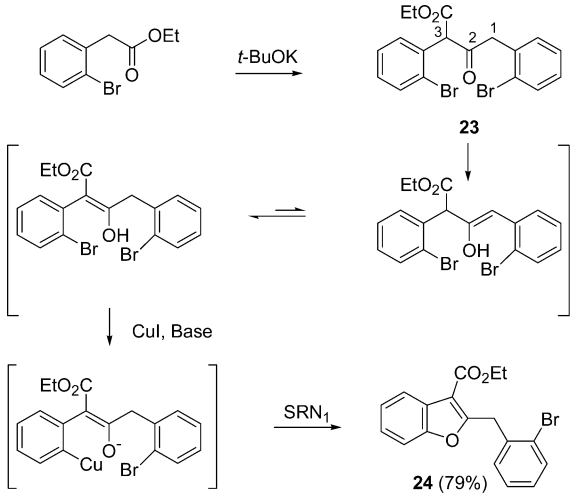
As summarized in Table 3, the CuI-catalyzed process worked equally well for α-substituted ketones,which afforded 2,3-disubstituted benzo[*b*]furans. Under the same conditions, bromoketones as well as iodoketones were readily cyclized to give benzofurans **13** and **14** in good yields. Aromatic ketones (R_2 = Ar) cyclized to give **14a** and **14b** more readily than the alkyl ketone (R_2 = alkyl), which was not completely converted to benzo[*b*]-furan **13** in 16 h. Presumably, the aromatic group facilitates the enolization of the ketones. This is further supported by the next example in which ketone **15** cyclized to benzo[*b*]furan **16** in 88% yield.[11] In this particular example, enolization was further enhanced by the presence of the *β*-ester moiety. Similarly, cyano ketone **17** gave 3-cyano-2-phenylbenzo[*b*]furan (**18**) smoothly. Competitive cyclization of the dibromoketone species **19** only afforded benzo[*b*]furan **20** without benzopyran being detected. Finally, ring closure of aldehyde **21** afforded 3-benzylbenzo[*b*]furan **22** in 92% yield,[12] which represented the first example using an aldehyde for this type of process. It is thus anticipated that this

(9) These substrates can be easily accessed via either the Friedel–Crafts acylation of the 2-halo phenyl acetyl chloride or alkylation/acylation of the 2-halo ketones/esters. See: (a) Friedel, C.; Crafts, J. M. *C. R. Hebd. Seances Acad. Sci.* **1877**, *84*, 1392, 1450. (b) Desage-El, M. M.; Nowczyk, S.; Le Gall, T.; Mioskowski, C.; Amekraz, B.; Moulin, C. *Angew. Chem., Int. Ed.* **2003**, *42*, 1289–1293. (c) Shimizu, S.; Suzuki, T.; Sasaki, Y.; Hirai, C. *Synlett* **2000**, *11*, 1664–1666. (d) Supporting Information.

(10) For a recent example on a highly effective synthetic method for substituted 2-arylbenzofurans using [3,3]-sigmatropic rearrangement, see: Miyata, O.; Takeda, N.; Naito, T. *Org. Lett.* **2004**, *6*, 1761–1763.

(11) Compound **16** was also prepared via the palladium-catalyzed annulation between iodophenol and acetelyne in 69% yield with formation of its regiosiomer in 32% yield, see: Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270–3271.

SCHEME 2. Ring Closure of Bisbromoketone 23



procedure will prove useful for the synthesis of 3-substituted benzo[*b*]furans.

The reaction is believed to proceed via an intramolecular $S_{RN}1$ mechanism where formation of five-membered rings is preferred over the six-membered rings.[6,13] This proposed mechanism is supported by the observation that the process relied on the enolization of the ketone, and also by the exclusive formation of the five-membered ring from ketone **19**. To provide more evidence for the mechanism of this reaction, we prepared substrate **23** by the treatment of ethyl 2-bromophenyl acetate with *t*-BuOK under solvent-free conditions according to a reported procedure.[14] The crude mixture was used directly in the benzo[*b*]furan formation. Though both bromo moieties are available for cyclization to form a benzo[*b*]furan ring, compound **24** was obtained as a sole product, again due to the preferred enolization at C_3 over C_1 (Scheme 2). This example highlights the versatility of our protocol for the synthesis of a highly functionalized benzo[*b*]furan such as **24** from a very simple substrate like 2-bromophenyl acetate.

In summary, we have identified a highly efficient protocol for the synthesis of benzo[*b*]furans via a CuI-catalyzed ring closure of 2-halo aromatic ketones. This process proved to be exceptionally effective with a wide variety of aromatic ketones and can be extended to aromatic aldehydes and heteroaromatic ketones. Many structurally interesting benzo[*b*]furans were readily prepared in a catalytic manner in good to excellent yields; we believe that the broad scope of this reaction will lead to easy access to other structurally diverse substrates.

Experimental Section

2-(4′-Methoxyphenyl)benzo[*b*]furan (7): A mixture of bromoketone **6** (0.61 g, 2 mmol), K_3PO_4 (0.64 g, 3 mmol), and CuI (39.0 mg, 0.2 mmol, 10 mol %) in DMF (5 mL) was degassed via nitrogen/vaccum three cycles and subsequently heated to 105 °C. The mixture was held at the same temperature for 12 h, and then cooled to ambient temperature. Water (20 mL) was added directly to the reaction mixture over 0.5 h to precipitate the product as pale organg solid **7** (0.43 g): mp 154−155 °C (lit.[15] mp 153−155 °C).

2-Tolylbenzo[*b*]furan (8): yellow crystals; mp 128−129 °C (lit.[16] mp 128−129 °C).

2-(4′-Methylsulfanylphenyl)benzo[*b*]furan (9): pale yellow solid; mp 159 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 7.9 Hz, 2H), 7.57 (d, J = 6.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.33 (d, J = 7.9 Hz, 2H), 7.25 (m, 2H), 6.98 (s, 1H), 2.54 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 154.8, 139.3, 129.3, 127.3, 126.5, 125.3, 124.2, 122.9, 120.8, 111.1, 100.9, 15.6. Anal. Calcd for $C_{15}H_{12}OS$: C, 74.97; H, 5.03. Found: C, 74.60; H, 4.92.

2-(2′,4′,6′-Trimethylphenyl)benzo[*b*]furan (10): pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 1H), 7.52 (m, 1H), 7.31 (td, J = 7.6, 1.6 Hz, 1H), 7.27 (td, J = 7.2, 1.6 Hz, 1H), 6.98 (s, 2H), 6.65 (s, 1H), 2.38 (s, 3H), 2.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.1, 154.8, 139.0, 138.4, 128.9, 128.4, 127.7, 123.7, 122.6, 120.7, 111.2, 106.1, 21.2, 20.5; exact mass *m/z* calcd for [M + H] 237.12739, found 237.12799.

2-(3′-Bromophenyl)furo[2,3-*c*]pyridine (12): pale yellow solid; mp 101−103 °C; ^{1}H NMR (400 MHz, CD_2Cl_2) δ 8.86 (s, 1H), 8.39 (d, J = 5.2 Hz, 1H), 8.01 (t, J = 1.7 Hz, 1H), 7.79 (dd, J = 8.0, 1.2 Hz, 1H), 7.52 (m, 2H), 7.33 (t, J = 8.0 Hz, 1H), 7.02 (s, 1H); ^{13}C NMR (100 MHz, CD_2Cl_2) δ 157.6, 152.7, 143.4, 135.6, 134.3, 133.1, 131.9, 131.1, 129.0, 124.7, 123.5, 116.2, 101.9. Anal. Calcd for $C_{13}H_8BrNO$: C, 56.96; H, 2.94. Found: C, 56.49; H, 2.76.

2-(4′-Methoxyphenyl)-3-methylbenzo[*b*]furan (14a): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (m, 2H), 7.53 (m, 1H), 7.48 (m, 1H), 7.29 (td, J = 7.2, 2.0 Hz, 1H), 7.26 (td, J = 7.2, 1.6 Hz, 1H), 7.03 (m, 2H), 3.89 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 153.7, 150.8, 131.35, 128.2, 124.2, 123.9, 122.3, 119.0, 114.1, 110.8, 109.7, 55.3, 9.4; exact mass *m/z* calcd for [M + H] 239.10666, found 239.10754.

3-Benzyl-2-(4′-methoxyphenyl)benzo[*b*]furan (14b): white solid; mp 98−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 2H), 7.51 (d, J = 8.1 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 7.29−7.24 (m, 5H), 7.22 (m, 1H), 7.16 (t, J = 7.6 Hz, 1H), 6.96 (m, 2H), 4.28 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 154.0, 152.3, 139.5, 130.7, 128.6, 128.4, 128.2, 126.3, 124.0, 123.6, 122.5,119.7, 114.2, 112.3, 110.9, 55.3, 30.1. Anal. Calcd for $C_{22}H_{18}O_2$: C, 84.05; H, 5.77. Found: C, 83.69; H, 5.57.

2-Phenylbenzo[*b*]furan-3-carbonitrile (18):[17] pale yellow solid; mp 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (m, 2H), 7.74 (m, 1H), 7.61−7.53 (m, 4H), 7.44 (td, J = 7.2, 1.6 Hz, 1H), 7.40 (td, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$) δ 160.8, 152.6, 130.7, 128.6, 127.0, 126.3, 126.0, 125.7, 124.2, 119.0, 113.4, 111.2, 87.2.

3-(2′-Bromobenzyl)-2-methylbenzo[*b*]furan (20): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (m, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.29 (d, J = 7.6 Hz, 1H), 7.25 (dd, J = 7.2, 1.6 Hz, 1H), 7.21 (dd, J = 6.0, 1.6 Hz, 1H), 7.19−7.08 (m, 4H), 4.11 (s, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.0, 152.1, 138.6, 132.7, 129.9, 129.5, 127.9, 127.4, 124.6, 123.2, 122.2, 119.1, 111.7, 110.6, 30.0, 12.2; exact mass *m/z* calcd for $C_{16}H_{13}BrO$, [M + Ag] 406.9201, found 406.9194.

3-(4′-Chlorobenzyl)benzo[*b*]furan (22): oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (m, 1H), 7.39 (m, 2H), 7.32−7.17 (m, 7H), 4.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 142.2, 127.7, 132.2, 130.0, 128.7, 127.8, 124.4, 122.5, 119.8, 111.5, 29.4; exact mass *m/z* calcd for $C_{15}H_{11}ClO$, [M + Ag] 348.9549, found 348.9549.

Ethyl 2-(2′-bromobenzyl)benzo[*b*]furan-3-carboxylic acid ester (24): colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (m, 1H), 7.61 (dd, J = 7.9, 1.2 Hz, 1H), 7.43 (m, 1H), 7.34 (td, J = 7.2, 1.6 Hz, 1H), 7.31 (td, J = 7.2, 2.0 Hz, 1H), 7.23 (td, J = 7.6, 1.2 Hz, 1H), 7.18 (dd, J = 7.6, 2.0 Hz, 1H), 7.12 (td, J = 7.6, 2.0 Hz, 1H), 4.73 (s, 2H), 4.44 (q, J = 7.2 Hz, 2H), 1.44 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 162.9, 154.0, 136.5, 132.8, 130.4, 128.4, 127.5, 126.0, 124.7, 124.5, 123.9, 122.2, 111.2,

(12) Compound **21** was prepared from the DIBAL-H reduction of the corresponding nitrile in toluene at ambient temperature in 90% yield.

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(16) Colas, C.; Goeldner, M. *Eur. J. Org. Chem.* **1941**, *6*, 1357−1366.

(17) Takagi, K.; Ueda, T. *Chem. Pharm. Bull.* **1972**, *20*, 2053−2056.

110.3, 60.5, 34.5, 14.3; exact mass *m/z* calcd for [M + H] 359.02773, found 359.02949.

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Supporting Information Available: NMR spectra for all new benzo[*b*]furans. This material is available free of charge via the Internet at http://pubs.acs.org.

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