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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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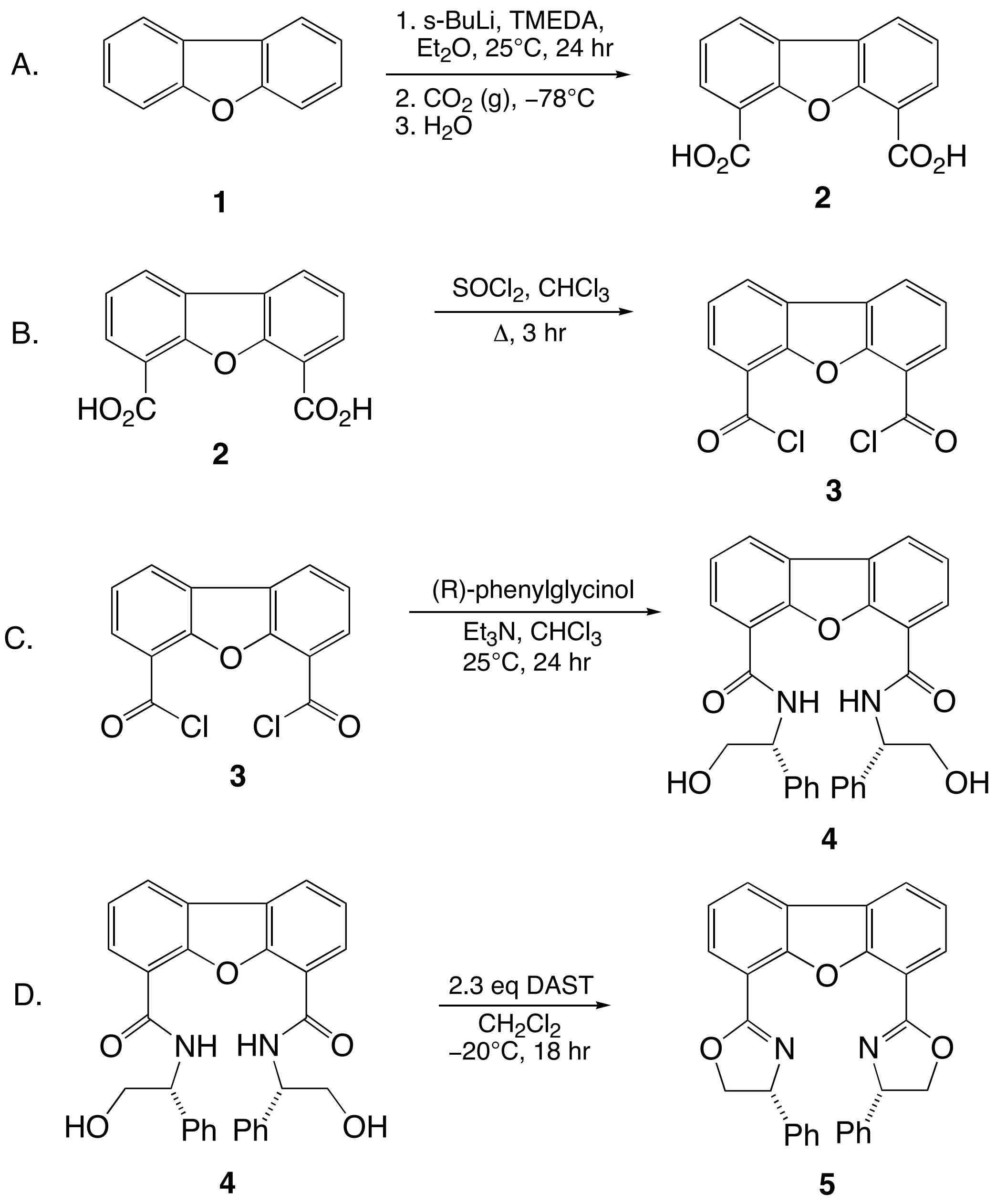
SYNTHESIS OF (*R,R*)-4,6-DIBENZOFURANDIYL-2,2'-BIS (4-PHENYLOXAZOLINE) (DBFOX/PH) – A NOVEL TRIDENTATE LIGAND

[[Oxazole, 2,2'-(4,6-dibenzofurandiyl)bis(4,5-dihydro-4-phenyl-, (4*R*,4'*R*)-]]



Submitted by Ulrich Iserloh, Yoji Oderaotoshi, Shuji Kanemasa, and Dennis P. Curran.[1]
Checked by Richard S. Gordon and Andrew B. Holmes.

1. Procedure

*A. Dibenzofuran-4,6-dicarboxylic acid (**2**).*[2] A 1-L, three-necked, round-bottomed flask (Note 1) is fitted with a large magnetic stirbar. Under argon, the flask is charged with 350 mL of dry, freshly distilled diethyl ether, 10.0 g (59.4 mmol) of dibenzofuran (Notes 2, 3) and 27 mL (179 mmol) of tetramethylethylenediamine (TMEDA). The mixture is cooled to −78 °C (bath temperature) with a dry ice/acetone bath, and stirred (Note 4) while 137 mL (178 mmol) of *sec*-butyllithium is added over 1 h via cannula and syringe (Note 5). After warming the reaction mixture to 25 °C, the suspension is stirred for 24 h. The mixture is cooled again to −78 °C under vigorous stirring and gaseous carbon dioxide (CO_2) (Note 6) is introduced over 1 h; the reaction mixture is then warmed to 25 °C over 4 h under a constant CO_2 stream (Note 7). After decanting the supernatant liquid, a brown solid is isolated by filtration using a Buchner funnel (Note 8). The residue is washed with 300 mL of diethyl ether and then suspended in 200 mL water, acidified with aqueous 2N HCl to pH 3, and stirred for 1 h. After filtration, the beige solids are washed first with 400 mL of water and then with 200 mL of diethyl ether. The solids are dried under vacuum over phosphorus pentoxide (P_2O_5) for three days to yield 14.5 g (96%) of the title compound **2** (Note 9).

B. Dibenzofuran-4,6-dicarbonyl chloride (**3**): A 250-mL, three-necked flask (Note 1), equipped with a magnetic stirbar, condenser, thermometer, and addition funnel, is charged with 5.0 g (19.6 mmol) of diacid **2** and 68 mL of chloroform ($CHCl_3$) (Note 10). At 25 °C, 44 mL (600 mmol) of thionyl chloride (Note 2) and 1 drop of dimethylformamide (DMF) are added, followed by heating the mixture at 68 °C for 3 h. After the initial suspension turns into a yellow solution (Note 11), the heating source is removed and the diacid chloride **3** precipitates as a white solid. After cooling the reaction mixture to 25 °C, the solid is collected via filtration using a Buchner funnel, washed with $CHCl_3$ (Note 12), and dried in a vacuum desiccator for 15 h to give 5.12 g (90%) of **3** as a white powder (Note 13).

C. (R,R)-Dibenzofuran-4,6-dicarboxylic acid bis(2-hydroxy-1-phenylethyl) amide (**4**): A 250-mL, three-necked flask (Note 1), equipped with a magnetic stirbar, is charged with 5.00 g (17.07 mmol) of diacid chloride **3** and 135 mL of freshly distilled $CHCl_3$. After cooling the suspension to 0 °C under nitrogen, a solution of 5.18 g (37.74 mmol) of (*R*)-phenylglycinol (Note 2) and 5.26 mL (37.74 mmol) of triethylamine (Et_3N) in 25 mL of $CHCl_3$ (Note 14) is added over 2 h via an addition funnel (Note 15). After the reaction mixture is stirred for 15 h at 25 °C, $CHCl_3$ (100 mL) and solid ammonium chloride (5 g) is added and the suspension is stirred for a further 0.5 h (Note 16). The suspension is filtered and the residue is washed with $CHCl_3$ (3 × 50 mL). The residue is put aside for suspension in tetrahydrofuran (THF). The combined filtrate and washings are evaporated to dryness under reduced pressure. The resulting residue is purified by two recrystallizations from ethyl acetate/hexane (ca. 9:1) to give the amide **4** (combined yield 5.2 g, 61.0%). The mother liquor from the recrystallizations is chromatographed using silica gel (eluting with ethyl acetate/hexanes initially in a 1:1 ratio and increasing to 4:1, then 1:0) to give more amide **4** (0.6 g, 7.0%). The original solid residue, obtained from the filtration, is suspended in THF (200 mL); the slurry is stirred using a magnetic stirbar for 30 min. The product is filtered. The THF extraction of this residue is repeated (Note 17) and the filtrates are combined. Removal of the solvent under reduced pressure afforded additional amide **4**, which was recrystallized as before (1.7 g, 20.0%). The overall yield of amide **4** is 5.9-7.5 g (11.9-14.9 mmol, 70-88%) (Note 18).

D. Caution! Diethylaminosulfur trifluoride is a powerful corrosive and reacts violently with water. Appropriate precautions should be taken whenever it is handled, since one of its decomposition products is hydrofluoric acid.

(R,R)-4,6-Dibenzofurandiyl-2,2'-bis(4-phenyloxazoline), DBFOX/Ph (**5**): A 100-mL, one-necked flask (Note 1) equipped with a magnetic stirbar is charged with 2.40 g (4.85 mmol) of **4** and 50 mL of dichloromethane (CH_2Cl_2). After the suspension is cooled (Note 19) to −20 °C, 1.49 mL (11.28 mmol) of diethylaminosulfur trifluoride (DAST, (Note 2)) is slowly added via syringe. After 18 h at −20 °C, 4 mL of aqueous 4N ammonium hydroxide (NH_4OH) is added and the resulting solution is stirred for 15 min at −20 °C. Subsequently, the cooling bath is removed and 10 mL of water is added. The orange aqueous phase is extracted with CH_2Cl_2 (3 × 15 mL) and the combined organic phases are dried over magnesium sulfate ($MgSO_4$) and concentrated under vacuum. The resulting material is chromatographed using silica gel (20% EtOAc/hexanes, (Note 20)) to yield 2.10 g (4.59 mmol,

94%) of **5** as an off-white foam. This foam can be recrystallized from EtOAc/hexanes to yield white crystals (Notes 21-23).

2. Notes

1. The checkers dried all glassware at 120 °C for at least 2 h, and cooled under argon where appropriate. The submitters dried all glassware at 140 °C for at least 4 h and cooled to 25 °C under a flow of argon. Solvents were distilled from the indicated drying agent and were used immediately: dichloromethane (CaH_2), diethyl ether and tetrahydrofuran (sodium/benzophenone), chloroform (potassium carbonate), and triethylamine (KOH).

2. Dibenzofuran (99%), sec-butyllithium (1.3 M in cyclohexane), *N,N,N′,N′*-tetramethylethylenediamine (99%), *N,N*-dimethylformamide (anhydrous, 99.8%), (*R*)-(−)-2-phenylglycinol (98%) and (diethylamino)sulfur trifluoride (DAST) were purchased from Aldrich Chemical Company, Inc. Thionyl chloride (99.5%) was purchased from Acros Organics and carbon dioxide (commercial grade) was purchased from Matheson Gas Products Inc. Except for dibenzofuran, all reagents were used as received.

3. Commercial dibenzofuran was not purified. The checkers used recrystallized and commercial dibenzofuran as received in separate experiments with no significant difference in yield.

4. The submitters used a large stirbar followed by a mechanical stirrer (upon introduction of CO_2) to ensure efficient stirring throughout. After initial experiments, the checkers carried out the whole procedure using a powerful magnetic stirrer (and a large magnetic stirbar) with no adverse effect on yield. The checkers observed no improvement in yield when a half-scale reaction was carried out using a mechanical stirrer.

5. To transfer 137 mL of sec-butyllithium, the contents of an entire 100-mL Sure/Seal™ bottle were transferred via cannula, while the remaining 37 mL were transferred via syringe from another bottle.

6. Carbon dioxide was dried by passing the gas through a gas-washing bottle (equipped with a fritted cylindrical gas-dispersion tube)

containing concentrated sulfuric acid. For safety reasons, empty gas-washing bottles were placed before and after the H_2SO_4-containing bottle. The gas was introduced into the flask through a wide pipette (0.8 cm i. d.) which was submerged below the level of the reaction mixture. The checkers observed very little difference in yield irrespective of whether the inlet tube was above or below the surface of the reaction mixture.

7. The beige-colored suspension turned white upon introduction of carbon dioxide. The submitters adjusted the rate of addition such that the internal temperature remained below −65 °C. At −25 °C, the white suspension turned red-brown. The checkers did not monitor the internal temperature of the reaction, but ensured that the CO_2 addition was slow and constant.

8. The yellow supernatant/filtrate comprises TMEDA in Et_2O, while the remaining solid is the lithiocarboxylate of diacid **2**. No precaution was taken during filtration to exclude air or moisture.

9. The submitters obtained 15.1 g (99%). Data for **2**: ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.53 (dd, 2 H, *J* = 7.5 and 7.5), 8.04 (d, 2 H, *J* = 7.5), 8.44 (d, 2 H, *J* = 7.5), 13.30 (bs, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.9, 123.7, 124.9, 126.2, 130.4, 154.6, 165.7; IR (solid phase) cm^{-1}: 2858, 1686, 1431, 1305, 1288, 1154; MS (EI) *m/z* 256 (M^+, 15), 181 (15), 69 (100); HRMS (ES, M + Na^+) *m/z* Calcd for $C_{14}H_8O_5Na$ 279.0264. Found 279.0269, Anal. Calcd for $C_{14}H_8O_5$: C, 65.6; H, 3.1. Found: C, 65.1; H, 3.2. The submitters reported mp 324-325 °C. The checkers could not obtain a mp for this material, but observed decomposition at temperatures > 320 °C (lit.[4] > 300 °C).

10. The checkers carried out the reaction with undistilled chloroform, with no difference in yields.

11. Although the solution is yellow, the reaction mixture remained cloudy throughout.

12. It is important not to use too much chloroform because the product is sparingly soluble.

13. The submitters obtained 5.0 g (87%). Data for **3**: mp 242-244 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, 2 H, *J* = 5 and 5), 8.31 (dd, 2 H, *J* = 5 and 1), 8.33 (dd, 2 H, *J* = 5 and 1); ^{13}C NMR (100 MHz, DMSO-d_6) δ 119.3, 123.9, 124.8, 127.7, 132.6, 163.4, 168.2; IR (solid phase) cm^{-1}: 1757, 1622, 1587, 1474, 1425, 1236, 1184, 1142; MS (EI) *m/z* 292 (M^+, 40), 257

(40), 169 (20), 119 (20); HRMS (EI, M$^+$) *m/z* Calcd for $C_{14}H_6Cl_2O_3$ 291.9694. Found: 291.9699; Anal. Calcd for $C_{14}H_6Cl_2O_3$: C, 57.5; H, 2.1. Found: C, 56.7; H, 2.1.

14. The checkers had to carefully warm the contents in the addition funnel (using a heat gun) to completely dissolve the (*R*)-(−)-2-phenylglycinol. The contents of the funnel were allowed to cool before addition to the reaction mixture.

15. The submitters observed that slow addition is necessary to avoid formation of a thick gel-like slurry and noted that adding additional $CHCl_3$ is beneficial if the slurry[3] is too viscous to stir. The submitters observed (over the course of 15 h) the formation of a thick slurry which in turn became a free flowing white suspension. The checkers observed the immediate formation of a clear yellow solution, which became cloudy, and sometimes a thick slurry, during the course of the reaction.

16. The product is partially soluble in $CHCl_3$ and additional $CHCl_3$ is added to recover as much product as possible. However, significant product still remains undissolved.

17. The submitters omitted the extraction of the first residue (which consists of triethylamine hydrochloride, excess ammonium chloride (NH_4Cl) and amide **4**) with THF, but the checkers found this essential in order to obtain the higher yield (88%) reported. To recover all amide **4**, it is necessary to repeat the procedure, because the product requires extended periods to dissolve completely. As an alternative work up procedure, the checkers removed the $CHCl_3$ under reduced pressure and stirred the reaction mixture in THF (250 mL containing ca. 5 g of NH_4Cl) for 1 h. After filtration of the suspension, recovery of **4** was poor (3.6 g from two recrystallizations).

18. The submitters obtained 7.4 g (87%) of **4**. Data for **4**: mp 185-186 °C; ^{1}H NMR (250 MHz, DMSO-d_6) δ 3.66-3.81 (m, 4 H, $C\underline{H}_2OH$), 4.98 (t, 2 H, *J* = 5, $CH_2O\underline{H}$), 5.20 (dd, 2 H, *J* = 7 and 14, $C\underline{H}Ph$), 7.16-7.27 (m, 6 H), 7.42-7.60 (m, 6 H), 8.00 (dd, 2 H, *J* = 1 and 8), 8.36 (dd, 2 H, *J* = 1 and 8), 8.81 (d, 2 H, *J* = 8, $PhCHN\underline{H}$); ^{13}C NMR (63 MHz, DMSO-d_6) δ 56.5, 65.3, 120.1, 123.9, 124.4, 124.7, 127.4, 127.6, 128.2, 128.7, 141.3, 153.1, 163.8; IR (solid phase) cm^{-1}: 3365, 3278, 1636, 1571, 1530, 1339, 1290, 1190, 1029; MS (ES) *m/z* 517 (M+Na$^+$, 40), 495 (M+H, 100), 375 (50), 255 (25); HRMS (ES, M + Na$^+$) *m/z* Calcd for $C_{30}H_{26}N_2O_5Na$: 517.1739. Found:

517.1732; Anal. Calcd for $C_{30}H_{26}N_2O_5$: C, 72.9; H, 5.3; N, 6.0. Found: C, 72.5; H, 5.4; N, 5.7.

19. The checkers used an electrical refrigeration bath to maintain this reaction temperature.

20. The silica gel is stirred for 30 min in 20% EtOAc/hexanes containing 5% (v/v) Et_3N prior to packing the column. Before applying the crude material, the column was equilibrated with 20% EtOAc/hexanes to remove excess Et_3N.

21. Data for recrystallized **5**: R_f (**5**) = 0.19 (40% EtOAc/hexanes), mp 126-127 °C (submitters observed mp 125.0-126 °C, lit.[4] 134.0-135 °C), $[\alpha]_D^{23}$ +46.92 (c 0.97, $CHCl_3$) [submitters observed $[\alpha]_D^{23}$ +50.75 (c 1.07, $CHCl_3$)]; [lit.[4] +47.75 (c 1.07 $CHCl_3$)], ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.38 (br t, 2 H, *J* = 8), 4.96 (dd, 2 H, *J* = 10 and 10), 5.54 (dd, 2 H, *J* = 9.5 and 9.5), 7.23-7.45 (m, 12 H), 8.10-8.19 (m, 4 H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 69.9, 74.9, 113.1, 123.2, 124.0, 124.9, 126.9, 127.6, 128.8, 142.4, 154.4, 162.4; IR (solid phase) cm^{-1}: 1642, 1424, 1412, 1283, 1184, 1120, 1072; MS (ES) *m/z* 459 (M+H, 95), 253 (10); HRMS (ES, M + H) *m/z* Calcd for $C_{30}H_{22}N_2O_3Na$: 459.1708. Found: 459.1721. Anal. Calcd for $C_{30}H_{22}N_2O_3$: C, 78.6; H, 4.8; N, 6.1. Found: C, 78.5; H, 4.8; N, 6.1.

22. The checkers also prepared (*S,S*)-**5** over two steps according to the same procedure from the reaction of **3** with (*S*)-(−)-2-phenylglycinol purchased from Aldrich Chemical Co., Inc. In addition to the spectroscopic properties of (*S,S*)-**5** which were identical to those reported above for the (*R,R*)-enantiomer, the checkers observed mp 126.0-127 °C, $[\alpha]_D^{23}$ −43.20 (c 1.00, $CHCl_3$).

23. The enantiomeric purities of (*R,R*)-**5** and (*S,S*)-**5** were measured separately by courtesy of Mr. Eric Hortense (GlaxoSmithKline, Stevenage). Chiral HPLC analysis [25 cm Chiracel OD-H, column no. ODHOCE-IF029, mobile phase ethanol/heptane 1:4 (v/v), UV detector at 215 nm, flow rate 1.0 mL/min at 25 °C] of (*R,R*)-**5** yielded a retention time of 7.4 min, while that of enantiomer (*S,S*)-**5** showed a retention time of 8.7 min. The enantiomeric ratio of (*R,R*)-**5** was in excess of 99.5:0.5, while that of (*S,S*)-**5** was also >99.5:0.5. The submitters determined the enantiomeric purity of (*R,R*)-5 as 99% ee by chiral HPLC on a Chiracel OD column (7% 2-propanol/hexanes, 1 mL/min, t(R) = 45 min, t(S) = 65 min).[4]

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academic Press; Washington, DC, 1995.

3. Discussion

(*R,R*)-4,6-Dibenzofurandiyl-2,2'-bis(4-phenyloxazoline), DBFOX/Ph (**5**), is a novel tridentate bisoxazoline ligand developed by Kanemasa and coworkers[5] that has been successfully used as a chiral Lewis acid in enantioselective Diels-Alder-reactions, nitrone cycloadditions and conjugate additions of radicals[6] and thiols[7] to 3-(2-alkenoyl)-2-oxazolidinones. Representative examples for cycloadditions using the $Ni(ClO_4)_2 \cdot 6H_2O$ derived complex are shown below.

The procedure described here is a variant of the original preparation[5] that offers the following advantages:

(1) The overall yield of the four-step ligand preparation is increased from 28% to 71%. The improved dicarboxylation of 4,6-dilithiodibenzofuran significantly contributes to this yield increase. Originally, the dilithiated dibenzofuran was quenched with dry ice (solid CO_2), which presumably led to competitive protonation and ketone formation. In this procedure, dry CO_2 is introduced as a gas and gives a quantitative yield of dicarboxylated material **2**.

(2) The original protocol was not amenable for scale-up. The current procedure performs reliably on a 2-5 gram scale.

(3) All intermediates are purified by recrystallization. This provides for clean bis(2-hydroxy-1-phenylethyl) amide **4**, which is essential for the excellent yields obtained in the final cyclodehydration.

(4) The DAST-mediated cyclodehydration gives higher yields of DBFOX than the original base-mediated cyclization.

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2. We acknowledge Professor X. Zhang, The Pennsylvania State University, for helpful suggestions and we also thank Dr. Ana Gabarda for helping with Step A. The dilithiation of dibenzofuran has been previously reported: (a) Haenel, M. W.; Jakubik, D.; Rothenberger, E.; Schroth, G. *Chem. Ber.* **1991**, *124*, 1705; (b) Jean, F.; Melnyk, O.; Tartar, A. *Tetrahedron Lett.* **1995**, *36*, 765.

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4. Gel formation was also observed by other researchers: Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3079.

5. Kanemasa, S.; Oderaotoshi, Y.; Tanaka, J.; Wada, E. *J. Am. Chem. Soc.* **1998**, *120*, 12355.

6. Iserloh, U.; Curran, D. P.; Kanemasa, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2417.

7. Kanemasa, S.; Oderaotoshi, Y.; Wada, E. *J. Am. Chem. Soc.* **1999**, *121*, 8675.

Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

(*R,R*)-4,6-Dibenzofurandiyl-2,2'-*bis*(4-phenyloxazoline) (DBFOX/PH): Oxazole, 2,2'-(4,6-dibenzofurandiyl)bis(4,5-dihydro-4-phenyl-, (4*R*,4'*R*- (9); (195433-00-2)

Dibenzofuran: (8,9); (132-64-9)

sec-Butyllithium: Lithium, (1-methylpropyl)- (9); (598-30-1)

N,N,N′,N′-Tetramethylethylenediamine, 1,2-Ethanediamine, *N,N,N′,N′*-tetramethyl- (9); (110-18-9)

Carbon dioxide: (8,9); (124-38-9)

Dibenzofuran-4,6-dicarboxylic acid: 4,6-Dibenzofurandicarboxylic acid (9); (88818-47-7)

Thionyl chloride (8,9); (7719-09-7)

N,N-Dimethylformamide: Formamide, *N,N*-diethyl- (8,9); (68-12-2)

Dibenzofuran-4,6-dicarbonyl chloride: 4,6-Dibenzofurandicarbonyl dichloride (9); (151412-73-8)

(*R*)-(−)-2-Phenylglycinol: Benzeneethanol, β-amino-, (β*R*)- (9); (56613-80-0)

Triethylamine: Ethanamine, *N,N*-diethyl- (9); (121-44-8)

Diethylaminosulfur trifluoride (DAST): Sulfur, (*N*-ethylethanaminato)trifluoro-, (T-4) (9); (38078-09-0)

(*R,R*)-Dibenzofuran-4,6-dicarboxylic acid bis(2-hydroxy-1-phenylethyl) amide: 4,6-Dibenzofurandicarboxamide, *N,N′*-bis[(1*R*)-2-hydroxy-1-phenylethyl]- (9); (247097-79-6)