# Synthesis of New Disugar Phosphine Ligands and Their Use in Asymmetric Hydrogenation

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Since the work of Knowles, the use of diphosphine ligands in asymmetric catalysis has expanded greatly.[1−5] Phosphines based on a wide variety of chiral molecules have been investigated with varying success.[6−13] One class of chiral molecule, that has been looked at sporadically, are the carbohydrates. Mono- and diphosphines have been synthesized from monosugars such as pyranose, furanose, glucose, galactose, and rhamnose.[14−19] The asymmetric results with these chiral phosphines have been variable.[20] Up to now, the work has focused on the use of monosugars as the chiral source. Figure 1 illustrates one of the more successful monosugar phosphines (**1**). Examination of the rhodium complex of this ligand (**2**) illustrates that the metal center is away from the chiral portion of the molecule. This indicates that transfer of chirality in reactions with sugar-derived ligands such as **1** is likely to take place by the same mechanism as with other simple chiral diphosphine ligands, through control of the orientation of the phenyl rings. Positioning transition metals into large biomolecules may offer the opportunity to control the environment of the metal in a more direct manner. Conformations can exist where the transition metal is positioned near the chiral portion of the ligand. This would allow for the chirality of the ligand to directly influence the outcome of reactions at the transition metal center.

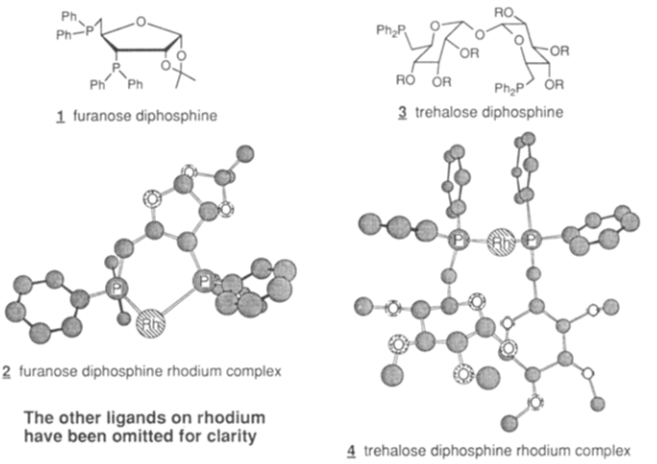


**Figure 1.**

Analysis of the metalated trehalose-derived diphos ligand **3** illustrates that its preferred conformation is such that the metal is beginning to be positioned closer to the chiral sugar portion of the complex (**4**). With design of the proper system this may allow for the development of more selective or more general catalyst systems. As part of a larger program to use biomolecules as chiral scaffolds for catalytic transition metals, this paper reports our first efforts in the area of phosphine-containing sugars. We have synthesized what is to our knowledge the first phosphine-containing disugar by a route amenable to the synthesis of a number of disugar diphosphine ligands. We also report our inital studies on the use of this ligand for asymmetric catalysis.

## Results and Discussion

D-Trehalose (**5**) is an inexpensive readily available disugar that we feel has potential as an asymmetric ligand. For this molecule, and others like it, to be of use, a convenient route to phosphine derivatives is required. Scheme 1 illustrates our route to the benzyl- and methyl-protected diphosphines **9** and **10**. Reaction of trityl chloride with trehalose protects the two primary hydroxyls (**6**). Reaction of **6** with benzyl bromide and sodium hydride followed by *p*-toluenesulfonic acid gives trehalose with the secondary hydroxyls benzyl protected and the primary hydroxyls free (**7**). Reaction of **6** with sodium hydride and iodomethane followed by *p*-toluenesulfonic acid yields the corresponding methyl-protected diol **8**. Reaction of each of these compounds with trifluoromethanesulfonic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine gives the ditriflates, which can be reacted with lithium diphenylphosphide to obtain the diphosphines **9** and **10**. In other work we have found that conversion of phosphines to their sulfides is an effective method for protection of the, potentially oxidizable, phosphine group.[21] Reaction of **9** and **10** with elemental sulfur gives the diphosphine sulfide trehalose derivatives **11** and **12**.

We have tested these ligands (**9** and **10**) in the asymmetric hydrogenation of α-(*N*-acetylamino)acrylate (Table 1). We found that the benzyl-protected sugar gives higher ees than the methylated sugar, reaction 2 vs 3 and 4 vs 5. We also observed that THF is a superior

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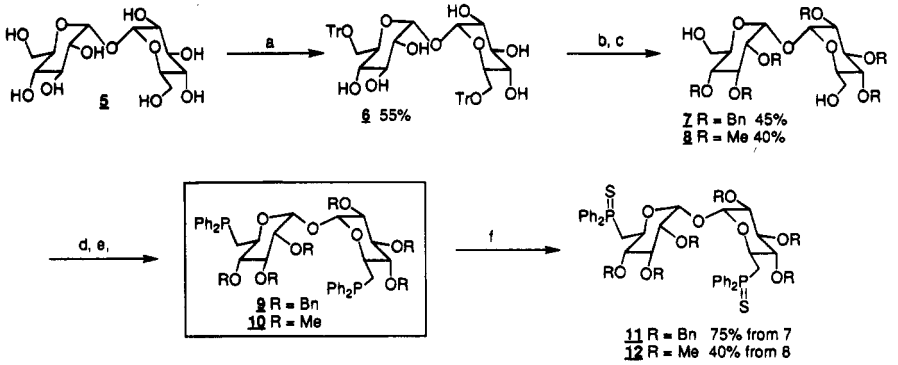
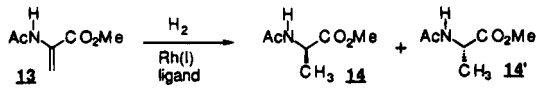
**Scheme 1**[a]




[a] (a) TrCl, pyridine (neat), 40 °C, 6 h; (b) R = benzyl, NaH, BnBr, $nBu_4NI$, DMF, 0 °C to rt; R = methyl, NaH, $CH_3I$, rt; (c) TsOH, MeOH, $CH_2Cl_2$; (d) $Tf_2O$, DBMP $CH_2Cl_2$, 0 °C; (e) $Ph_2PLi$, THF, −78 °C; (f) $S_8$, $C_6H_6$, rt.

**Table 1. Hydrogenation of Enamide with Rh(I) Phosphine Complexes**




| reactn no. | ligand | solvent | time, h | temp, °C | % ee[a] |
|---|---|---|---|---|---|
| 1 | 10 | MeOH | 96 | RT | 4 |
| 2 | 10 | $CH_2Cl_2$ | 6 | RT | 2 |
| 3 | 9 | $CH_2Cl_2$ | 10 | RT | 16 |
| 4 | 10 | THF | 5 | RT | 10 |
| 5 | 9 | THF | 47 | RT | 23 |
| 6 | 9 | $CH_2Cl_2$ | 41 | −10 | 57 |
| 7 | 9 | THF | 60 | −10 | 82 |

[a] 95 to 100% conversion of starting material to product. Yield 80 to 90%.

solvent to methylene chloride or methanol. Benzyl-protected sugar, THF solvent, and −10 °C represent the optimal reaction conditions we found for this reaction (82% ee). While this is not yet competitive with the 99% ee ligands such as DuPHOS[12,13,22] give in this reaction, it illustrates the potential for this type of ligand. There are many other catalytic reactions diphos ligands participate in. Now that there is a viable route to this type of ligand, its use in these reactions can be studied. Since the type of protecting group on the sugar appears to have an effect on the outcome of the reaction, we are currently investigating the use of sugars with protecting groups other than methyl and benzyl.

## Conclusion

This work represents our first attempt to use disugars as phosphine ligands. The route presented here should be useful in the synthesis of a variety of other polysugar diphosphines. We are currently investigating other disugars with both natural and unnatural linking groups connecting the two sugar molecules.

## Experimental Section

**6,6′-Bis(triphenylmethyl)-α-D-trehalose (6).** To a clear solution of trehalose dihydrate (5.0 g, 13.22 mmol) in dried pyridine (100 mL) was added triphenylmethyl chloride (25.8 g, 92.5 mmol). The mixture was stirred under nitrogen at 40 °C for 6 h or longer (monitored by TLC, $CH_2Cl_2$/MeOH = 6/1). After completion of the reaction, dry MeOH (40 mL) was added and the reaction mixture was stirred for another 30 min. Evaporation of solvent afforded yellowish solid as the crude product.

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**2,2′,3,3′,4,4′-Hexamethyl-α-D-trehalose (8).** The crude bistritylated trehalose **6** was dissolved in DMF and then transferred into a flask containing washed NaH (4.8 g, 198 mmol). After stirring under nitrogen at room temperature for 45 min, methyl iodide (12.3 mL, 198 mmol) was added and the reaction mixture was stirred overnight. The reaction mixture was poured into a 0 °C 10% $NaHCO_3$/ether solution. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$. After evaporation of solvent, the yellowish oil was dissolved in $CH_2Cl_2$ and MeOH, and TsOH−$H_2O$ (2 g, 10.5 mmol) was added. After stirring for 12 h, the reaction was quenched with 5 mL of $Et_3N$, and the mixture was stirred for another 15 min. Evaporation of solvent and purification of the crude product by gradient flash chromatography [silica gel, hexane/ethyl acetate (80/20) to ethyl acetate/methanol (80/20)] afforded **8** as a viscous oil (0.63 g, 15% yield from **5**): $^1H$ NMR (300 MHz, $CDCl_3$) δ 5.1 (d, $J_{HH}$ = 3.6 Hz, 2H), 3.9 (ddd, $J_{HH}$ = 3.5 Hz, $J_{HH}$ = 3.1 Hz, $J_{HH}$ = 10.1 Hz, 2H), 3.8 (m, 4H), 3.63(s, 6H), 3.58(s, 6H), 3.5 (dd, $J_{HH}$ = 9.3 Hz, $J_{HH}$ = 9.3 Hz, 2H), 3.43 (s, 6H), 3.19 (d, $J_{HH}$ = 10.01, 2H), 3.16 (d, $J_{HH}$ = 9.4 Hz, 1H), 3.15 (d, $J_{HH}$ = 9.4 Hz, 1H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 93.1 (s), 82.7 (s), 81.5 (s), 79.4 (s), 71.1 (s), 61.8 (s), 60.8 (s), 60.6 (s), 60.4 (s), 58.5 (s); IR (thin film) 3200−3600 (broad), 2946 (s), 2832 (s), 1738 (m), 1466 (s), 1446 (s), 1376 (s), 1330 (m), 1240 (m), 1187 (s), 1153 (s), 1144 (s), 1091 (s), 1076 (s), 1038 (s), 1003 (s), 970 (m), 958 (m), 929 (w), 792 (m), 616 (m), 610 (m), 594 (m), 570 (s), 563 (s); MS-FAB (EI+) *m/z* (rel intensity) 449 (M + $Na^+$, 100). Anal. Calcd for $C_{18}H_{34}O_{11}$: C, 50.70; H, 8.04. Found: C, 51.02; H, 7.97.

**2,2′,3,3′,4,4′-Hexamethyl-6,6′-bis(diphenylphosphinothioyl)-6,6′-dideoxy-α-D-trehalose (12).** A clear solution of **7** (0.34 g, 0.80 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (0.66 g, 3.2 mmol) in 10 mL of dry $CH_2Cl_2$ was cooled to 0 °C under nitrogen, and $Tf_2O$ (0.54 mL, 3.2 mmol) was slowly added. After stirring of the cloudy white solution for 1 h, $CH_2Cl_2$ and saturated $NaHCO_3$ were added, and the mixture was vigorously stirred for 2 min. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic layers were dried over $Na_2SO_4$. Evaporation of the solvent afforded crude product as colored crystals which were used without purification.

tBuLi (1.7 M, 1.9 mL, 3.2 mmol) was added to a clear solution of diphenylphosphine (0.56 mL, 3.2 mmol) in 5 mL of THF at −78 °C under nitrogen. The orange solution was stirred for 20 min and then transferred to the bistriflated trehalose in 15 mL of THF. After stirring for 1 h, the dry ice bath was removed and 1 mL of dry tBuOH was added. Benzene (30 mL) was added to the light brownish solution followed by elemental sulfur (0.1 g, 3.2 mmol). The reaction mixture was stirred under $N_2$ for 24 h at room temperature. Evaporation of solvent and purification of the crude product by gradient column chromatography [silica gel, hexane/ethyl acetate (90/10 to 50/50)] afforded **12** (0.25 g, 40%) as yellow-white crystals: $^1H$ NMR (300 MHz, $CDCl_3$) δ 7.7−7.9 (m, 8H), 7.4−7.5 (m, 12H), 5.0 (d, $J_{HH}$ = 3.4 Hz, 2H), 4.2 (ddd, $J_{HH}$ = 10 Hz, $J_{HH}$ = 10 Hz, $J_{HP}$ = 10 Hz, 2H), 3.5−3.7 (m, 14H), 3.3 (s, 6H), 3.0 (dd, $J_{HH}$ = 3.4 Hz, $J_{HH}$ = 9.6 Hz, 2H), 2.8−2.9 (m, 4H), 2.6 (ddd, $J_{HH}$ = 9.2Hz, $J_{HH}$ = 15 Hz, $J_{HP}$ = 9 Hz, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 134.5 (d, $J_{CP}$ = 41 Hz), 133.4 (d, $J_{CP}$ = 41 Hz), 131.3 (d, $J_{CP}$ = 10 Hz), 131.1 (d, $J_{CP}$ = 2.5 Hz), 131.0 (d, $J_{CP}$ = 2.5 Hz), 130.9 (d, $J_{CP}$ = 10 Hz), 128.5

(d, $J_{CP}$ = 12 Hz), 128.1 (d, $J_{CP}$ = 12 Hz), 90.7 (s), 84.3 (d, $J_{CP}$ = 12.4 Hz), 82.1 (s), 81.7 (s), 66.0 (d, $J_{CP}$ = 4 Hz), 60.4 (s), 60.1 (s), 59.7 (s), 36.1 (d, $J_{CP}$ = 58.6 Hz); $^{31}$P NMR (120 MHz, $CDCl_3$), $\delta$ 40.1 (s); IR (thin film) 3056 (w), 3006 (w), 2980 (m), 2933 (s), 2915 (s), 2833 (m), 1436 (s), 1378 (w), 1187 (m), 1170 (m), 1147 (s), 1111 (s), 1092 (s), 1081 (s), 1071 (s), 1061 (s), 1027 (w), 1011 (s), 993 (s), 953 (w), 789 (w), 761 (s), 712 (m), 692 (s), 613 (s); MS-FAB (EI+) $m/z$ (rel intensity) 826 ($M^+$, 10), 217 ($Ph_2PS^+$, 100). Anal. Calcd for $C_{42}H_{52}O_9P_2S_2$: C, 61.05; H, 6.34. Found: C, 61.12 H, 6.24. Melting point: 211–214 °C.

**2,2′,3,3′,4,4′-Hexabenzyl-α-D-trehalose (7).** The crude bistritylated trehalose **6** (1 g, 1.2 mmol) was dissolved in 20 mL of DMF. The solution was then transferred to a flask containing washed NaH (0.9 g, 22.5 mmol). Tetrabutylammonium iodide (0.01g, 0.03 mmol) was added followed by the slow addition of benzyl bromide (1.7 mL, 14.5 mmol). The cloudy yellowish solution was stirred under nitrogen at room temperature for 48 h. The reaction mixture was poured into 10% $NaHCO_3$/ether solution. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$. After evaporation of solvent, the yellowish oil was dissolved in $CH_2Cl_2$ (15 mL) and MeOH (15 mL), and TsOH–$H_2O$ (0.69 g, 3.6 mmol) was added. After stirring for 12 h, the reaction was quenched with $Et_3N$ (5 mL). Evaporation of solvent and purification of the crude oil by gradient flash chromatography [silica gel, hexane/ethyl acetate (80/20) to ethyl acetate/methanol (80/20)] afforded **7** as a viscous oil (0.53 g, 25% yield from **5**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.3–7.4 (m, 30H), 5.1 (d, $J_{HH}$ = 3.5 Hz, 2H), 5.0 (d, $J_{HH}$ = 10.9 Hz, 2H), 4.9 (d, $J_{HH}$ = 11.1 Hz, 4H), 4.7 (m, 4H), 4.64 (d, $J_{HH}$ = 10.9 Hz, 2H), 4.05 (m, 2H), 3.6 (m, 8H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.8 (s), 138.2 (s), 138.0 (s), 128.4 (s), 128.3 (s), 128.3 (s), 128.2 (s), 128.1 (s), 128.0 (s), 127.8 (s), 127.6 (s), 127.5 (s), 93.9 (s), 81.6 (s), 79.5 (s), 77.4 (s), 75.5 (s), 75.0 (s), 73.0 (s), 71.3 (s), 61.6 (s); IR (thin film) 3200–3600 (broad), 3090 (w), 3063 (m), 3031 (s), 2941 (s), 2928 (s), 2873 (s), 1498 (s), 1455 (s), 1361 (m), 1208 (w), 1155 (m), 1137 (m), 1091 (s), 1068 (m), 1027 (m), 1001 (m), 756 (w), 731 (m), 694 (m), 563 (w); MS-FAB (EI+) $m/z$ (rel intensity) 905 (M + $Na^+$, 100); HRFAB calcd for $C_{54}H_{58}O_{11}Na^+$ $m/e$ 905.3877, measured $m/e$ 905.3880. Anal. Calcd for $C_{54}H_{58}O_{11}$: C, 73.44; H, 6.62. Found: C, 72.92; H, 6.48.

**2,2′,3,3′,4,4′-Hexabenzyl-6,6′-bis(diphenylphosphinothioyl)-6,6′-dideoxy-α-D-trehalose (11).** This compound was synthesized from **7** by the same procedure as the preparation of **12**. Gradient flash chromatography on silica gel [hexane/ethyl acetate (90/10 to 65/35)] afforded **11** (0.22 g, 0.17 mmol, 75% yield from **7**) as white crystals: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.6–7.7 (m, 8H), 7.1–7.4 (m, 42H), 5.2 (d, $J_{HH}$ = 3.2 Hz, 2H), 4.9 (d, $J_{HH}$ = 9.5 Hz, 2H), 4.9 (d, $J_{HH}$ = 11 Hz, 2H), 4.78 (d, $J_{HH}$ = 11 Hz, 2H), 4.74 (d, $J_{HH}$ = 11 Hz, 2H), 4.6 (d, $J_{HH}$ = 11 Hz, 2H), 4.5 (d, $J_{HH}$ = 11 Hz, 2H), 4.3 (ddd, $J_{HH}$ = 10 Hz, $J_{HH}$ = 10 Hz, $J_{HP}$ = 10 Hz, 2H), 4.2 (dd, $J_{HH}$ = 9.3 Hz, $J_{HH}$ = 9.3 Hz, 2H), 3.5 (dd, $J_{HH}$ = 3.2 Hz, $J_{HH}$ = 9.3 Hz, 2H), 2.8 (dd, $J_{HH}$ = 14 Hz, $J_{HP}$ = 14 Hz, 2H), 2.4 (ddd, $J_{HH}$ = 14 Hz, $J_{HH}$ = 10 Hz, $J_{HP}$ = 10 Hz, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 138.7 (s), 138.3 (s), 134.5 (d, $J_{CP}$ = 23 Hz), 133.4 (d, $J_{CP}$ = 23 Hz), 131.2 (s), 131.1 (s), 131.0 (s), 130.9 (s), 128.5 (s), 128.4 (s), 128.2 (s), 128.1 (s), 128.0 (s), 127.8 (s), 127.7 (s), 127.6 (s), 127.5 (s), 127.4 (s), 127.1 (s), 127.0 (s), 127.0 (s), 90.4 (s), 82.1 (d, $J_{CP}$ = 12 Hz), 81.0 (s), 79.4 (s), 75.4 (s), 74.6 (s), 72.5 (s), 66.8 (d, $J_{CP}$ = 4.2 Hz), 35.2 (d, $J_{CP}$ = 58 Hz); $^{31}$P NMR (120 MHz, $CDCl_3$) $\delta$ 34.5 (s); IR (thin film) 3061 (m), 3029 (m), 2975 (w), 2933 (w), 2918 (w), 2894 (m), 2873 (m), 1498 (m), 1454 (s), 1436 (s), 1363 (w), 1150 (s), 1102 (s), 1067 (s), 1028 (m), 998 (s), 740 (m), 692 (s), 628 (m), 613 (m); MS-FAB (EI+) $m/z$ (rel intensity) 1304 (M + $Na^+$, 10), 633 ((M − O)$^+$/2, 70), 217 ($Ph_2S^+$, 54). Anal. Calcd for $C_{78}H_{76}O_9P_2S_2$: C, 72.99 H, 5.97. Found: C, 72.57; H, 5.92. Melting point: 157–158 °C.

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