Synthesis of 2,3-Disubstituted Benzofurans from *ortho*-Acylphenols

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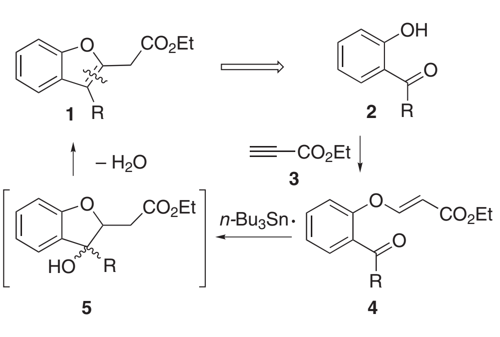
Abstract: 2,3-Disubstituted benzofuran derivatives were synthesized from *ortho*-acylphenols in two steps. The β-aryloxyacrylates prepared from the *ortho*-acylphenols were treated with *n*-Bu_3SnH/AIBN and then with 5% HCl–EtOH to afford 2,3-disubstituted benzofurans.

Key words: benzofurans, cyclizations, dehydrations, phenols, radical reactions

Molecules containing the benzofuran scaffold show a wide range of biological activities.[1] Many synthetic efforts have been devoted to the synthesis of this privileged structure and recently combinatorial approaches to this class of compounds have also been an active research area.[2] General synthetic strategies of this structure include the condensation reactions between ketones (or aldehydes) and several different forms of nucleophiles under acidic or basic conditions.[3] Alternatively, the palladium catalyzed heteroannulation reactions of *ortho*-alkynylphenols under mild conditions have been utilized a lot.[4] Although these methods are commonly employed in the synthesis of benzofuran derivatives, they either require strongly acidic or basic conditions or have difficulties in the introduction of diverse substituent patterns starting from the readily available materials.

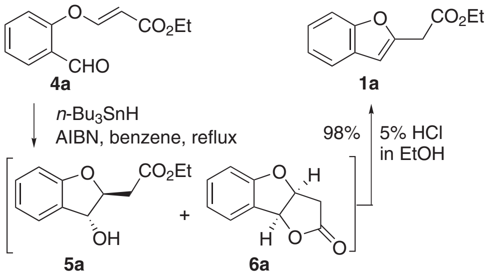


Scheme 1

2,3-Disubstututed benzofurans **1** could be readily synthesized from the *ortho*-acylphenols **2** utilizing the enol ethers **4** as shown in Scheme 1. β-Aryloxyacrylates **4** could be prepared from the reaction between **2** and ethyl propiolate (**3**).[5,6] Radical cyclization of **4** under tin hydride conditions would generate **5** which could be subsequently dehydrated to give benzofurans **1**.[7] Here we report an efficient and mild two-step synthetic method of 2,3-disubstituted benzofuran derivatives from readily available *ortho*-acylphenols.

The β-aryloxyacrylates **4a**–**i** were prepared from *ortho*-acylphenols **2a**–**i**[8] and ethyl propiolate (**3**) according to the literature procedure. The yields for the synthesis of β-aryloxyacrylates **4a**–**i** were uniformly good (90–97%) as shown in Table 1. Sterically less hindered aldehydes **2a** and **2g** (R^3 = H) proved to be slightly better substrates in the *O*-conjugate addition reactions (entries 1 and 7, Table 1).

We then investigated one-pot radical cyclization/dehydration sequence. Treatment of **4a** with tributyltin hydride (1.2 equiv *n*-Bu_3SnH) under standard conditions (cat. AIBN, benzene, 80 °C) produced two products **5a** and **6a** as a mixture (Scheme 2).[5] The direct dehydration of these products into **1a** under the reaction conditions was not observed. Therefore, upon completion of the radical cyclization reaction, the reaction solution was condensed under vacuum to remove benzene and then treated with an acidic ethanol solution. Dehydration reaction was completed with 5% HCl–EtOH in less than 10 minutes and led to the benzofuran **1a** in 98% overall yield.



Scheme 2

Synthesis of 2,3-disubstituted benzofurans were then examined. The results of the synthesis of benzofurans **1a**–**i** are summarized in Table 1. The one-pot radical cyclization and dehydration reactions proved to be efficient for various substrates (93–99%). Substitutions on the aromatic ring (R^1 and R^2) were generally tolerated. Sterically bulky substituents at C-3 position (R^3 = *i*-Bu, Ph) were also successfully introduced in excellent yields (entries 4, 5, 8, and 9). The overall two-step sequence (**2** → **4** → **1**) is a highly efficient synthetic method in terms of overall yields (84–94%) and facile introduction of diverse substituents.

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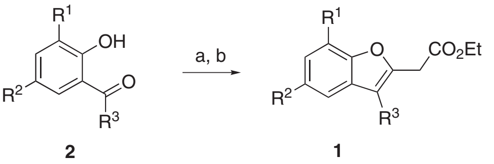
Table 1 Synthesis of Benzofurans from *ortho*-Acylphenols[a]



Entry	**2**	R^1	R^2	R^3	**4** (% yield)	**1** (% yield)
1	**2a**	H	H	H	**4a** (96)	**1a** (98)
2	**2b**	H	H	Me	**4b** (92)	**1b** (97)
3	**2c**	H	H	*n*-Bu	**4c** (92)	**1c** (96)
4	**2d**	H	H	Ph	**4d** (90)	**1d** (99)
5	**2e**	H	H	*i*-Bu	**4e** (91)	**1e** (93)
6	**2f**	H	*t*-Bu	Me	**4f** (90)	**1f** (99)
7	**2g**	OMe	H	H	**4g** (97)	**1g** (96)
8	**2h**	OMe	H	Ph	**4h** (92)	**1h** (99)
9	**2i**	OMe	H	*i*-Bu	**4i** (91)	**1i** (93)

[a] Reagents and conditions: a) 1.2 equiv ethyl propiolate (**3**), 1.2 equiv *N*-methylmorpholine, CH_2Cl_2, 25 °C; b) 1.2 equiv *n*-Bu_3SnH, cat. AIBN, benzene, 80 °C; 5% HCl in EtOH.

In conclusion, we have developed an efficient two-step synthetic method of 2,3-disubstituted benzofuran derivatives starting from readily available *ortho*-acylphenols. Applications of this reaction sequence for the synthesis of complex benzoforan skeletons are under investigation.

Radical Cyclization/Dehydration Reaction; General Procedure

An anhyd benzene (5 mL) solution of **4a** (722 mg, 3.28 mmol), *n*-Bu_3SnH (1.06 mL, 3.94 mmol), and catalytic amount of AIBN (10 mg) was refluxed at 80 °C for 10 h under N_2 atmosphere. The solvent was removed under reduced pressure and the residue was dissolved in 5% HCl in EtOH (3 mL). After 10 min at r.t., the solvent was removed under reduced pressure and purified by column chromatography over silica gel (elution with 10% EtOAc in hexane) to give **1a** (659 mg, 98%) as an oil.

1a

R_f 0.52 (hexane–EtOAc, 3:1).

IR (film): 2960, 2935, 2873, 1747, 1460, 1250, 1194, 1035, 753 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.53–7.51 (m, 1 H), 7.45–7.43 (m, 1 H), 7.26–7.18 (m, 2 H), 6.63 (s, 1 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.82 (s, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.02, 155.05, 150.92, 128.67, 124.04, 122.84, 120.87, 111.19, 105.19, 61.55, 34.86, 14.29.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{13}O_3$: 205.0865; found: 205.0865.

1b

R_f 0.51 (CH_2Cl_2).

IR (film): 2960, 2873, 1765, 1475, 1265, 1199, 1168, 1030 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.48–7.40 (m, 2 H), 7.26–7.21 (m, 2 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 3.78 (s, 2 H), 2.21 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.27, 154.24, 146.21, 130.01, 124.03, 122.34, 119.24, 112.93, 111.06, 61.47, 32.94, 14.30, 8.10.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{15}O_3$: 219.1021; found: 219.1018.

1c

R_f 0.71 (CH_2Cl_2).

IR (film): 2960, 2930, 2863, 1737, 1634, 1460, 1240, 1184, 1163, 1030, 748 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.52–7.40 (m, 2 H), 7.28–7.16 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.77 (s, 2 H), 2.64 (t, *J* = 7.6 Hz, 2 H), 1.79–1.58 (m, 2 H), 1.45–1.30 (m, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H), 0.93 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.28, 154.42, 146.22, 129.39, 123.91, 122.28, 119.57, 117.67, 111.19, 61.45, 33.04, 31.91, 23.48, 22.68, 14.27, 14.07.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}O_3$: 261.1491; found: 261.1494.

1d

R_f 0.74 (CH_2Cl_2).

IR (film): 3042, 2981, 2935, 1732, 1624, 1455, 1194, 1030, 748, 702 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.26–7.25 (m, 9 H), 4.22 (q, *J* = 7.1 Hz, 2 H), 3.87 (s, 2 H), 2.77 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.35, 154.50, 146.83, 132.03, 129.12, 129.03, 128.40, 127.68, 124.55, 122.99, 120.07, 119.94, 111.38, 61.62, 33.55, 14.29.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{17}O_3$: 281.1178; found: 281.1179.

1e

R_f 0.69 (CH_2Cl_2).

IR (film): 3068, 2960, 2935, 2873, 1742, 1455, 1245, 1184, 1035, 753 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.50–7.41 (m, 2 H), 7.27–7.16 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.77 (s, 2 H), 2.51 (d, *J* = 7.2 Hz, 2 H), 2.10–1.93 (m, 1 H), 1.25 (t, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.24, 154.41, 146.84, 129.60, 123.89, 122.27, 119.75, 116.76, 111.15, 61.43, 33.06, 33.00, 28.96, 22.78, 14.26.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}O_3$: 261.1491; found: 261.1493.

1f

R_f 0.74 (CH_2Cl_2).

IR (film): 2965, 2865, 2357, 1749, 1475, 1362, 1262, 1202, 1161, 1028, 814, 654 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44 (s, 1 H), 7.35–7.31 (m, 2 H), 4.18 (q, *J* = 7.1 Hz, 2 H), 3.76 (s, 2 H), 2.21 (s, 3 H), 1.38 (s, 9 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.34, 152.43, 146.28, 145.43, 129.54, 121.93, 115.36, 113.02, 110.37, 61.45, 34.85, 33.02, 32.04, 14.32, 8.16.

HRMS: *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{23}O_3$: 275.1647; found: 275.1649.

1g

R_f 0.56 (CH_2Cl_2).

IR (film): 2991, 2960, 2930, 2878, 2242, 1737, 1460, 1382, 1281, 1189, 1153, 1096, 1030 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.13–7.12 (m, 2 H), 6.78–6.76 (m, 1 H), 6.64 (s, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 4.00 (s, 3 H), 3.84 (s, 2 H), 1.28 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.18, 151.37, 145.50, 144.49, 130.62, 123.79, 113.57, 106.49, 105.82, 61.75, 56.38, 34.94, 14.55.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{15}O_4$: 235.0970; found: 235.0978.

1h

R_f 0.66 (CH_2Cl_2).

IR (film): 2925, 2851, 1742, 1496, 1276 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.54–7.53 (m, 2 H), 7.49–7.37 (m, 3 H), 7.20–7.16 (m, 2 H), 6.84–6.83 (m, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 4.03 (s, 3 H), 3.88 (s, 2 H), 1.26 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 169.27, 147.08, 145.40, 132.10, 130.16, 129.13, 129.01, 127.71, 123.69, 120.44, 112.49, 106.75, 61.56, 56.24, 33.48, 14.29.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{19}O_4$: 311.1283; found: 311.1281.

1i

R_f 0.74 (CH_2Cl_2).

IR (film): 3053, 2955, 2873, 2848, 1737, 1496, 1276, 1214, 1184, 1066, 1035 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.14–7.08 (m, 2 H), 6.78–6.76 (m, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 4.00 (s, 3 H), 3.79 (s, 2 H), 2.49 (d, *J* = 7.2 Hz, 2 H), 2.03–1.98 (m, 1 H), 1.24 (t, *J* = 7.1 Hz, 3 H), 0.94 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.15, 147.08, 145.26, 131.37, 122.98, 117.28, 112.28, 106.23, 61.39, 56.13, 33.14, 33.97, 28.95, 22.77, 14.28.

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{22}O_4$: 290.1518; found: 290.1517.

4a

R_f 0.39 (*n*-hexane–EtOAc, 3:1).

IR (film): 3089, 2991, 2934, 2899, 2873, 1731, 1711, 1650, 1603, 1219, 1194, 1168, 1117, 1035, 759 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.37 (s, 1 H), 7.94–7.90 (m, 1 H), 7.85 (d, *J* = 12.2 Hz, 1 H), 7.69–7.62 (m, 1 H), 7.35–7.29 (m, 1 H), 7.18–7.15 (m, 1 H), 5.64 (d, *J* = 12. Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 188.15, 166.57, 158.03, 157.59, 136.09, 128.97, 126.54, 125.42, 118.33, 104.22, 60.42, 14.33.

4b

R_f 0.35 (*n*-hexane–EtOAc, 3:1).

IR (film): 2981, 2966, 1716, 1685, 1650, 1486, 1450, 1286, 1224, 1132, 1102, 770 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.82–7.74 (m, 2 H), 7.57–7.50 (m, 1 H), 7.29–7.23 (m, 1 H), 7.12–7.08 (m, 1 H), 5.60 (d, *J* = 12.2 Hz, 1 H), 4.19 (q, *J* = 7.1 Hz, 2 H), 2.58 (s, 3 H), 1.28 (t, *J* = 7.1 Hz, 2 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 197.82, 166.76, 158.31, 154.67, 134.02, 130.74, 130.12, 125.42, 118.99, 103.69, 60.41, 31.48. 14.38.

4c

R_f = 0.33 (CH_2Cl_2).

IR (film): 3078, 2960, 2935, 2878, 1716, 1685, 1649, 1603, 1578, 1475, 1445, 1281, 1219, 1163, 1133, 1112, 764 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 12.2 Hz, 1 H), 7.72–7.71 (m, 1 H), 7.53–7.50 (m, 1 H), 7.28–7.25 (m, 1 H), 7.11–7.09 (m, 1 H), 5.59 (d, *J* = 12.2 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 2.90 (t, *J* = 7.2 Hz, 2 H), 1.69–1.61 (m, 2 H), 1.39–1.33 (m, 2 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 201.37, 166.85, 158.49, 154.14, 133.43, 130.84, 130.51, 125.48, 118.93, 103.59, 60.42, 43.31, 26.45, 22.53, 14.42, 14.02.

4d

R_f 0.44 (*n*-hexane–EtOAc, 5:1).

IR (film): 3063, 2976, 2925, 2858, 1711, 1670, 1650, 1481, 1450, 1224, 1117, 927, 769, 702 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.79–7.76 (m, 2 H), 7.65–7.42 (m, 6 H), 7.35–7.29 (m, 1 H), 7.18–7.15 (m, 1 H), 5.30 (d, *J* = 12.2 Hz, 1 H), 4.41 (q, *J* = 7.1 Hz, 2 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 194.75, 166.92, 158.47, 153.34, 137.38, 133.54, 132.47, 130.93, 130.39, 129.89, 128.58, 125.24, 118.62, 103.12, 60.24, 14.39.

4e

R_f 0.36 (*n*-hexane–EtOAc, 5:1).

IR (film): 3088, 2960, 2930, 2868, 1716, 1685, 1649, 1603, 1480, 1450, 1296, 1276, 1224, 1158, 1112, 764 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.77 (d, *J* = 12.3 Hz, 1 H), 7.71–7.68 (m, 1 H), 7.56–7.49 (m, 1 H), 7.30–7.24 (m, 1 H), 7.12–7.08 (m, 1 H), 5.60 (d, *J* = 12.2 Hz, 1 H), 4.21 (q, *J* = 7.1 Hz, 2 H), 2.78 (d, *J* = 6.9 Hz, 2 H), 2.27–2.16 (m, 1 H), 1.29 (t, *J* = 7.1 Hz, 3 H), 0.95 (d, *J* = 6.6 Hz, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 201.11, 166.77, 158.38, 153.91, 133.34, 130.94, 130.33, 125.41, 118.74, 103.47, 60.34, 52.44, 24.97, 22.66, 14.35.

4f

R_f 0.56 (*n*-hexane–EtOAc, 5: 1).

IR (NaCl): 2966, 2914, 2868, 1716, 1685, 1650, 1496, 1368, 1235, 1153, 1102, 1045, 953, 835 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (s, 1 H), 7.77 (d, *J* = 12.2 Hz, 1 H), 7.57–7.55 (m, 1 H), 7.05–7.03 (m, 1 H), 5.58 (d, *J* = 12.2 Hz, 1 H), 4.20 (q, *J* = 7.1 Hz, 2 H), 2.59 (s, 3 H), 1.3 (s, 9 H), 1.29 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (126 MHz, $CDCl_3$): δ = 198.22, 166.86, 158.80, 152.55, 148.62, 131.15, 129.49, 127.43, 118.80, 103.22, 60.35, 34.72, 31.56, 31.34, 14.39.

4g

R_f 0.31 (*n*-hexane–EtOAc, 3:1).

IR (film): 2986, 2950, 2909, 2873, 2838, 1706, 1650, 1634, 1583, 1486, 1322, 1276, 1204, 1178, 1117, 794 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 10.23 (s, 1 H), 7.80 (d, *J* = 12.3 Hz, 1 H), 7.51–7.47 (m, 1 H), 7.35–7.23 (m, 2 H), 5.29 (d, *J* = 12.3 Hz, 1 H), 4.17 (q, *J* = 7.1 Hz, 2 H), 3.90 (s, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 188.33, 166.85, 161.34, 151.36, 145.88, 128.97, 126.80, 119.67, 118.45, 101.09, 60.23, 56.38, 14.31.

4h

R_f 0.20 (*n*-hexane–EtOAc, 5:1).

IR (film): 2925, 2853, 1716, 1675, 1650, 1460, 1322, 1276, 1112, 968, 707 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.79–7.01$ (m, 9 H), 5.11 (d, J = 12.2 Hz, 1 H), 4.10 (q, J = 7.1 Hz, 2 H), 3.89 (s, 3 H), 1.22 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 194.34, 167.12, 161.22, 151.34, 141.39, 137.09, 133.54, 129.93, 128.50, 126.56, 121.01, 114.93, 100.42, 59.95, 56.28, 14.33.

4i

R_f 0.25 (*n*-hexane–EtOAc, 5:1).

IR (film): 3083, 2960, 2930, 2873, 1711, 1655, 1578, 1470, 1373, 1312, 1271, 1184, 1112, 1020, 953, 789, 748 cm^{-1}.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.65 (d, J = 12.3 Hz, 1 H), 7.28–7.09 (m, 3 H), 5.31 (d, J = 12.3 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.87 (s, 3 H), 2.73 (d, J = 6.9 Hz, 2 H), 2.22–2.18 (m, 1 H), 1.27 (t, J = 7.1 Hz, 3 H), 0.94 (d, J = 6.6 Hz, 6 H).

^{13}C NMR (63 MHz, $CDCl_3$): δ = 201.43, 167.22, 161.44, 151.41, 142.04, 133.90, 126.67, 120.90, 115.78, 100.68, 60.20, 56.43, 52.39, 25.01, 22.69, 14.41.

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(8) (a) Substrates **2a**, **2b**, and **2g** were purchased from Aldrich. Substrate **2f** was prepared from 4-*tert*-butylphenol according to the known literature procedure: Bensari, A.; Zaveri, N. T. *Synthesis* **2003**, 267. (b) Other substrates were prepared from salicyl aldehyde and *ortho*-vanillin in two steps [1) RMgBr, THF; 2) MnO_2, benzene].