An efficient and modular route to C3*-TunePhos type ligands


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**General procedures.** All reactions were carried out under argon atmosphere using flame-dried glassware unless otherwise noted. THF were distilled over sodium metal. All reagents were commercially available and used without further purification unless indicated otherwise. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on GF254 plates (0.25 mm layer thickness) using UV light as visualizing agent and aqueous ammonium cerium nitrate/ammonium molybdate and sulfuric acid/ethanol solution (15%) as developing agents. Flash chromatography was performed with 300–400 mesh silica gels.

$^1$H and $^{13}$C–NMR experiments were performed on a Bruker AM-400 spectrometer at ambient temperature. The residual solvent protons ($^1$H) or the solvent carbons ($^{13}$C) were used as internal standards. $^1$H-NMR data are presented as follows: chemical shift in ppm downfield from tetramethylsilane (multiplicity, coupling constant, integration). The following abbreviations are used to designate multiplicities in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; qt, quartet of triplets; dd, doublet of doublets; dt, doublet of triplets; AB, AB quartet; m, multiplet. High-resolution mass spectra (HRMS) was taken on Agilent ESITOF (time of flight) mass spectrometer at a 4000 V emitter voltage.
Typical procedure for preparation of 3-bromophenyl diethylcarbamate (2) \(^1\): To a suspension of NaH (1.92 g, 80 mmol) in anhydrous THF (100 mL) was added a solution of 3-bromophenol (6.92g, 40 mmol) in THF (10 mL) dropwise at 0 °C under argon. Upon the completion of addition, the mixture was warmed to the room temperature and was stirred at this temperature for another 3 hours. Then a solution of N,N-diethyl carbamoylchloride in THF (10 mL) was added to the reaction mixture dropwise. The resulting suspension was stirred at room temperature overnight. Then the reaction was quenched with aqueous NH\(_4\)Cl solution and was extracted with EtOAc (50 mL) for three times. The combined organic layers were washed with saturated brine, dried over anhydrous Na\(_2\)SO\(_4\). The solvent was evaporated off under vacuum. The crude mixture was purified by chromatography on silica gel eluting with PE/EtOAc (10:1), affording the desired product (9.68g, 91% yield).

3-bromophenyl diethylcarbamate (2): \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.30\) (s, 1H), 7.26 (d, \(J = 8.5\) Hz, 1H), 7.15 (t, \(J = 8.5\)Hz, 1H), 7.04 (d, \(J = 8.5\) Hz, 1H), 3.36-3.33 (m, 4H), 1.18-1.14 (m, 6H); \(^{13}\)C NMR (400 MHz, CDCl\(_3\)) \(\delta = 153.7, 152.4, 130.4, 128.3, 125.4, 122.2, 120.9, 42.6, 42.2, 14.5, 13.6\).

Typical procedure for preparation of 3-bromo-2-iodophenyl diethylcarbamate (3): To a solution of N,N-diisopropyl amine (1.54 mL, 11 mmol) in anhydrous THF (30 mL) at -78 °C under argon was added a solution of n-BuLi in THF (4.4 mL, 2.5M in hexane) dropwise. The mixture was stirred at this temperature for 45 minutes. Then a solution of 3-bromophenyl diethylcarbamate (2.72g, 10 mmol) in THF (10 mL) was added to the reaction mixture dropwise. The resulting solution was stirred at -78°C for 0.5 hour. Next, a solution of I\(_2\) (3.05 g, 12 mmol) in THF (10 mL) was added to the mixture dropwise and was stirred at this temperature for another 0.5 hour. Upon the completion of the reaction by TLC, the reaction was quenched with saturated aqueous
NH$_4$Cl solution and saturated Na$_2$SO$_3$ solution. The aqueous layer was extracted with EtOAc (25 mL) for three times. The combined organic layers were washed with saturated brine, dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated off under vacuum. The crude mixture was purified by chromatography on silica gel eluting with PE/EtOAc (10:1), affording the desired product (3.34g, 84% yield).

The spectra data of 3 was in consistent with that reported in literature$^2$: $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.47 (dd, $J =$ 8.1, 1.5 Hz, 1H), 7.22 (t, $J =$ 8.1 Hz, 1H), 7.08 (dd, $J =$ 8.1, 1.5 Hz, 1H), 3.52 (q, $J =$ 7.1 Hz, 2H), 3.38 (q, $J =$ 7.1 Hz, 2H), 1.31 (t, $J =$ 7.1 Hz, 3H), 1.22 (t, $J =$ 7.1 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta =$ 153.4, 152.8, 130.6, 130.0, 129.7, 121.8, 99.9, 42.5, 42.2, 14.5, 13.4.

Typical procedure for preparation of 3-bromo-2-iodophenyl (4): To a solution of 3-bromo-2-iodophenyl diethylcarbamate (3.96 g, 10 mmol) in EtOH (100 mL) was added powdered NaOH (4.0g, 100 mmol) in two portions. The mixture was heated to reflux for 24 hours. Upon the completion of the reaction by TLC, the reaction was cooled to the room temperature and was quenched with aqueous HCl solution (2M). The aqueous layer was extracted with EtOAc (30 mL) for three times. The combined organic layers were washed with saturated brine, dried over anhydrous Na$_2$SO$_4$. The solvent was evaporated off under vacuum. The crude mixture was purified by chromatography on silica gel eluting with PE/EtOAc (8:1), affording the desired product (2.66g, 89% yield).

3-bromo-2-iodophenol (4). The spectra data of compound 4 was in consistent with that reported in literature$^1$: $^1$H NMR (400 MHz, CDCl$_3$) $\delta =$ 7.20 (dd, $J =$ 8.1, 1.5 Hz, 1H), 7.12 (t, $J =$ 8.1 Hz, 1H), 6.92 (dd, $J =$ 8.1, 1.5 Hz, 1H), 5.54 (br s, 1H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta =$ 156.6, 130.8, 129.6, 125.0, 13.3, 94.4.
Typical procedure for preparation of 3, 3’-(2R, 4R)-pentane-2, 4-diylbis(oxy)bis(1-bromo-2-iodobenzene) 6: To a solution of 3-bromo-2-iodophenyl (2.48g, 8.3 mmol) in anhydrous THF (40 mL) at 0 °C under argon were added (2S, 4S)-2,4-pentandiol (417 mg, 4.0 mmol) and PPh$_3$ (2.19 g, 8.3 mmol) successively. The mixture was stirred at this temperature for 15 minutes and then DIAD (1.63g, 8.3 mmol) was added to the reaction mixture dropwise. The resulting solution was ultrasonicated in ice-bath for 1 hour. Upon the completion of the reaction by TLC, Et$_2$O was added to dilute the suspension and the insoluble was filtered off. The filtrate was evaporated under vacuum and the crude mixture was purified by chromatography on silica gel eluting with PE/EtOAc (6:1), affording the desired product as white solid (2.34g, 88% yield).

3, 3’-(2R, 4R)-pentane-2, 4-diylbis(oxy)bis(1-bromo-2-iodobenzene) (6): 1H NMR (400 MHz, CDCl$_3$) δ = 7.11 (dd, J = 8.0, 1.4 Hz, 2H), 6.98 (t, J = 7.6 Hz, 2H), 6.56 (dd, J = 8.2, 1.2 Hz, 2H), 4.77 (m, 2H), 2.09 (m, 2H), 1.39(d, J = 6.4 Hz, 6H); 13C NMR (400 MHz, CDCl$_3$) δ = 157.6, 129.9, 129.1, 124.1, 110.7, 95.1, 72.5, 44.0, 19.4. HR-ESI-MS (m/z): calcd. for C$_{17}$H$_{17}$Br$_2$I$_2$O$_2$ [M+ H]$^+$, 666.7659, found 666.7643.

Typical procedure for preparation of (S)-(6,6’-(2R,4R-Pentadioxy)]-(2,2’)-dibromo-(1,1’)-biphenyl [(S$_{a0}$RR)-7]: To a solution of 3, 3’-(2R, 4R)-pentane-2, 4-diylbis(oxy)bis(1-bromo-2-iodobenzene) (1.332g, 2.0 mmol) in anhydrous THF (20 mL) and LiCl (0.127 g, 3 mmol) at -40 °C under argon were added a solution of isopropylmagnesium bromide in THF (2.5 mL, 2M) dropwise. The mixture was stirred at this temperature for 4 hours to give the Grignard reagent. The resulting mixture was added to another flask of CuCl$_2$ (1.056g, 8.0 mmol) and TMEDA (1.8
mL, 12 mmol) in THF (20 mL) at -78 °C dropwise. The mixture was stirred at this temperature for another 4 hours. Upon the completion of the reaction by TLC, the reaction was quenched with aqueous HCl solution (2M) and was extracted with EtOAc (30 mL) for three times. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄. The solvent was evaporated off under vacuum. The crude mixture was purified by chromatography on silica gel eluting with PE/EtOAc (80:1), affording the dibromide as white solid (0.52g, 60% yield).

(S)-[6,6’-(2R,4R-Pentadioxy)]-1-(2,2’)-dibromo-(1,1’)-biphenyl] (Sax, RR)-7. The spectra data of (Sax RR)-7 was in consistent with that reported in literature⁴: ¹H NMR (400 MHz, CDCl₃) δ = 7.41 (d, J = 8.0 Hz, 2H), 7.25 (t, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 4.53 (m, 2H), 1.79 (m, 2H), 1.34 (d, J = 6.4 Hz, 6H); ¹³C NMR (400 MHz, CDCl₃) δ = 158.6, 132.2, 130.2, 127.2, 125.0, 117.5, 76.7, 40.9, 22.4.

![Lewis structure of (S)-[6,6’-(2R,4R-Pentadioxy)]-1-(2,2’)-dibromo-(1,1’)-biphenyl]

Typical procedure for preparation of (Sax)-[6,6’-(2R,4R-Pentadioxy)]-1-(2,2’)-bis(diphenylphosphino)-(1,1’)-biphenyl] (Sax, RR)-8: To a solution of 3, 3’-(2R, 4R)-pentane-2, 4-diylbis(oxy)bis(1-bromo-2-iodobenzene) (1.332g, 2.0 mmol) in anhydrous THF (20 mL) and LiCl (0.127 g, 3 mmol) at -40 °C under argon were added a solution of isopropylmagnesium bromide in THF (2.5 mL, 2M) dropwise. The mixture was stirred at this temperature for 4 hours to give the Grignard reagent. The resulting mixture was added to another flask of CuCl₂ (1.056g, 8.0 mmol) and TMEDA (1.8 mL, 12 mmol) in THF (20 mL) at -78 °C dropwise. The mixture was stirred at this temperature for another 4 hours. Upon the completion of the reaction by TLC, the reaction was quenched with aqueous HCl solution (2M) and was extracted with EtOAc (30 mL) for three times. The combined organic layers were washed with saturated brine, dried over anhydrous Na₂SO₄. The solvent was evaporated off under vacuum. The crude mixture was purified by chromatography on silica gel eluting with PE/EtOAc (80:1), affording the dibromide
as white solid (0.52g, 60% yield).

\((S_{\alpha})-\left[6, 6^\prime-(2R, 4R\text{-Pentadioxy})\right]-\left(2, 2^\prime\right)-\text{bis(diphenylphosphino)}\)-(1,1')-biphenyl\] \((S_{\alpha}, R R)-8\). The spectra data of \((S_{\alpha}, R R)-8\) was in consistent with that reported in literature\(^5\):

\(^1\)H NMR (CD\(_2\)Cl\(_2\), 300 MHz) \(\delta = 1.25\) (d, \(J = 6.4\) Hz, 6H), 1.74 (t, \(J = 3.9\) Hz, 2H), 4.22-4.66 (m, 2H), 6.67 (d, \(J = 7.4\) Hz, 2H), 6.92 (d, \(J = 8.0\) Hz, 6H), 7.05-7.21 (m, 12H), 7.26-7.27 (m, 6H), 7.44-7.46 (m, 4H); \(^{13}\)C NMR (CD\(_2\)Cl\(_2\), 75 MHz) \(\delta = 22.1, 40.9, 75.6, 118.6, 127.9, 128.1, 128.1, 128.2, 128.6, 128.6, 129.1, 133.5, 133.7, 133.8, 133.9, 134.1, 134.2, 135.8, 136.0, 136.2, 137.7, 137.7, 137.8, 138.6, 138.6, 138.7, 138.8, 138.9, 139.0, 158.1, 158.2, 158.2; \(^{31}\)P NMR (CD\(_2\)Cl\(_2\), TMS, 145 MHz) \(\delta = -11.9\).

Synthetic procedure of compound 9 followed that of compound 8 (58% yield). \((S_{\alpha})-\left[6, 6^\prime-(2R, 4R\text{-Pentadioxy})\right]-\left(2, 2^\prime\right)-\text{bis(dicyc]hexylphosphino)}\)-(1,1')-biphenyl\] \((S_{\alpha}, RR)-9\). The spectra data of \((S_{\alpha}, RR)-9\) was in consistent with that reported in literature\(^4\). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.16\) (d, \(J = 7.8\) Hz, 2H), 7.02 (d, \(J = 7.5\) Hz, 2H), 6.88 (d, \(J = 7.9\) Hz, 2H), 4.37 (dt, \(J = 6.4, 4.1\) Hz, 2H), 1.96 (d, \(J = 11.7\) Hz, 2H), 1.70 – 0.80 (m, 50H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta = 22.1, 26.6, 27.0, 27.3, 27.8, 27.9, 28.6, 29.5, 30.2, 30.7, 32.2, 35.5, 40.6, 74.5, 116.96, 125.94, 126.69, 136.2, 157.7; \(^{31}\)P-NMR(162 MHz, CDCl\(_3\)): \(\delta = -11.4\) (s).
Spectra data for (S)-[6,6’-(2R,4R-Pentadioxy)]-(2,2’)-dibromo-(1,1’)-biphenyl [(SRR)-7]
Spectra data for (S$_{ax}$)-[6,6’-(2$R$,4$R$-Pentadioxy)]-(2,2’)-bis(diphenylphosphino)-(1,1’)-biphenyl (S$_{ax}$,RR)-8
Spectra data for \((S)-[6,6’-(2R,4R-Pentadioxy)]-(2,2’)-\text{bis(dicyclohexylphosphino)}-(1,1’)-\text{biphenyl} \left[(S_{axx}, RR)-9\right]\)
References