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<tr>
<td>Author(s)</td>
<td>Yohda, Masaaki; Yamamoto, Yasunori</td>
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<tr>
<td>Citation</td>
<td>Organic &amp; biomolecular chemistry, 13(44): 10874-10880</td>
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HOKKAIDO UNIVERSITY
Enantioselective Addition of Arylboronic Acids to Methyl 2-Formylbenzoates by using a Ruthenium/Me-BIPAM Catalyst for Synthesis of Chiral 3-Aryl-isobenzofuranones

Masaaki Yoshida and Yasunori Yamamoto

Abstract text goes here. The abstract should be a single paragraph that summarises the content of the article.

carbonyl compounds. Herein, we report the synthesis of optically active 3-aryl-isobenzofuranones by using enantioselective addition of arylboronic acids to methyl 2-formylbenzoates. Our initial investigation began by screening catalysts to evaluate their ability to promote enantioselective arylation of methyl 2-formylbenzoate with phenylboronic acid. As shown in Table 1, when [RuCl2(p-cymene)]2, RuCl2(PPh3)3 or RuCl2(nbhd)(MeCN)2 with Me-BIPAM, which were used in our

Table 1. Reaction Conditions

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Base</th>
<th>Solvent</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R,R)-Me-BIPAM</td>
<td>K2CO3</td>
<td>toluene</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R,R)-Me-BIPAM</td>
<td>K2CO3</td>
<td>toluene</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R,R)-Me-BIPAM</td>
<td>KOH</td>
<td>toluene</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R,R)-Me-BIPAM</td>
<td>KOH</td>
<td>toluene</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>5</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R,R)-Me-BIPAM</td>
<td>KOH</td>
<td>toluene</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>RuCl2(PPh3)3</td>
<td>(R,R)-Me-BIPAM</td>
<td>K2CO3</td>
<td>DCE</td>
<td>52</td>
<td>93</td>
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<tr>
<td>7</td>
<td>RuCl2(PPh3)3</td>
<td>(R,R)-Me-BIPAM</td>
<td>K2CO3</td>
<td>toluene</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>8</td>
<td>RuCl2(nbhd)(MeCN)2</td>
<td>(R,R)-Me-BIPAM</td>
<td>K2CO3</td>
<td>toluene</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>RuCl2(PPh3)3</td>
<td>(R,R)-Me-BIPAM</td>
<td>K2CO3</td>
<td>toluene</td>
<td>67</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R)-BINAP</td>
<td>K2CO3</td>
<td>toluene</td>
<td>26</td>
<td>-12</td>
</tr>
<tr>
<td>11</td>
<td>[RuCl2(p-cymene)]2</td>
<td>(R)-Monophos</td>
<td>K2CO3</td>
<td>toluene</td>
<td>70</td>
<td>78</td>
</tr>
</tbody>
</table>

Reactions were carried out at 50-80 °C for 18 h by using methyl 2-formylbenzoates 1a (0.5 mmol), 2a (0.75 mmol), Ru catalyst (0.01 mmol), ligand (0.011 mmol), K2CO3 (0.5 mmol) and toluene/H2O (5/1, 3.0 mL). Isolated yield. *The ee value of 3 was determined by chiral HPLC analysis. †50 °C, 18 h. ‡MeCN (20 mol %) was added.

Optically active 3-substituted isobenzofuranones are important structures in medicinal chemistry as well as in synthetic chemistry. Recently, various methods for the synthesis of these chiral compounds have been developed. Reported methods include lacticization followed by the hydrogenation of the corresponding ketones, intramolecular ketone hydroacylation, aldol reaction, addition reaction, and cyclization reaction.

Over the past decade, transition metal-catalyzed addition reactions of arylboronic acids with 2-formylbenzoates have become useful tools for accessing 3-aryl-isobenzofuranones. However, to our knowledge, there have been only a few reports on the synthesis of optically active 3-aryl-isobenzofuranones using this strategy.

We have already developed a bidentate chiral phosphoramidite (Me-BIPAM) and have used it in ruthenium-catalyzed asymmetric addition of arylboronic acids to various

Figure: Optically active 3-substituted isobenzofuranones are important structures in medicinal chemistry as well as in synthetic chemistry. Recently, various methods for the synthesis of these chiral compounds have been developed. Reported methods include lacticization followed by the hydrogenation of the corresponding ketones, intramolecular ketone hydroacylation, aldol reaction, addition reaction, and cyclization reaction. Over the past decade, transition metal-catalyzed addition reactions of arylboronic acids with 2-formylbenzoates have become useful tools for accessing 3-aryl-isobenzofuranones. However, to our knowledge, there have been only a few reports on the synthesis of optically active 3-aryl-isobenzofuranones using this strategy.

We have already developed a bidentate chiral phosphoramidite (Me-BIPAM) and have used it in ruthenium-catalyzed asymmetric addition of arylboronic acids to various...
previous works, were used for this reaction, addition products were obtained in high yields with high enantioselectivities (entries 2, 7, and 8). Use of KOH and DCE resulted in lower yields (entries 4 and 5). Among the chiral ligands screened, the use of (R)-BINAP (entry 10) and monodentate phosphoramidite, (R)-MonoPhos (entry 11) resulted in lower enantioselectivities, -12% ee and 78% ee, respectively.11

We then studied the substrate scope for various arylboronic acids with [RuCl2(p-cymene)]2- or RuCl2(PPh3)3-Me-BIPAM catalyst (Table 1). Arylboronic acids with electron-donating and -withdrawing groups at para- and meta-positions afforded 3-aryl-isobenzofuranones in high yields with high enantioselectivities in the range of 91–97% ee. The addition of para-biphenyboronic acid and 3-thienylboronic acid resulted in para- enantiomer from X-ray crystallographic analysis of the absolute configuration of the product was assigned as (R)-MonoPhos (entry 11). Use of KOH and DCE resulted in lower enantioselectivities, 85%, 92% ee for the electron-withdrawing arylboronic acids. The structure of [RuCl2(p-cymene)]2 with (R,R)-Me-BIPAM catalyst gave higher enantioselectivities for the electron-donating arylboronic acids. 3-aryl-isobenzofuranones in high yields with high enantioselectivities when the temperature was increased and the solvent ratio of toluene/H2O was changed (entries 5 and 12). The structure of 3aa was confirmed unequivocally by its X-ray crystal structure (entry 12). The absolute configuration of the product was assigned as S enantiomer from X-ray crystallographic analysis of the compound of 3aa (Figure 1).13

From the above results, [RuCl2(p-cymene)]2 with (R,R)-Me-BIPAM catalyst gave higher enantioselectivities for the electron-donating arylboronic acids, but RuCl2(PPh3)3 with (R,R)-Me-BIPAM catalyst gave higher yields and enantioselectivities for the electron-withdrawing arylboronic acids. The structure of [RuCl2(p-cymene)]2 with (R,R)-Me-BIPAM showed cationic complex,14 but the structure of RuCl2(PPh3)3 with (R,R)-Me-BIPAM complex showed neutral complex.15 The difference in reactivity between [RuCl2(p-cymene)]2 and RuCl2(PPh3)3 catalyst is correlated with the electronic effect of the arylruthenium intermediates.

Next, we investigated the substrate scope with focus on substrates on the aromatic ring of methyl 2-formylbenzoates (Table 3). Arylation of methyl 2-formylbenzoates gave the corresponding products in high yields (84–99%) with excellent enantioselectivities (87–97% ee). The arylation product of 5,6-desmethylenedioxy-5-methoxy-aglalactone (3fb) which was isolated from the CHCl3 soluble extract of the leaves and twigs of Aglaia ponapensis exhibit the NF-kB inhibitory activity.12

We propose a possible catalytic cycle of this reaction. The reaction may proceed through transmetalation of an arylboronic acid to a Ru/Me-BIPAM complex giving an Ar-[Ru]. Insertion of the C=O bond of methyl 2-formyl benzoates into the Ar-Ru bond gave the Ru-O intermediate, and then produced 3-aryl-isobenzofuranones by hydrolysis and lactonization (Figure 2). The enantioselectivity is determined at the step of insertion of the C=O bond into an ary ruthenium intermediate. Thus, the S configuration in Tables 1–3 caused by (R,R)-Me-BIPAM is rationalized by the coordination of an methyl 2-formyl benzoate with its Si-face. The si-coordination of the substrate is preferred without significant steric interaction to give the experimentally observed S enantiomer by parallel coordination of the C=O bond to the Ar-Ru bond for the subsequent insertion step (Figure 3).

Table 2. Substrate Scope for the Arylboronic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ar = [Ar-B(OH)]2 catalyst yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C6H5</td>
<td>96</td>
</tr>
<tr>
<td>2*a</td>
<td>4-MeOC6H4</td>
<td>84</td>
</tr>
<tr>
<td>3*a</td>
<td>4-MeC6H4</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>4-CH3=C6H4</td>
<td>93</td>
</tr>
<tr>
<td>5*a</td>
<td>4-PhC6H4</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>4-FC6H4</td>
<td>98</td>
</tr>
<tr>
<td>7</td>
<td>4-ClC6H4</td>
<td>97</td>
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<tr>
<td>8</td>
<td>4-FC6H4</td>
<td>74</td>
</tr>
<tr>
<td>9</td>
<td>2-naphthyl</td>
<td>92</td>
</tr>
<tr>
<td>10</td>
<td>3,5-MeC6H4</td>
<td>99</td>
</tr>
<tr>
<td>11</td>
<td>3-CIC6H4</td>
<td>84</td>
</tr>
<tr>
<td>12*b</td>
<td>3-thienyl</td>
<td>92</td>
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</tbody>
</table>

*aReactions were carried out at 50–80 °C for 18 h by using methyl 2-formylbenzoates 1a (0.5 mmol), 2 (0.75 mmol), Ru catalyst (0.01 mmol), ligand (0.011 mmol), K2CO3 (0.5 mmol) and toluene/H2O (5/1, 3 mL).

*bIsolated yield. The ee value of 3 was determined by chiral HPLC analysis. 

Figure 1. ORTEP diagram of 3aa (ORTEP drawing at 50% ellipsoid probability)
Wako Pure Chemical Industries, Ltd. Phthalide was purchased from commercial source and substituted phthalides were synthesized according to known literature.

Preparation of 2-formylbenzoates

To a solution of phthalides (2.0 mmol) in 10 mL of dry benzene was added NBS (0.41g, 2.2 mmol) and AIBN (0.14 mg, 0.1 mmol) was added at room temperature. Then the mixture was refluxed at 85 °C overnight. It was cooled to room temperature and purified by flash chromatograph (silica gel, petroleum ether and ethyl acetate as eluent). The product was then suspended in 20 mL of H2O and heated to 100 °C. After 1 h, the mixture was cooled to room temperature and then extracted with EtOAc (3×30 mL). The combined extracts were dried over MgSO4, filtered and concentrated under reduced pressure to give a corresponding 2-formylbenzoic acid as a solid. To a solution of the corresponding 2-formylbenzoic acid in acetone were added Me2SO4 (0.126 g, 1 mmol) and K2CO3 (0.276 g, 2 mmol). After stirring for 2 h at room temperature, the mixture was refluxed for 1 h and cooled to ambient temperature, filtered and washed with acetone (3×15 mL). The combined filtrates were concentrated in vacuo and the residue was purified by flash chromatography (silica gel, eluent: petroleum/ethyl acetate = 20:1) to give methyl 2-formylbenzoate.

General Procedure for Ruthenium/Me-BIPAM catalyzed Asymmetric Arylation of 2-formylbenzoates with Arylboronic Acids

A flask was charged with Ruthenium catalyst (0.01 mmol, 2 mol%) and Me-BIPAM (0.011 mmol, 2.2 mol%) under nitrogen atmosphere. Toluene (2.5 ml) was added and the mixture was stirred at room temperature for 30 min. Phenylboronic acid (0.75 mmol), 2-formylbenzoate (0.5 mmol), K2CO3 (0.5 mmol) and H2O (0.5 ml) were then added to this catalyst solution. The reaction mixture was then heated at 50 °C for 18 h. The mixture was quenched with aqueous saturated NH4Cl, extracted with AcOEt, dried over MgSO4, filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 7/1 to 5/1) to afford pure 3-aryl-2-hydroxy-benzofuran-2-one.

Conclusions

In summary, we have developed a ruthenium/Me-BIPAM-catalyzed addition of arylboronic acids to methyl 2-formylbenzoates for enantioselective synthesis of 3-aryl-isobenzofuranones. Various substituted chiral 3-aryl-isobenzofuranones were obtained with excellent enantioselectivities (87-97 % ee).

Experimental

General methods

1H–NMR spectra were recorded on a JEOL ECX-400 (400 MHz) or JEOL ECS-400 (400 MHz) in CDCl3 with tetramethylsilane (δ = 0.00) as internal standard. Chemical shifts are reported in part per million (ppm), and signal are expressed as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). 13C–NMR spectra were recorded on a JEOL ECX-400 (400 MHz) or JEOL ECS-400 (400 MHz) in CD2Cl2 with tetramethylsilane (δ = 0.00) as internal standard. Chemical shifts are reported in part per million (ppm). HPLC analysis was directly performed with chiral stationary phase column, Chiralpak AD–H or Chiralcel OD–H purchased from DAICEL Co., Ltd. High resolution mass spectra (HRMS) were recorded on a JEOL JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University. Optical rotations were measured on JMS 700TZ mass spectrometer at the Center for Instrumental Analysis, Hokkaido University.

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General Procedure for Ruthenium/Me-BIPAM catalyzed Asymmetric Amination of 2-formylbenzoates with Arylboronic Acids

A flask was charged with Ruthenium catalyst (0.01 mmol, 2 mol%) and Me-BIPAM (0.011 mmol, 2.2 mol%) under nitrogen atmosphere. Toluene (2.5 ml) was added and the mixture was stirred at room temperature for 30 min. Phenylboronic acid (0.75 mmol), 2-formylbenzoate (0.5 mmol), K2CO3 (0.5 mmol) and H2O (0.5 ml) were then added to this catalyst solution. The reaction mixture was then heated at 50 °C for 18 h. The mixture was quenched with aqueous saturated NH4Cl, extracted with AcOEt, dried over MgSO4, filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 7/1 to 5/1) to afford pure 3-aryl-2-hydroxy-benzofuran-2-one.

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A flask was charged with Ruthenium catalyst (0.01 mmol, 2 mol%) and Me-BIPAM (0.011 mmol, 2.2 mol%) under nitrogen atmosphere. Toluene (2.5 ml) was added and the mixture was stirred at room temperature for 30 min. Phenylboronic acid (0.75 mmol), 2-formylbenzoate (0.5 mmol), K2CO3 (0.5 mmol) and H2O (0.5 ml) were then added to this catalyst solution. The reaction mixture was then heated at 50 °C for 18 h. The mixture was quenched with aqueous saturated NH4Cl, extracted with AcOEt, dried over MgSO4, filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 7/1 to 5/1) to afford pure 3-aryl-2-hydroxy-benzofuran-2-one.

General Procedure for Ruthenium/Me-BIPAM catalyzed Asymmetric Amination of 2-formylbenzoates with Arylboronic Acids

A flask was charged with Ruthenium catalyst (0.01 mmol, 2 mol%) and Me-BIPAM (0.011 mmol, 2.2 mol%) under nitrogen atmosphere. Toluene (2.5 ml) was added and the mixture was stirred at room temperature for 30 min. Phenylboronic acid (0.75 mmol), 2-formylbenzoate (0.5 mmol), K2CO3 (0.5 mmol) and H2O (0.5 ml) were then added to this catalyst solution. The reaction mixture was then heated at 50 °C for 18 h. The mixture was quenched with aqueous saturated NH4Cl, extracted with AcOEt, dried over MgSO4, filtered, and the solvents were evaporated. The crude product was purified by flash column chromatography (Hexane/AcOEt = 7/1 to 5/1) to afford pure 3-aryl-2-hydroxy-benzofuran-2-one.
(S)-3-(4-methylphenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ae).21 White solid; mp 133–134 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(4-phenylphenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ad).11e,11f White solid; mp 128–132 ºC; m/z: (ES) [M]+ c; 229.06; 228.06 (57); HRMS (EI) found: 228.063709; 228.063025; 228.05473;

(S)-3-(3,5-dimethylphenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3aj).11f White solid; mp 115 ºC; m/z: (ES) [M]+ c; 239.05; 238.05 (107 mg); [α]25 = +54.0 (c 0.50, CHCl3), 96% ee [lit. [α]25 = +18.8 (c 0.07, CHCl3), 67% ee (S)11] [HPLC condition: Chiralcel OD-H column, hexane:2-propanol = 90/10, flow = 0.5 ml/min, wavelength = 230 nm, tR = 16.3 min (major)];

(S)-3-(3-phenylphenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3af).21 White solid; mp 132 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(3-phenylphenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ae).21 White solid; mp 139–142 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(3-phenylphenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ad).21 White solid; mp 249–251 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(3-fluorophenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3af).21 White solid; mp 121–124 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(4-fluorophenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ae).21 White solid; mp 156–159 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(4-chlorophenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ag).21 White solid; mp 128–133 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(3-thiophen-3-yl)-1,3-dihydropyridine-2-benzofuran-1-one (3as).21 White solid; mp 91–93 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(3-chlorophenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3aj).11e,11f White solid; mp 118–121 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(3-trifluoromethyl)phenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ah).21 White solid; mp 118–121 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;

(S)-3-(4-chlorophenyl)-1,3-dihydropyridine-2-benzofuran-1-one (3ad).21 White solid; mp 149–150 ºC; m/z: (ES) [M]+ c; 239.07; 238.07; 191.09 (20); 209.05 (10); 236.08 (100); MS (EI) found: 244.028509; 244.02859;
MHz, CDCl3; δ = 7.96 (d, J = 7.3 Hz, 1H), 7.69 (t, J = 7.3 Hz, 1H), 7.58 (t, J = 7.5 Hz, 1H), 7.43 (d, J = 7.8 Hz, 1H), 7.36–7.33 (m, 2H), 6.96–6.34 (m, 1H), 6.52 (s, 1H), 1.13 ppm (major) and 32.4 min (minor); 1H NMR (400 MHz, CDCl3); δ = 7.75 (s, 1H), 7.46 (d, J = 7.8 Hz, 1H), 7.38–7.36 (m, 3H), 7.28–7.26 (m, 2H), 7.21 (d, J = 7.8 Hz, 1H), 6.37 (s, 1H), 2.47 (s, 3H); 13C NMR (100 MHz, CDCl3); δ = 170.61, 147.01, 139.55, 136.54, 135.42, 129.10, 128.81, 126.84, 125.59, 125.40, 122.47, 82.52, 21.16; MS (EI) m/z 41.04 (16), 91.05 (16), 105.02 (13), 119.04 (100), 147.03 (13), 165.05 (25), 178.06 (9), 224.06 (52); HRMS (El) m/z caled for C16H13O2 [M]+: 224.08373, found: 224.08364. 

(-)-5-methyl-1,3-dihydro-2-benzofuran-1-one (3fa). White solid; mp 138–141 ºC; 87% yield (110 mg); [α] D 25 = +17.0 (c 0.50, CHCl3), 95% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t R = 19.6 min (major) and 24.3 min (minor)]; 1H NMR (400 MHz, CDCl3); δ = 7.84 (d, J = 7.8 Hz, 1H), 7.41–7.34 (m, 4H), 7.29–7.26 (m, 2H), 7.11 (s, 1H), 6.35 (s, 1H), 2.44 (s, 3H); 13C NMR (100 MHz, CDCl3); δ = 170.54, 158.18, 150.49, 135.52, 130.45, 129.11, 128.84, 126.92, 125.23, 123.01, 122.80, 82.35, 21.96; MS (EI) m/z 43.99 (16), 77.03 (14), 91.05 (20), 119.04 (100), 147.03 (12), 165.05 (26), 178.06 (9), 195.06 (6), 224.06 (45); HRMS (El) m/z caled for C16H14O2 [M]+: 224.08373, found: 224.08364.

(-)-6-chloro-1,3-dihydro-2-benzofuran-1-one (3ia). White solid; mp 102–106 ºC; 87% yield (106 mg); [α] D 25 = +17.0 (c 0.50, CHCl3), 95% ee [HPLC condition: Chiralcel OD-H column, hexane/2-propanol = 90/10, flow = 0.5 mL/min, wavelength = 230 nm, t R = 19.7 min (major) and 24.4 min (minor)]; 1H NMR (400 MHz, CDCl3); δ = 7.84 (d, J = 7.8 Hz, 1H), 7.41–7.34 (m, 4H), 7.29–7.26 (m, 2H), 7.11 (s, 1H), 6.35 (s, 1H), 2.44 (s, 3H); 13C NMR (100 MHz, CDCl3); δ = 170.54, 158.18, 150.49, 135.52, 130.45, 129.11, 128.84, 126.92, 125.23, 123.01, 122.80, 82.35, 21.96; MS (EI) m/z 43.99 (16), 77.03 (14), 91.05 (20), 119.04 (100), 147.03 (12), 165.05 (26), 178.06 (9), 195.06 (6), 224.06 (45); HRMS (El) m/z caled for C16H14O2 [M]+: 224.08373, found: 224.08364.

Notes and references


2 Selected examples of chiral 3-aryl-isobenzofuranones see: (a) J. P. Clayton, M. Cole, S. W. Elson, H. Ferres, J. C. Hanson, L. W. Mizen and R. Sutherland, *J. Med. Chem.* 1976, 19, 1385–1391; (b) M. Azuma, K. Hori, Y. Ohashi,