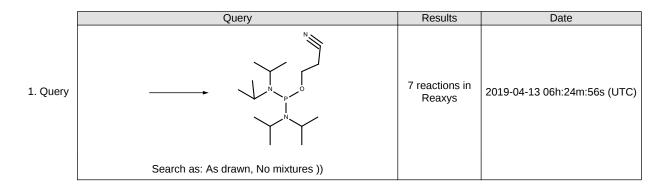
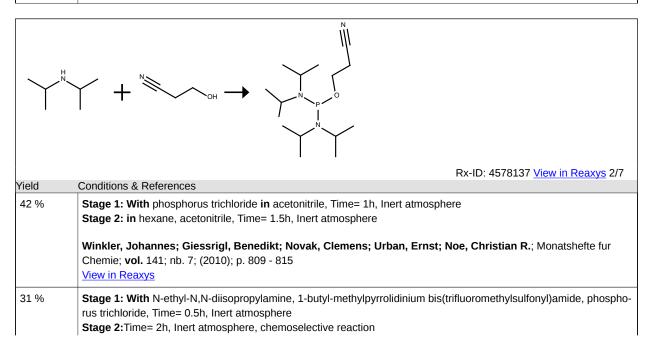
#### Query



| CI<br>CI | $ _{N} + \xrightarrow{H} _{N} _{P} _{N} _{P} _{N} _$  |
|----------|---|
|          | Rx-ID: 3311383 View in Reaxys 1/7   |
| rield    | Conditions & References   |
| 88.5 %   | 1 : Example 1; Preparation and Stabilization of 2-Cyanoethyl-N,N,N',N'-tetraisopropylphosphoro-diamidite (PDA)  |
|          | Example 1; Preparation and Stabilization of 2-Cyanoethyl- N, N, N', N'-tetraisopropylphosphoro-diamidite (PDA) 2-<br>(cyanoethoxy) dichlororphosphine (CDP) can be easily prepared by various processes described in the prior art. For<br>example, the reaction of phosphorous trichloride (PCI3) with either 2-cyanoethanol or trimethylsilyloxypropionitrile<br>(TMSOP) gives CDP in good yield. If desired, the product can be purified with careful vacuum distillation. The CDP<br>used in this example, and Example 2 was obtained by reacting PCI3 with TMSOP in a molar ratio of 2: 1 in acetoni-<br>trile at 5°C. Upon completion of the reaction, the solvent and the excess POS were removed by distillation. The<br>crude product was further purified by vacuum distillation, and gave CDP with greater than 98percent purity. A solu-<br>tion comprising 1.80 moles of freshly distilled 2-(cyanoethoxy) dichlorophosphine (CDP) (310 grams) in 2.9 Kg of tet<br>rahydrofuran (THF) as solvent was stirred and cooled to -12 °C under a nitrogen blanket and then treated with 8.12<br>moles (820 grams) of diisopropylamine over a period of ninety minutes, maintaining a temperature of-10 °C. Stirring<br>of the slurry was continued at ambient temperature for a period of 72 hours, at which time examination by 31P NMR<br>showed no reaction intermediates remaining. The slurry was filtered through a sintered glass filter to remove diiso-<br>propylamine hydrochloride (DIPA. HCI) solids. The clear filtrate was passed through a column of 350 grams of<br>Brockmann activated neutral alumina that had been dried at 165°C at less than 1 Torr for 16 hours. The filtrate was<br>concentrated on a rotary evaporator at a maximum bath temperature of 45°C. The distilled THF was used to rinse<br>the DIPA. HCI and the alumina to collect additional product, which was combined with the first pass product and ther<br>concentrated until the vacuum reached 3 Torr. The yield of the pale yellow syrup was 485 grams (88.5percent of<br>theoretical) and the initial assay by 31P NMR was 99.7percent. Table 1 shows a comparison of the sta |
|          | in tetrahydrofuran, Time= 73.5h, T= -10 - 20 °C   |
|          | Patent; RHODIA, INC.; WO2003/106468; (2003); (A1) English<br>View in Reaxys   |
| 79 %     | in diethyl ether, Time= 12h, T= 20 °C   |
|          | Ching, Shi Min; Tan, Wan Jun; Chua, Kim Lee; Lam, Yulin; Bioorganic and Medicinal Chemistry; vol. 18; nb. 18; (2010); p. 6657 - 6665<br>View in Reaxys  |
| 64 %     | in diethyl ether, 1 h, -10 degC, r.t., overnight  |
|          | Bannwarth, Willi; Trzeciak, Arnold; Helvetica Chimica Acta; vol. 70; (1987); p. 175 - 186<br>View in Reaxys   |
|          | <b>3 : 2-Cyanoethyl tetraisopropylphosphorodiamidite</b><br>[0260] Diisopropylamine (1 L, 7.12 mol), hexane (1 L) were cooled to 0° C. Phosphorus oxychloride (4.5 ml) was<br>added and the mixture was stirred for 20 min. The crude dichlorophosphite (258 g, 1.5 mol) was added with temper-<br>ature below 0° C. over 1 hour. The reaction mixture was stirred at room temperature overnight and poured into hex-<br>ane (1 L). The mixture was washed with water (1 L) and acetonitrile-water (70:30, v/v, 4.x.500 ml). The hexane layer<br>was evaporated to give the desired product as a colorless liquid (239 g).  |
|          | Stage 1: With trichlorophosphate in hexane, Time= 0.3333333, T= 0 °C<br>Stage 2: in hexane, Time= 6h, T= 0 - 20 °C  |
|          | Patent; Song, Quanlai; Ross, Bruce; US2003/225284; (2003); (A1) English View in Reaxys  |

| [0257] A mixture of diisopropylamine, hexane and anhydrous potassium carbonate was stirred at -15° C. for 20 min. The crude dichlorophosphite was added at a temperature below -5° C. for 20 min. The reaction mixture was stirred at 0° C. for 2 h, then allowed to warm to room temperature overnight, and then poured into hexanes (5 L). The mixture was washed (2 L) with water and acetonitrile-water (60:40, v/v, 4.x.1 L). The hexane layer was evaporated to give the desired product as a clear, colorless liquid (1080 g, yield: 72percent).   |
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| <b>Stage 1: With</b> potassium carbonate <b>in</b> hexane, Time= 0.3333333h, T= -15 °C<br><b>Stage 2: in</b> hexane, T= -5 - 20 °C  |
| Patent; Song, Quanlai; Ross, Bruce; US2003/225284; (2003); (A1) English<br><u>View in Reaxys</u>  |
| <b>1</b> : <b>2-Cyanoethyl tetraisopropylphosphorodiamidite</b><br>[0253] A mixture of diisopropylamine (4.0 kg, 39.5 mol), hexanes (2 L) and anhydrous potassium carbonate (200 g) was stirred at -15° C. for 20 min. The crude dichlorophosphite was added to the diisopropylamine mixture while maintaining the reaction temperature below 0° C. The reaction mixture was stirred at 0° C. for 2 h and then allowed to warm to room temperature overnight and then poured into hexanes (18 L). The mixture was washed with water (4 L) and acetonitrile-water (60:40, v/v, 4.x.2 L). The hexane layer was evaporated and dried under vacuum (25° C. at 0.1 mmHg for 2 h) to give the desired product as a colorless, clear liquid (1870.5 g, total yield: 62percent).                            |
| <b>Stage 1: With</b> potassium carbonate <b>in</b> hexanes, Time= 0.3333333h, T= -15 °C<br><b>Stage 2:</b> , T= -5 - 20 °C  |
| Patent; Song, Quanlai; Ross, Bruce; US2003/225284; (2003); (A1) English<br><u>View in Reaxys</u>  |
| <b>4 : 2-Cyanoethyl tetraisopropylphosphorodiamidite</b><br>[0264] Phosphorus oxychloride (25 ml) was added to the solution of diisopropylamine (5.5 L, 39.2 mol) and hexanes<br>(4 L) at 0° C. and the mixture was stirred for 20 min. The above crude dichlorophosphite was added while maintain-<br>ing the reaction temperature below 10° C. over 1 hour. The reaction mixture was then allowed to warm to room tem-<br>perature and stirred for 5 h. The mixture was poured into hexanes (8 L). The mixture was washed with water (6 L),<br>acetonitrile-0.1 N NaOH (70:30, v/v, 4.x.2 L) and acetonitrile-water (70:30, v/v, 2.x.2 L). The hexane layer was<br>evaporated and dried under vacuum (25° C./0.5 mmHg/2 h) to give the desired product as a colorless, clear liquid<br>(1.88 kg). |
| <b>Stage 1: With</b> trichlorophosphate <b>in</b> hexanes, Time= 0.3333333h, T= 0 °C<br><b>Stage 2: in</b> hexanes, Time= 6h, T= 0 - 20 °C  |
| Patent; Song, Quanlai; Ross, Bruce; US2003/225284; (2003); (A1) English<br>View in Reaxys   |



| <ul> <li>With phosphorus trichloride, 1.) Et<sub>2</sub>O, -78 deg C, 1 h, 24 deg C, 1 h, 2.) -20 deg C, 10 min, 24 deg C, 1.5 h, Yield given. Multistep reaction</li> <li>Gu, Qu-Ming; Prestwich, Glenn D.; Journal of Organic Chemistry; vol. 61; nb. 24; (1996); p. 8642 - 8647 View in Reaxys</li> <li>1.a : a. <ul> <li>a.</li> <li>Bis-(diisopropylamino)-(β-cyanoethoxy)phosphane 3</li> <li>Preparation of the titled compound was in accord with the procedure of Kraszewski and Norris, Nucleic Acids Research Sump. Ser. 18: 177-80 (1987).</li> <li>β-Cyanoethanol (7 g; 0.1 mole) in absolute CH<sub>3</sub> CN (40 ml was added dropwise within 30 min to a solution of freshidistilled PCl<sub>3</sub> (40 ml; 0.4 mole) at room temperature ("r.t.") and under nitrogen atmosphere.</li> <li>After stirring for 3.5 h, the solvent and excess PCl<sub>3</sub> were removed in high vacuum, the residue was dissolved in 450 ml of absolute ether and at -10° C. reacted with N,N-diisopropylamine (127 ml; 0.9 mole) by dropwise addition withi 1 h under nitrogen atmosphere.</li> <li>The reaction mixture was stirred at -10° C. for 30 min and at r.t. for 15 h.</li> <li>The precipitate was filtered under nitrogen and the solvent was removed in vacuo.</li> <li>The yellow crude product was fractionally distilled over CaH<sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118° C.</li> <li>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl<sub>3</sub>): 3.75 (s, 2H, CH<sub>2</sub>); 3.52 (m, 4H, 4 NCH); 2.6</li> </ul> </li> </ul> |
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| <ul> <li>View in Reaxys</li> <li><b>1.a</b>: <b>a</b>.</li> <li><b>a</b>.</li> <li>Bis-(diisopropylamino)-(β-cyanoethoxy)phosphane 3</li> <li>Preparation of the titled compound was in accord with the procedure of Kraszewski and Norris, Nucleic Acids Research Sump. Ser. 18: 177-80 (1987).</li> <li>β-Cyanoethanol (7 g; 0.1 mole) in absolute CH<sub>3</sub> CN (40 ml was added dropwise within 30 min to a solution of freshidistilled PCl<sub>3</sub> (40 ml; 0.4 mole) at room temperature ("r.t.") and under nitrogen atmosphere.</li> <li>After stirring for 3.5 h, the solvent and excess PCl<sub>3</sub> were removed in high vacuum, the residue was dissolved in 450 ml of absolute ether and at -10° C. reacted with N,N-diisopropylamine (127 ml; 0.9 mole) by dropwise addition withi 1 h under nitrogen atmosphere.</li> <li>The reaction mixture was stirred at -10° C. for 30 min and at r.t. for 15 h.</li> <li>The precipitate was filtered under nitrogen and the solvent was removed in vacuo.</li> <li>The yellow crude product was fractionally distilled over CaH<sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118° C.</li> <li>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl<sub>3</sub>): 3.75 (s, 2H, CH<sub>2</sub>); 3.52 (m, 4H, 4 NCH); 2.6</li> </ul>   |
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| <ul> <li>Bis-(diisopropylamino)-(β-cyanoethoxy)phosphane 3</li> <li>Preparation of the titled compound was in accord with the procedure of Kraszewski and Norris, Nucleic Acids Research Sump. Ser. 18: 177-80 (1987).</li> <li>β-Cyanoethanol (7 g; 0.1 mole) in absolute CH<sub>3</sub> CN (40 ml was added dropwise within 30 min to a solution of freshid distilled PCl<sub>3</sub> (40 ml; 0.4 mole) at room temperature ("r.t.") and under nitrogen atmosphere.</li> <li>After stirring for 3.5 h, the solvent and excess PCl<sub>3</sub> were removed in high vacuum, the residue was dissolved in 450 ml of absolute ether and at -10° C. reacted with N,N-diisopropylamine (127 ml; 0.9 mole) by dropwise addition within 1 h under nitrogen atmosphere.</li> <li>The reaction mixture was stirred at -10° C. for 30 min and at r.t. for 15 h.</li> <li>The precipitate was filtered under nitrogen and the solvent was removed in vacuo.</li> <li>The yellow crude product was fractionally distilled over CaH<sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118° C.</li> <li>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl<sub>3</sub>): 3.75 (s, 2H, CH<sub>2</sub>); 3.52 (m, 4H, 4 NCH); 2.6</li> </ul>  |
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| <ul> <li>β-Cyanoethanol (7 g; 0.1 mole) in absolute CH<sub>3</sub> CN (40 ml was added dropwise within 30 min to a solution of fresh distilled PCl<sub>3</sub> (40 ml; 0.4 mole) at room temperature ("r.t.") and under nitrogen atmosphere.</li> <li>After stirring for 3.5 h, the solvent and excess PCl<sub>3</sub> were removed in high vacuum, the residue was dissolved in 450 ml of absolute ether and at -10° C. reacted with N,N-diisopropylamine (127 ml; 0.9 mole) by dropwise addition within 1 h under nitrogen atmosphere.</li> <li>The reaction mixture was stirred at -10° C. for 30 min and at r.t. for 15 h.</li> <li>The precipitate was filtered under nitrogen and the solvent was removed in vacuo.</li> <li>The yellow crude product was fractionally distilled over CaH<sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118° C.</li> <li>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl<sub>3</sub>): 3.75 (s, 2H, CH<sub>2</sub>); 3.52 (m, 4H, 4 NCH); 2.6</li> </ul>   |
| After stirring for 3.5 h, the solvent and excess PCl <sub>3</sub> were removed in high vacuum, the residue was dissolved in 450 ml of absolute ether and at -10° C. reacted with N,N-diisopropylamine (127 ml; 0.9 mole) by dropwise addition with 1 h under nitrogen atmosphere.<br>The reaction mixture was stirred at -10° C. for 30 min and at r.t. for 15 h.<br>The precipitate was filtered under nitrogen and the solvent was removed in vacuo.<br>The yellow crude product was fractionally distilled over CaH <sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118° C.<br>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 3.75 (s, 2H, CH <sub>2</sub> ); 3.52 (m, 4H, 4 NCH); 2.6  |
| 1 h under nitrogen atmosphere.<br>The reaction mixture was stirred at -10° C. for 30 min and at r.t. for 15 h.<br>The precipitate was filtered under nitrogen and the solvent was removed in vacuo.<br>The yellow crude product was fractionally distilled over CaH <sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118°<br>C.<br>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 3.75 (s, 2H, CH <sub>2</sub> ); 3.52 (m, 4H, 4 NCH); 2.6  |
| The precipitate was filtered under nitrogen and the solvent was removed in vacuo.<br>The yellow crude product was fractionally distilled over CaH <sub>2</sub> to give 14.7 g (49percent) of pure 3 of b.p. 114°-118°<br>C.<br>This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 3.75 (s, 2H, CH <sub>2</sub> ); 3.52 (m, 4H, 4 NCH); 2.6  |
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| This reagent was stored at -20° C. under nitrogen. <sup>1</sup> H-NMR (CDCl <sub>3</sub> ): 3.75 (s, 2H, CH <sub>2</sub> ); 3.52 (m, 4H, 4 NCH); 2.6   |
|  |
| (t, 2H, β-CH <sub>2</sub> ); 1.17+1.14 (2d, 24H, 4 NC(CH <sub>3</sub> ) <sub>2</sub> ).  |
| <sup>31</sup> P-NMR (CDCl <sub>3</sub> ): 124.6 ppm.   |
| With phosphorus trichloride in acetonitrile  |
| Patent; Temple University-Of The Commonwealth System of Higher Education; US5863905; (1999); (A) Eng-<br>lish<br>View in Reaxys  |
| 1 · Example 1· Manufacture of 2-ovanoethyl tetraiconronyl phosphorodiamidite using hexane co-solvent   |
| <b>1 : Example 1; Manufacture of 2-cyanoethyl tetraisopropyl phosphorodiamidite using hexane co-solvent</b> 27.5 g of phosphorus trichloride at ambient temperature was added to a stirred mixture of acetonitrile (200g) and diisopropylamine (121g) over 1 hour. 200g of hexane is then added followed by 14g of hydroxypropionitrile at ambient temperature over 30 minutes. The reaction mixture is then stirred for 1 hour and is then filtered to remove the solid by-product. The upper hexane layer of the filtered reaction mixture is separated and subjected to vacuum strip ping to remove the hexane solvent. This leaves 20g of 2-cyanoethyl tetraisopropylphosphorodiamidite which has a purity of 96. 9percent when analysed by 31P-NMR. The lower acetonitrile layer is stirred with a further 200g of hexane for 2 hours. The upper hexane layer from this re- extraction contains product of 98percent purity when assayed by 31P-NMR. Following vacuum stripping a further 11g of high purity 2-cyanoethyl tetraisopropylphosphorodiamidite is isolated.   |
| <b>Stage 1: With</b> phosphorus trichloride <b>in</b> acetonitrile, Time= 1h, T= 20 °C<br><b>Stage 2: in</b> hexane, acetonitrile, Time= 1.5h, T= 20 °C  |
| Patent; RHODIA CONSUMER SPECIALTIES LIMITED; HARRIS, Christopher, John; JACKSON, Sheena, Les-<br>ley; WILSON, David, James; WO2004/58779; (2004); (A1) English<br><u>View in Reaxys</u>  |
| <b>2 : Example 2; Manufacture of 2-cyanoethyl tetraisopropyl phosphorodiamidite using heptane co-solvent</b> 27.5g of phosphorus trichloride was added to a stirred mixture of 200g of acetonitrile and 121g of diisopropylamine at ambient temperature. 200g of heptane was then added to this mixture followed by 14.3g of hydroxypropionitrile ambient temperature over 30 minutes. The reaction mixture was then stirred for an hour and was then filtered to remove the solid by-product. The upper heptane layer was then separated and subjected to vacuum stripping to remove the heptane solvent leaving 22g of 2-cyanoethyl tetraisopropylphosphorodiamidite which had a purity of 96.7percent when assayed by 31P-NMR.  |
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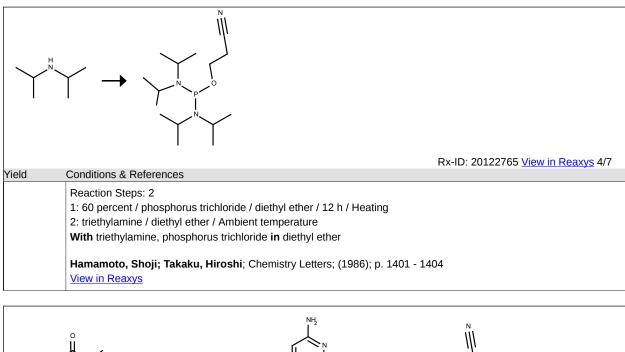
Patent; RHODIA CONSUMER SPECIALTIES LIMITED; HARRIS, Christopher, John; JACKSON, Sheena, Lesley; WILSON, David, James; WO2004/58779; (2004); (A1) English View in Reaxys

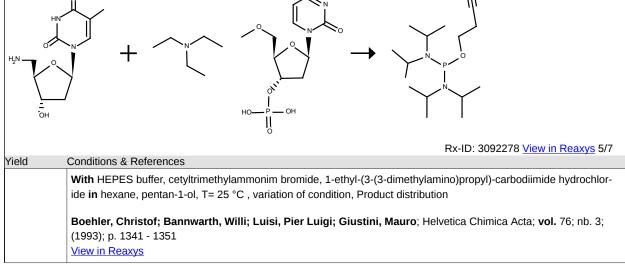
**1** :Example 1 First Step:  $PCI_3$  (8.09 g; 0.0589 moles) was added slowly to a mixture of MeCN (200 g) and diisopropylamine (DIPA) (120.84 g; 1.194 moles). The resultant mixture was stirred for 5 hours. The reaction mixture obtained was then vacuum distilled, whereby a purified DIPA/MeCN solution was obtained (163.97 g, namely 41 wt percent DIPA determined by 1H NMR). Second Step: PCI3 (15.07 g; 0.110 moles) was added slowly to the purified DIPA/MeCN solution obtained in the first step (95.89 g MeCN/66.63 g DIPA, 0.658 moles). The reaction mixture was left stirring overnight. Third Step: Heptane (110 g) was added to the reaction mixture obtained in the second step and then cyanoethanol (7.64 g, 0.107 moles) was added slowly Recovery of the Phosphorodiamidite Solid by-products of the reaction were removed by filtration and the filtrate was then washed (1 H<sub>2</sub>O wash and then 2 MeCN/H2 washes and then a final MeCN wash). Heptane was removed under vacuum to give the crude product as a clear colourless liquid.

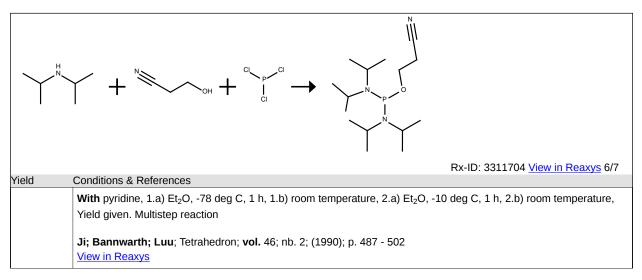
Stage 1: With phosphorus trichloride in acetonitrile Stage 2: in n-heptane, acetonitrile

Patent; RHODIA OPERATIONS; WOODWARD, Gary; (4 pag.); US2016/333034; (2016); (A1) English View in Reaxys

|       | $\begin{array}{c} & & & \\ & & & \\ & & & \\$ |
|-------|---|
| Yield | Conditions & References   |
|       | With triethylamine in diethyl ether, Ambient temperature  |
|       | Hamamoto, Shoji; Takaku, Hiroshi; Chemistry Letters; (1986); p. 1401 - 1404<br>View in Reaxys   |
|       | <ul> <li>b : Step b)</li> <li>Triethylamine (49.4g), toluene (649.5g) and calcium hydride (5g) were charged to a nitrogen-flushed, 1 L round-bottom flask equipped with a magnetic stirrer and cold-finger distillation head attached to an N2 bubbler and the mixture heated under TOTAL REFLUX (98C) for 2 hrs to remove all traces of water. The dried mixture was distilled into an oven-dried, nitrogen-flushed, 2L 3-neck, jacketed round-bottom flask equipped with a mechanical stirrer, a thermowell and a 50 mL pressure-equalizing addition funnel attached to an N2 bubbler and the mixture cooled to below-1</li> <li>5C using a circulating chiller pumping ethylene glycol/water through the reactor jacket and the product of step (a) (130. 3g) added. Neat 2-cyanoethanol (39.9g) was added from the addition funnel over approximately 30 min, keeping the temperature BELOW-10C. The mixture was stirred under nitrogen for 18 hrs at-15 TO-18C to complete the reaction. The mixture was warmed to ambient temperature and pressure-filtered under nitrogen to remove triethylamine hydrochloride salt, all equipment being oven-dried before use. The toluene was stripped out on a rotary evaporator (bath temperature ca. 50C). The vacuum was broken with nitrogen and the distillation vessel connected via a cold trap directly to a vacuum pump and residual toluene removed to yield 139.5g of crude product. The crude product was distilled through a wiped-film evaporator (heated zone 70C ; pressure 0.008 mmHg) over 1.5 hrs to afford 115. 9g of product. If desired, the product can be further purified by flash chromatography, for example using pentane and dry basic alumina, and additional wiped-film distillations.</li> <li>With triethylamine in toluene, Time= 18.5h, T= -1810 °C , Nitrogen atmosphere</li> <li>Patent; AVECIA LIMITED; WO2004/55030; (2004); (A1) English View in Reaxys</li> </ul>   |







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|--------------|--|--|
|              |  |  |
| Yield        | Conditions & References         Rx-ID: 22986501 View in Reaxys 7/7   |  |
| 100 %        | 2  |  |
|              | Patent; RHODIA, INC.; WO2003/106468; (2003); (A1) English<br>View in Reaxys  |  |
| 76.93 %      | <ul> <li>1:1.1</li> <li>In a 500 ml. 3-necked flask fitted with a temperature probe, a condenser, and an addition funnel was placed 42.47 g of 2,2'-methylene-bis-(4,6-di-tert-butylphenol) and 111.26 g of tributylamine.</li> <li>The reaction mixture was stirred well with a magnetic stir bar and 33.71 g of neopentylglycol monochlorophosphite was placed in the addition funnel and added into the reaction mixture during about 5 minutes.</li> <li>The reaction flask was heated slowly to about 95-103°C and held for nearly for 4 hours.</li> <li>Reaction mixture was allowed to cool to about 35°C and no solids were formed.</li> <li>About 100 ml. of heptane was added into the reaction mixture, stirred, filtered out the precipitated salts and the heptane solubles were stripped off to dryness.</li> <li>The oily residue was purified by adding about 150 ml. of acetonitrile and slowly heated to dissolve completely.</li> <li>Upon cooling to room temperature the product obtained was filtered through a sintered glass funnel to isolate white colored product and dried to collect 53.00g (76.93 percent yield) of the bisphosphite, m.p. 166-167.5°C.</li> <li>A sample crystallized from heptane as white crystalline platelets had m.p. 166-167.5°C.</li> <li>Patent; GENERAL ELECTRIC COMPANY; EP940407; (1999); (A1) English View in Reaxys</li> </ul> |  |
| 65%          | <ul> <li>2: EXAMPLE 2         <ul> <li>Under an atmosphere of nitrogen, a cold (-35° C.) anhydrous diethyl ether solution (20 mL) of 2,2'-dihydroxy-1,1'-binaphthalene-3,3'-bis(diphenylether) (0.405 g, 0.65 mmol) was added to the phosphochlorodite of 5,6,7,8-tetrahydro-1-naphthol (0.588 g, 1.63 mmol) dissolved in diethyl ether (10 mL).</li> <li>While maintaining this temperature, triethylamine (0.23 mL, 1.63 mmol) was added dropwise to the above mixture resulting in the formation of a white precipitate.</li> <li>After stirring at room temperature for three hours, the reaction mixture was filtered through a pad of basic alumina and Celite.(R)</li> <li>The filtrate was evaporated to yield the desired diphosphite as a white powder (0.537 g, 65percent).</li> <li><sup>31</sup>P {<sup>1</sup>H} NMR (202.4 MHz, C<sub>6</sub>D<sub>6</sub>): 132.75 ppm.</li> </ul> </li> <li>Patent; E. I. du Pont de Nemours and Company; US6380421; (2002); (B1) English View in Reaxys</li> </ul>   |  |
| 58%          | <b>3 : EXAMPLE 3</b><br>EXAMPLE 3<br>Under an atmosphere of nitrogen, a cold (-35° C.) anhydrous diethyl ether solution (5 mL) of 2,2'-dihydroxy-1,1'-bi-<br>naphthalene-3,3'-bis(diphenyl) (0.050 g, 0.08 mmol) was added to the phosphochlorodite of 5,6,7,8-tetrahydro-1-<br>naphthol (0.076 g, 0.21 mmol) dissolved in diethyl ether (5 mL).<br>While maintaining this temperature, triethylamine (0.03 mL, 0.21 mmol) was added dropwise to the above mixture<br>resulting in the formation of a white precipitate.<br>After stirring at room temperature for three hours, the reaction mixture was filtered through a pad of basic alumina<br>and Celite.(R)<br>The filtrate was evaporated to yield the desired diphosphite as a white powder (0.043 g, 58percent).<br><sup>31</sup> P { <sup>1</sup> H} NMR (202.4 MHz, C <sub>6</sub> D <sub>6</sub> ): 127.83, 132.14, 132.60 (major), 133.66, 141.51, 143.99 ppm.<br>Patent; E. I. du Pont de Nemours and Company; US6380421; (2002); (B1) English  |  |
|              | Patent; E. I. du Pont de Nemours and Company; US6380421; (2002); (B1) English         View in Reaxys   |  |

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| 1 : Preparation of the Diphosphite of (s)-(-)-1,1'-Bi-2-naphthol and Compound I Where R2 =R3 =t-butyl and R1<br>is methyl<br>EXAMPLE 1   |
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| Preparation of the Diphosphite of (s)-(-)-1,1'-Bi-2-naphthol and Compound I Where $R_2 = R_3 = t$ -butyl and $R_1$ is methyl A 0.881 g (1.75mmol) portion of 2,2'-ethylidinebis(4,6-di-t-butylphenyl) chlorophosphite (l) (mp 195°-229° C.) was combined with 0.249 g (0.87 mmol) of (S)-(-)-1,1'-bi-2-naphthol and 15.205 g of dry tetrahydrofuran in a 50-ml single-necked flask in a nitrogen-filled glove box.<br>The clear colorless solution was then treated with 0.697 g (6.89 mmol) of dry triethylamine.<br>After stirring the mixture for 24 hr at room temperature, the mixture was filtered in the glove box through a 0.45-mi-   |
| cron syringe filter to remove the white triethylamine hydrochloride by-product.<br>The clear colorless filtrate was evaporated to dryness under vacuum (0.2 torr/40° C.) to obtain 1.205 g of white crystalline diphosphite (B) having a melting range of 114°-170° C.   |
| Patent; Ethyl Corporation; US5210243; (1993); (A) English<br>View in Reaxys  |
| IX : Beta-Cyanoethyl Phosphoramidite Method.   |
| The $^{31}$ P NMR (CDCI <sub>3</sub> ) showed a single peak at 178.8 ppm (reference 85percent H <sub>3</sub> PO <sub>4</sub> ).  |
| To 28 g (163 mmol) of this compound dissolved in 300 mL of anhydrous diethyl ether and stirred under $N_2$ at -20° C. was added dropwise 96 mL (685 mmol, 4.2 equiv) of disopropylamine.   |
| The ice bath was removed, and the mixture was stirred for 1 h.<br>The ether solution was transferred with filtration under $N_2$ pressure to a dry flask.  |
| The remaining salt was washed twice with 70-mL portions of anhydrous ether which was transferred as above.   |
| The solution was concentrated on a rotary evaporator and filtered into a small, dry flask.   |
| The liquid was stirred under vacuum for 20 min and then distilled under vacuum (400-500 mT) with the falling-film distillation apparatus with refluxing toluene as the heat source to give 18.5 g (61 mmol, 37percent yield) of clear, colorless product.  |
| The <sup>31</sup> P NMR (CDCl <sub>3</sub> ) spectrum showed a single peak at 123.6 ppm (reference 85percent H <sub>3</sub> PO <sub>4</sub> ).   |
| Compound 2 from Example VII, (5-DMT-6-pentafluorophenoxy-guanine-nucleoside) was then reacted with the 2-cya-<br>noethyl N,N,N',N'-tetraisopropylphosphorodiamidite prepared above.  |
| Patent; Rutgers, The State University; US5412088; (1995); (A) English<br>View in Reaxys  |
| <b>3 : Example 3; Purification of low purity 2-cyanoethyl tetraisopropylphosphorodiamidite</b><br>60g of low purity 2-cyanoethyl tetraisopropylphosphorodiamidite (92percent purity when assayed by 31P-NMR con-<br>taining 1. 3percent diester) was added to a mixture of 200g acetonitrile and 200g of heptane after stirring for ten<br>minutes the upper heptane layer was separated and the lower acetonitrile layer stirred with a further 200g of heptane<br>for a further 10 minutes. The second heptane fraction was then separated and the two heptane fraction subsequently<br>combined and subjected to vacuum stripping to remove heptane solvent. 30g of 2-cyanoethyl tetraisopropylphos-<br>phorodiamidite was obtained at a purity of 98.3percent when assayed by 31P-NMR. This extracted phosphorodiami-<br>dite compound contained less than 0.1percent of the diester impurity. |
| , Purification / work up   |
| Patent; RHODIA CONSUMER SPECIALTIES LIMITED; HARRIS, Christopher, John; JACKSON, Sheena, Les-<br>ley; WILSON, David, James; WO2004/58779; (2004); (A1) English<br>View in Reaxys   |