Synthesis of New Chiral Aryl Diphosphite Ligands Derived from Pyranoside Backbone of Monosacharides and Their Application in Copper-Catalyzed Asymmetric Conjugate Addition of Diethylzinc to Cyclic Enones

Lailai Wang,[a,b] Yue-Ming Li,[a] Chiu-wing Yip,[a,*] Liqin Qiu,[a] Zhongyuan Zhou,[a] Albert S. C. Chan[a,*]

[a] Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis, and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong, People's Republic of China
Fax: (+852)-2364-9932, e-mail: bcachan@polyu.edu.hk

[b] State Key Laboratory for Oxo Synthesis & Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, People's Republic of China

Received: February 21,2004; Accepted: June 15, 2004

Abstract: New chiral aryl diphosphite ligands based on the pyranoside backbones of glucose and galactose were prepared. These ligands were tested in the Cu-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones with up to 88% ee. The stereoselectivity was found to be dependent on the ring size of the substrate as well as the ligand and copper source. The enantioselectivity depends on the absolute configuration of the C-4 stereogenic center of the ligand backbone, while the sense of enantioselectivity is mainly controlled by the configuration of the binaphthyl phosphite moieties.

Keywords: asymmetric; C–C bond formation; conjugate addition; copper salt; P ligands; zinc

Introduction

The asymmetric conjugate addition of carbon nucleophiles to α,β-unsaturated carbonyl compounds is a useful method for the formation of new carbon-carbon bonds and the synthesis of chiral compounds. Recently, conjugate additions of nucleophiles to cyclic enones have been extensively studied as the products may be useful for the synthesis of biologically active compounds.[1] Several successful chiral ligands such as P,N ligands,[2] phosphoramidites,[3] phosphites[4] and aryl diphosphites[5] have been synthesized and employed in asymmetric conjugate addition reactions, and good results have been obtained. One of the main problems revealed in these investigations is the dynamic behaviour with equilibria between several species of organocopper compounds in solution. If the more reactive cuprates lead to the racemic product, a loss of enantioselectivity is unavoidable. It is therefore desirable to design and synthesize new chiral catalysts which can react rapidly with the substrate and therefore suppress the formation of the undesired competing reactions.

Using carbohydrates (and derivatives) as starting materials for the synthesis of chiral ligands has several advantages: 1) the raw materials are of high optical purity and are readily available; 2) the multifunctional property makes it possible to design various structures through a series of modifications. Spescha reported the use of sulphur ligands derived from glucose in the addition of Grignard reagents to enones,[6] Selke et al. reported the use of a series of chiral phosphinite ligands derived from glucose in the Rh-catalyzed asymmetric hydrogenation of dehydroamino acid derivatives to give good to excellent results.[7] Further improvements of ligands of this type were achieved by Rajanbabu et al.[8] Recently, new chelating chiral aryl diphosphite ligands, based on a furanoside backbone of glucose, were synthesized. These ligands gave good results in the Rh-catalyzed asymmetric hydroformylation of styrene,[9] Rh-catalyzed asymmetric hydrogenation,[10] as well as Pd-catalyzed asymmetric allylic substitution,[11] and up to 63% ee was obtained when these chiral ligands were used in the Cu-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones.[12] In this paper, we describe the synthesis of new chiral aryl diphosphite ligands based on the pyranoside backbones of glucose and galactose. These ligands have been applied to the Cu-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones to give the desired products with good ees and yields.

 DOI: 10.1002/adsc.200404053

Results and Discussion

Synthesis of Chiral Diphosphite Ligands

Diphosphite ligands **1**–**4**, based on pyranoside backbones of glucose and galactose, were synthesized stereospecifically in three steps from phenyl β-D-galactopyranoside (**7**) and phenyl β-D-glucopyranoside (**10**) as shown in Scheme 1. Ligands **1** and **2** have the same configuration at the stereogenic center C-4, which is opposite to that of ligands **3** and **4** (Figures 1 and 2). The binaphthyl phosphite moieties of ligands **1** and **3** have the same configuration which is opposite to that of ligands **2** and **4** (Figure 1). Tosylation of compounds **7** and **10** produced the expected 6-tosyl derivatives **8** and **11** in low to moderate yields.[13] Treating the tosylated compounds with sodium hydroxide in ethanol at 80–85 °C produced colourless syrups **9** and **12**.[14] Mixing with ether induced crystallization and after recrystallization from ether, the colourless crystals were obtained in moderate to good yields. An ORTEP drawing of phenyl 3,6-anhydro-β-D-glucopyranoside (**12**) is shown in Figure 2. The bond angles (°) of O(3)–C(4)–C(3) and O(2)–C(2)–C(3) are 116.1° and 111.5°, respectively (Figure 2). The reaction of **9** and **12** with 2.2 equivalents of a suitable chlorodiarylphosphine afforded the corresponding ligands **1**–**4**. All the ligands were stable during purification on silica gel under an atmosphere of nitrogen. The white solid ligands **1**–**4** were air-stable at room temperature.

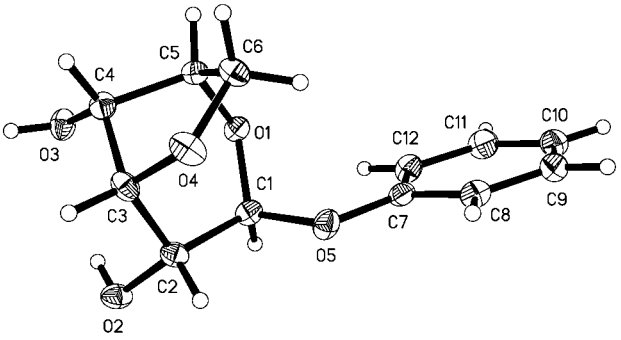


Figure 2. ORTEP diagram of phenyl 3,6-anhydro-β-D-glucopyranoside (C_{12} H_{14} O_5). Selected bond lengths [Å] and angles [°]: O(1)–C(5), 1.444(2); O(1)–C(1), 1.401(2); C(2)–C(3), 1.527(3); C(3)–C(4), 1.518(2); O(3)–C(4), 1.407(2); O(2)–C(2), 1.420(2); O(3)–C(4)–C(3), 116.14(14); O(2)–C(2)–C(3), 111.51(15); O(1)–C(1)–O(5), 115.4(14); O(5)–C(1)–C(2), 105.42(12); C(3)–O(4)–C(6), 107.48(12); O(4)–C(6)–C(5), 105.16(13); C(4)–C(5)–C(6), 100.49(13).

The ^{1}H and ^{13}C NMR spectra were consistent with the expectation for these ligands. The ^{31}P NMR spectra of ligands **1** and **2** displayed two singlets, one for each phosphorus moiety. For ligands **3** and **4**, two doublets, one for each phosphorus, were observed. The coupling constants for ligands **3** and **4** were consistent with other phosphorus-phosphorus coupling constants in similar diphosphites ligands [$J_{(P,P)} = 12$ Hz].[15]

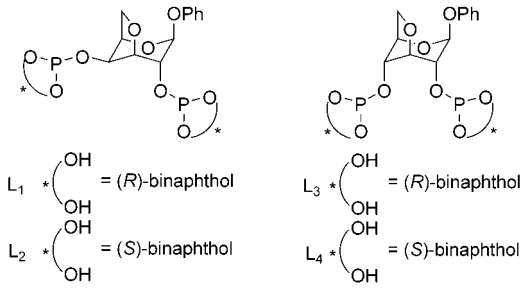
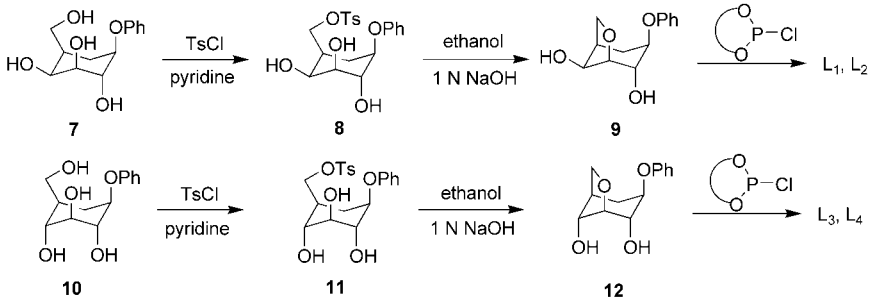


Figure 1. The chiral diphosphite ligands with the pyranoside backbone of galactose (L_1 and L_2) and glucose (L_3 and L_4).

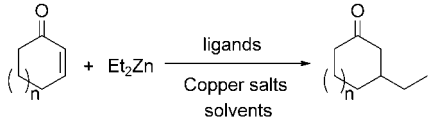
Enantioselective Copper-Catalyzed 1,4-Addition of Diethylzinc to Cyclic Enones

Based on the experience from previous studies,[3a,5a–c] $Cu(OTf)_2$ was chosen as the Cu source for the preparation of the active catalysts. In the first set of experiments, 2-cyclohexenone (**5b**) was treated with diethyzinc in the presence of $Cu(OTf)_2$ and ligands **1**–**4** in toluene, respectively (Table 1, entries 1–4). No 1,2-addition product was observed from the gas chromatographic analysis. It was found that the catalyst prepared *in situ* from $Cu(OTf)_2$ and ligand **3** was more effective than that



Scheme 1. Preparation of ligands L_1–L_4.

Table 1. Cu-catalyzed enantioselective addition of diethylzinc reagents to cyclic enones using ligands **1–4**.[a]



n = 0, **5a**
1, **5b**
2, **5c**

n = 0, **6a**
1, **6b**
2, **6c**

Entry	Substrate	L	Copper salts	T [°C]	t [h]	Conversion [%][b]	Yield [%][b]	ee [%][b]
1	**5b**	L_1	$Cu(OTf)_2$	−30	19	>99%	86%	2% (*S*)
2	**5b**	L_2	$Cu(OTf)_2$	−40	13	>99%	94%	9% (*S*)
3	**5b**	L_3	$Cu(OTf)_2$	−30	19	>99%	83%	59% (*R*)
4	**5b**	L_4	$Cu(OTf)_2$	−30	17	66%	72%	13% (*S*)
5	**5a**	L_3	$Cu(OTf)_2$	−30	17	>99%	18%	35% (*R*)
6	**5c**	L_3	$Cu(OTf)_2$	−30	17	97%	12%	11% (*R*)
7	**5a**	L_3	$(CuOTf)_2 \cdot C_6H_6$	−40	17	>99%	36%	64% (*R*)
8	**5b**	L_3	$(CuOTf)_2 \cdot C_6H_6$	−40	17	>99%	94%	74% (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (0.01 mmol), ligand (0.02 mmol), $ZnEt_2$ (1.2 mmol), substrate (0.5 mmol), toluene (4 mL).
[b] The data on conversion and yield were determined by GC-MS using dodecane as an internal standard on an HPG 1800C GCD system with a Bexs column (30 m × 0.25 mm I. D.). The enantiomeric excess of the product was determined by GC using an HP5890 gas chromatograph equipped with a Chiraldex A-TA column (50 m × 0.25 mm I. D.). The absolute configuration of the product 3-ethylcyclohexenone was determined by comparison with authentic materials.

from either ligands **1**, **2**, or **4** (Table 1, entries 1, 2, and 4 *vs.* entry 3). The use of ligand **3** gave 3-ethylcyclohexenone (**6b**) in 83% yield and 59% ee (Table 1, entry 3). In contrast, the use of other diastereomeric ligands gave substantially lower ees (entries 1, 2, and 4). The use of ligand **4**, which was based on the same pyranoside backbone of glucose as ligand **3** and an oppositely configurated binaphthyl moiety, gave 72% yield and 13% ee (Table 1, entry 4). Ligand **2**, bearing the same configuration of the binaphthyl phosphite moieties as ligand **4**, in which the configuration at the stereogenic center C-4 is opposite to that of ligand **3**, gave 94% yield and 8.6% ee (Table 1, entry 2). The above-mentioned comparison of entries 1–4 clearly shows the synergistic effects of the different chiral elements of ligands on the enantioselectivity of the reactions: one between the backbone stereocenters C-2 and C-4 (Figure 2); another between the stereocenters of the ligand backbone and the configuration of the binaphthyl phosphite moieties (Figure 1). The value of the enantiomeric excess is controlled by all chiral elements, whereas the sense of enantioselectivity is mainly controlled by the configuration of the binaphthyl phosphite moieties.

2-Cyclopentenone (**5a**) and 2-cycloheptenone (**5c**) were also reacted with diethylzinc in the presence of ligand **3** and $Cu(OTf)_2$, respectively. A significant dependence of the stereoselectivity on the ring size of the substrate was observed: 35% ee for 2-cyclopentenone (Table 1, entry 5), 59% ee for 2-cyclohexenone (Table 1, entry 3), and 11% ee for 2-cycloheptenone (Table 1, entry 6).

When $(CuOTf)_2 \cdot C_6H_6$ was used as the source of copper ion, it was interesting to find enhanced yield and enantioselectivity for both substrates **5a** and **5b**. Substrate **5b** gave 94% yield and 74% ee (Table 1, entry 8), while substrate **5a** gave 36% yield and 64% ee (Table 1, entry 7). These results (Table 1, entries 3, 5, 7, and 8) suggested that the matched combination of $(CuOTf)_2 \cdot C_6H_6$, and ligand **3** under the reaction conditions gave better enantioselectivity and chemical yield of the product **6b** (Table 1, entry 7).

A profound solvent effect on enantioselectivity was observed and the results are summarized in Table 2. Contrary to the common notion that the use of a coordinating solvent is detrimental to either the yield or the ee values in most asymmetric catalytic reactions involving the use of diethylzinc as a reagent, Alexakis et al. have shown that asymmetric conjugate addition of diethylzinc to enones gave higher ees compared to reactions carried out in other reaction media.[16] In our cases, we also found that ethereal solvents (ether and THF, Table 2, entries 6, 7) proved to be more effective than the non-coordinating toluene and dichloromethane solvents (Table 2, entries 4, 5). When the reaction was carried out in THF, higher enantioselectivity (84% ee) was observed (Table 2, entry 7).

The effect of reaction temperature on enantioselectivity was also investigated. Like many similar reactions, higher enantioselectivity was obtained at a lower reaction temperature (Table 2). When the reaction temperature was lowered from 0 ^{0}C to −78 ^{0}C, enantioselectivity increased from 82% ee to 88% ee in THF (Table 2, entries 2, 7, and 8). When the reaction temperature was lowered from 0 ^{0}C to −40 ^{0}C, enantioselectivity rose from 63% ee to 74% ee in toluene (Table 2, entries 3 and 4). This finding is consistent with that obtained by Alexakis et al.

Table 2. The effect of reaction temperature on the conjugate addition of diethylzinc to 2-cyclohexenone catalyzed by $(CuOTf)_2 \cdot C_6H_6$-L_3 complex.[a]

Entry	Solvent	T [^{0}C]	t [h]	Conversion [%][b]	Yield [%][b]	ee [%][b]
1	THF	0	3	96%	76%	82% (*R*)
2	toluene	0	3	>99%	96%	63% (*R*)
3	toluene	−40	17	>99%	94%	74% (*R*)
4	CH_2Cl_2	−40	17	>99%	82%	67% (*R*)
5	ether	−40	17	>99%	80%	81% (*R*)
6	THF	−40	17	>99%	95%	84% (*R*)
7	THF	−78	5	64%	54%	88% (*R*)

[a] Reaction conditions: $(CuOTf)_2 \cdot C_6H_6$ (0.01 mmol), L_3 (0.02 mmol), $ZnEt_2$ (1.2 mmol), 2-cyclohexenone (0.5 mmol), solvent (4 mL).
[b] The data on yield, and the enantiomeric excess of the product were determined using the same conditions as noted in Table 1.
[c] $ZnEt_2$ (1.2 mmol) in 0.5 mL THF.

Conclusion

New chiral aryl diphosphite ligands, based on the pyranoside backbones of glucose and galactose, have been synthesized. Their copper complexes are efficient catalysts for the asymmetric conjugate addition of diethylzinc to cyclic enones. Two cooperative effects of the stereochemistry of ligands on the enantioselectivity were observed in the reactions: one between the backbone stereocenters C-2 and C-4; another between the stereocenters of the ligand backbone and the configuration of the binaphthyl phosphite moieties.

Experimental Section

Reagents and Materials

All experiments were carried out under a nitrogen atmosphere. $(CuOTf)_2 \cdot C_6H_6$, $Cu(OTf)_2$ and Et_2Zn (neat) were purchased from Aldrich and were used without further purification. 2-Cyclohexenone, 2-cyclopentenone and 2- cycloheptenone were dried with anhydrous sodium sulphate, distilled and degassed with dry nitrogen before use. Toluene, ether and THF were distilled from sodium. Dichloromethane was distilled over calcium hydride. The other commercially available reagents were used as received without further purification. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR were recorded on a Varian AS 500 at room temperature. ^{1}H NMR spectra are reported in ppm with TMS as an internal standard ($\delta = 0$ ppm). ^{31}P NMR spectra are reported in ppm with 85% H_3PO_4 as an external reference. Mass spectrometry was performed using a Finnigan MAT 95S model spectrometer.

The crystals of phenyl 3,6-anhydro-β-D-glucopyranoside were coated in an inert oil prior to transfer to a cold nitrogen gas stream on a Bruker CCD area-detector diffractomer system equipped with Mo Kα radiation ($\lambda = 0.71073$E). Data were collected with narrow ($R_{(int)} = 0.0175$) frame exposures. Intensities were corrected empirically for absorption, based on the SADABS (Sheldrick, 1996) program, $T_{min} = 0.9670$, $T_{max} = 0.9888$, and 3777 measured reflections. The structure was refined on F^2 values for all unique data. All H atoms were obtained by geometrical analysis with 1740 Friedel pairs, and Flack parameter = 0.8(9). Programs used were SHELXS97 (Sheldrick, 1997) and SHELXTL-NT for structure solution, refinement and molecular graphics.

Phenyl 6-*O*-*p*-Tolylsulphonyl-β-D-galactopyranoside (8) and Phenyl 6-*O*-*p*-Tolylsulphonyl-β-D-glucopyranoside (11)

Phenyl β-D-galactopyranoside (**7**; 0.996 g, 3.89 mmol) was dissolved in 20 mL of dry pyridine, and mixed at −15 °C with toluene-*p*-sulphonyl chloride (0.744 g, 3.92 mmol) in 10 mL of dry pyridine. The reaction mixture was kept for 30 min. at −15 °C and 12 h at 20 °C, and the pyridine was distilled off under reduced pressure at 40 °C. The residue was dissolved in chloroform. The chloroform solution was washed with saturated potassium hydrogen sulphate solution, saturated sodium hydrogen carbonate solution, and dried with anhydrous sodium sulphate. Since the solution had a tendency to gel, all these operations were conducted at 50 °C. After the removal of chloroform, the dry powder was dissolved in 200 mL of toluene under reflux, and the solution was left to crystallize. Compound **8** was obtained as a colourless crystal; yield: 0.407 g (25%). ^{1}H NMR (500 MHz, CD_3OD): $\delta = 2.34$ (s, 3H, CH_3), 3.50 (dd, 1H, C3-H, $J_{(3,4)} = 3.5$ Hz, $J_{(2,3)} = 10$ Hz), 3.67 (m, 1H, C5-H), 3.77 (d, 1H, C4-H, $J_{(3,4)} = 3.5$ Hz), 3.88 (dd, 1H, C6-H, $J_{(5,6)} = 3.5$ Hz, $J_{(6,6)} = 8.0$ Hz), 4.12 (dd, 1H, C6-H, $J_{(5,6)} = 10.5$ Hz, $J_{(6,6)} = 8.0$ Hz), 4.22 (dd, 1H, C2-H, $J_{(2,3)} = 10$ Hz, $J_{(1,2)} = 7.5$ Hz), 4.76 (d, 1H, C1-H, $J_{(1,2)} = 7.5$ Hz), 6.97–7.67 (m, 9H, Ar-H); anal. calcd. for $C_{19}H_{22}O_8S$: C 55.6, H 5.4, S, 7.8.; found: C 55.0, H 5.7, S 7.5.

Treatment of phenyl β-D-glucopyranoside (**10**) and toluene-*p*-sulphonyl chloride as described for compound **8** afforded compound **11** as a colourless crystal; yield: 0.65 g (41%). ^{1}H NMR (500 MHz, DMSO): $\delta = 2.36$ (s, 3H, CH_3), 3.60 (t, 1H, C3-H), 4.04 (dd, 1H, C5-H, $J_{(4,5)} = 10.5$ Hz, $J_{(5,6)} = 5.5$ Hz), 4.30 (d, 1H, C4-H, $J_{(4,5)} = 10.5$ Hz), 4.90 (d, 1H, C6-H, $J_{(6,6)} = 7.5$ Hz), 5.20 (d, 1H, C6-H, $J_{(5,6)} = 5.5$ Hz), 5.30 (d, 1H, C2-H, $J_{(2,1)} = 5$ Hz), 5.40 (d, 1H, C1-H, $J_{(2,1)} = 5$ Hz), 6.96–7.71 (m, 9H, Ar-H); anal. calcd. for $C_{19}H_{22}O_8S$: C 55.6, H 5.4, S 7.8; found: C 55.1, H 5.6, S, 7.7.

Phenyl 3,6-Anhydro-β-D-galactopyranoside (9) and Phenyl 3,6-Anhydro-β-D-glucopyranoside (12)

Phenyl 6-*O*-*p*-tolylsulphonyl-β-D-galactopyranoside (**8**; 0.65 g, 1.585 mmol) in ethanol (20 mL) was converted by a solution of sodium hydroxide (20 mL, 1 N) at 80–85 °C in 2 h into compound **9**, which was extracted with ether-acetone (1:1, v/v). Evaporation of the extract yielded a colourless syrup. Trituration with ether induced crystallization and a colourless powder was obtained after recrystallization from ether; yield: 0.372 g (94%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.80 (dd, 1H, C5-H, $J_{(5,6)}$ = 10 Hz, $J_{(4,5)}$ = 3 Hz), 4.35 (d, 1H, C4-H, $J_{(4,5)}$ = 3 Hz), 4.15 (m, 4H, C2-H, C3-H, C6-H), 5.24 (s, 1H, C1-H), 6.89–7.22 (m, 5H, Ar-H); anal. calcd. for $C_{12}H_{14}O_5$: C 60.5, H 5.9%; found: C 60.4, H 5.5%.

Treatment of phenyl 6-*O*-*p*-tolylsulphonyl-β-D-glucopyranoside (**11**) as described for compound **9** afforded compound **12** as colourless crystals; yield: 0.210 g (53%). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.80 (m, 2H, C2-H, C4-H), 4.07 (t, 1H, C5-H), 4.13 (m, 3H, C6-H, C3-H), 5.50 (s, 1H, C1-H), 6.66–7.22 (m, 5H, Ar-H); anal. calcd. for $C_{12}H_{14}O_5$: C 60.5, H 5.9; found: C 60.2, H 5.8.

2,4-Bis{[(*R*)-1,1′-binaphthyl-2,2′-diyl] Phosphite}-phenyl 3,6-Anhydro-β-D-galactopyranoside (1)

(*R*)-(1,1′-Binaphthyl-2,2′-dioxy)-chlorophosphine (2.2 mmol) was synthesized *in situ*,[17] dissolved in toluene (5 mL), and pyridine (0.36 mL, 4.6 mmol) was added. Phenyl 3,6-anhydro-β-D-galactopyranoside (**9**; 0.238 g, 1 mmol) was azeotropically dried with toluene (3 × 5 mL) and then dissolved in toluene (10 mL) to which pyridine (0.18 mL, 2.3 mmol) had been added. The diol solution was transferred slowly at room temperature to the solution of phosphorochloridite. The reaction mixture was stirred overnight at reflux, and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (toluene, R_f = 0.68) to produce a white powder; yield: 0.396 g (46%). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 133.5 (s, 1P), 146.7 (s, 1P); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.80 (dd, 1H, C2-H, $J_{(1,2)}$ = 3 Hz, $J_{(2,3)}$ = 20 Hz), 4.09 (d, 1H, C3-H, $J_{(2,3)}$ = 20 Hz), 4.30 (s, 1H, C4-H), 4.51 (dd, H, C6-H, $J_{(5,6)}$ = 0.5 Hz, $J_{(6,6)}$ = 5.0 Hz), 4.64 (d, 1H, C6-H, $J_{(6,6)}$ = 5.0 Hz), 4.98 (dd, C5-H, $J_{(6,\ 5)}$ = 2 Hz, $J_{(6,5)}$ = 8 Hz), 5.24 (s, 1H, C1-H), 6.87–8.04 (m, 29H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 70.0 (s, C6), 73.5(d, C4), 74.8 (s, C3), 77.1 (d, C5), 79.0 (d, C2), 97.4 (s, C1), 115.8 (CH=), 120.5 (CH=), 121.4 (CH=), 121.6 (CH=), 122.0 (CH=), 122.1(CH=), 122.6 (CH=), 123.8 (CH=), 123.9 (CH=), 124.2 (CH=), 124.3 (CH=), 125.0 (CH=), 125.2 (CH=), 125.3 (CH=), 125.4 (CH=), 126.2 (CH=), 126.3 (CH=), 126.4 (CH=), 126.5 (CH=), 126.9 (CH=), 127.0 (CH=), 128.2 (CH=), 128.3 (CH=), 128.4 (CH=), 128.5 (CH=), 129.0 (CH=), 129.5 (CH=), 130.1 (CH=), 130.5 (CH=), 130.7 (CH=), 130.9 (CH=), 131.2 (CH=), 131.6 (C), 131.7 (CH=), 132.5 (CH=), 132.7 (CH=), 132.8 (CH=), 137.8 (C), 146.8 (C), 147.1 (C), 147.6 (C), 147.7 (C), 147.8 (C), 147.9 (C), 156.4 (C); MS (5.48×10^4 eV): *m/e* (int (%) = 867 (1.9) [M + 1], 889 (1.1) [M + Na], 317 (100), 235 (19), 285 (24).

2,4-Bis{[(*S*)-1,1′-binaphthyl-2,2′-diyl] Phosphite}-phenyl 3,6-Anhydro-β-D-galactopyranoside (2)

Treatment of *in situ* formed[17] (*S*)-(1,1′-binaphthyl-2,2′-dioxy)-chlorophosphine (2.2 mmol) and compound **9** as described for compound **1** afforded diphosphite **2**, which was purified by flash chromatography (toluene, R_f = 0.64) to produce a white powder; yield: 0.405 g (47%). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 137.1 (s, 1P), 140.5 (s, 1P); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.86 (dd, 1H, C2-H, $J_{(1,2)}$ = 3 Hz, $J_{(2,3)}$ = 9.5 Hz), 4.11 (d, 1H, C3-H, $J_{(2,3)}$ = 9.5 Hz), 4.35 (s, 1H, C4-H), 4.38 (d, H, C6-H, $J_{(6,6)}$ = 5.0 Hz), 4.46 (dd, 1H, C6-H, $J_{(5,6)}$ = 10 Hz, $J_{(6,6)}$ = 5.0 Hz), 4.88 (dd, C5-H, $J_{(6,5)}$ = 2 Hz, $J_{(6,5)}$ = 9.5 Hz), 5.22 (s, 1H, C1-H), 6.73–7.93 (m, 29H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 71.0 (s, C6), 73.8 (d, C4), 75.8 (s, C3), 77.9 (d, C5), 79.9 (d, C2), 90.4 (s, C1), 118.8 (CH=), 120.5 (CH=), 121.5 (CH=), 121.6 (CH=), 121.9 (CH=), 122.3 (CH=), 122.6 (CH=), 123.7 (CH=), 123.9 (CH=), 124.2 (CH=), 124.9 (CH=), 125.0 (CH=), 125.2 (CH=), 125.3 (CH=), 125.4 (CH=), 126.2 (CH=), 126.3 (CH=), 126.4 (CH=), 126.5 (CH=), 126.8 (CH=), 127.7 (CH=), 128.2 (CH=), 128.3 (CH=), 128.4 (CH=), 128.5 (CH=), 129.1 (CH=), 129.5 (CH=), 130.1 (CH=), 130.5 (CH=), 130.7 (CH=), 130.9 (CH=), 131.2 (CH=), 131.6 (C), 131.7 (CH=), 132.5 (CH=), 132.7 (CH=), 132.8 (CH=), 137.8 (C), 146.8 (C), 147.3 (C), 147.6 (C), 147.7 (C), 147.8 (C), 147.9 (C), 150.4 (C); MS (5.34×10^4 eV): *m/e* (int (%) = 867 (2.2) [M + 1], 889 (1.9) [M + Na], 317 (100), 235 (23), 285 (34).

2,4-Bis{[(*R*)-1,1′-binaphthyl-2,2′-diyl] Phosphite}-phenyl 3,6-Anhydro-β-D-glucopyranoside (3)

Treatment of *in situ* formed (*R*)-(1,1′-binaphthyl-2,2′-dioxy)-chlorophosphine (2.2 mmol) and compound **12** as described for compound **1** afforded diphosphite **3**, which was purified by flash chromatography (toluene, R_f = 0.54) to produce a white powder; yield: 0.324 g (37%). ^{31}P NMR (202 MHz, $CDCl_3$): δ = 109.6 (d, 1P, $J_{(P,P)}$ = 5.5 Hz), 146.0 (d, 1P, $J_{(P,P)}$ = 5.5 Hz); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.00 (s, 1H, C3-H), 3.34 (dd, 1H, C2-H, $J_{(2,3)}$ = 2.5 Hz, $J_{(1,2)}$ = 10.5 Hz), 3.65 (t, 1H, C5-H), 3.79 (t, 1H, C4-H), 3.90 (d, 1H, C6-H, $J_{(6,6)}$ = 10.5 Hz), 3.94 (t, 1H, C6-H), 5.23 (s, 1H, C1-H), 6.44–7.97 (m, 29H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 66.0 (q, C6), 69.2 (q, C4), 69.5 (s, C3), 71.5 (m, C5), 75.0 (d, C2), 98.7 (d, C1), 116.3 (CH=), 120.4 (CH=), 120.5 (CH=), 121.3 (CH=), 121.4 (CH=), 121.5 (CH=), 121.9 (CH=), 122.0 (CH=), 122.1 (CH=), 122.2 (CH=), 122.3 (CH=), 122.8 (CH=), 123.6 (CH=), 124.5 (CH=), 124.6 (CH=), 125.1 (CH=), 125.2 (CH=), 125.3 (CH=), 125.4 (CH=), 126.3 (CH=), 126.5 (CH=), 127.3 (CH=), 128.4 (CH=), 128.6 (CH=), 129.8 (C), 129.9 (CH=), 130.0 (CH=), 130.4 (CH=), 130.5 (CH=), 130.8 (CH=), 131.1 (CH=), 131.4 (CH=), 131.8 (CH=), 132.6 (CH=), 133.0 (C), 134.2 (C), 134.5 (C), 138.2 (C), 147.3 (C), 147.8 (C), 147.9 (C), 148.3 (C), 148.4 (C), 148.9 (C), 149.0 (C), 156.8.4 (C); MS (5.07×10^4 eV): *m/e* (int (%) = 867 (3.2) [M + 1], 889 (1.1) [M + Na], 317 (100), 235 (19), 285 (50).

2,4-Bis{[(*S*)-1,1′-binaphthyl-2,2′-diyl] Phosphite}-phenyl 3,6-Anhydro-β-D-glucopyranoside (4)

Treatment of *in situ* formed (*S*)-(1,1′-binaphthyl-2,2′-dioxy)-chlorophosphine (2.2 mmol) and compound **12** as described for compound **1** afforded diphosphite **4**, which was purified by flash chromatography (toluene, $R_f = 0.41$) to produce a white powder; yield: 0.224 g (26%); ^{31}P NMR (202 MHz, $CDCl_3$): δ = 110.0 (d, 1P, $J_{(P,P)} = 3.7$ Hz), 146.8 (d, 1P, $J_{(P,P)} = 3.7$ Hz); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.20 (s, 1H, C3-H), 3.39 (dd, 1H, C2-H, $J_{(2,3)} = 2.0$ Hz, $J_{(1,2)} = 10$ Hz), 3.41 (t, 1H, C5-H), 3.68 (t, 1H, C4-H), 3.75 (d, 1H, C6-H, $J_{(6,6)} = 10$ Hz), 3.94 (t, 1H, C6-H), 5.23 (s, 1H, C1-H), 6.12–8.03 (m, 29H, Ar-H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 62.0 (q, C6), 64.2 (q, C4), 68.5 (s, C3), 70.5 (m, C5), 74.0 (d, C2), 92.7 (d, C1), 116.3 (CH=), 120.4 (CH=), 120.5 (CH=), 121.3 (CH=), 121.4 (CH=), 121.5 (CH=), 121.9 (CH=), 122.0 (CH=), 122.1 (CH=), 122.2 (CH=), 122.3 (CH=), 122.8 (CH=), 123.6 (CH=), 124.5 (CH=), 124.6 (CH=), 125.1 (CH=), 125.2 (CH=), 125.3 (CH=), 125.4 (CH=), 126.3 (CH=), 126.5 (CH=), 127.3 (CH=), 128.4 (CH=), 128.6 (CH=), 129.8 (C), 129.9 (CH=), 130.0 (CH=), 130.4 (CH=), 130.5 (CH=), 130.8 (CH=), 131.1 (CH=), 131.4 (CH=), 131.8 (CH=), 132.6 (CH=), 133.0 (C), 134.2 (C), 134.5 (C), 138.2 (C), 147.3 (C), 147.8 (C), 147.9 (C), 148.3 (C), 148.4 (C), 148.9 (C), 149.0 (C), 156.8 (C); MS (5.17×10^4 eV): *m/e* (int (%) = 867 (4.2) [M + 1], 889 (2.1) [M + Na], 317 (100), 235 (18), 285 (40).

Typical Procedure for the Conjugate Addition of Diethylzinc to 2-Cyclohexenone

A solution of $(CuOT_f)_2 \cdot C_6H_6$ (2.52 mg, 0.01 mmol) and L_3 (17.3 mg, 0.02 mmol) in 4 mL THF was stirred for 1.0 hour. The solution was cooled to −40 °C, and 2-cyclohexenone (48 μL, 0.5 mmol) and diethylzinc (123 μL, 1.2 mmol) were added. After stirring for 17.0 hours at −40 °C, the solution was mixed with 2.0 mL water and 2.0 mL of hydrochloric acid solution (2.0 M), and the product was extracted with 3 × 5.0 mL ethyl acetate. The combined organic layer was washed with saturated sodium hydrogen carbonate solution, brine, and then dried over anhydrous sodium sulphate. Most of the solvent was removed at reduced pressure. The crude product, 3-ethylcyclohexenone, was obtained. The conversion and yield were determined by GC-MS using dodecane as an internal standard on an HPG 1800C GCD system with a Bexs column (30 m × 0.25 mm I. D.). The enantiomeric excess of the product was determined by GC using an HP5890 gas chromatograph equipped with a Chiraldex A-TA column (50 m × 0.25 mm I. D.). The absolute configuration of the product 3-ethylcyclohexenone was determined by comparison with authentic samples.

Acknowledgements

We thank the Hong Kong Research Grants Council (Project No. PolyU 5185/00P), and The Hong Kong Polytechnic University ASD Fund for financial support of this study.

References and Notes

[1] For recent reviews on asymmetric conjugate addition: see: a) M. P. Sibi, S. Manyem, *Tetrahedron* **2000**, *56*, 8033–8061; b) N. Krause, A. A. Hoffmann-Röder *Synthesis* **2001**, 171–196; c) A. Alexakis, C. Benhaim *Eur. J. Org. Chem.* **2002**, 3221–3236.

[2] a) A. W. Hird, A. H. Hoveyda, *Angew Chem. Int. Ed.* **2003**, *43*, 1276–1279; b) H. Mizutani, S. J. Degrado, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 779–781; c) C. A. Luchaco-Cullis, A. H. Hoveyda, *J. Am. Chem. Soc.* **2002**, *124*, 8192–8193; d) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; e) I. H. Escher, A. Pfaltz, *Tetrahedron* **2000**, *56*, 2879–2888.

[3] a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353; b) R. Naasz, L. A. Arnold, M. Pineschi, E. Keller, B. L. Feringa, *J. Am. Chem. Soc.* **1999**, *121*, 1104–1105; c) B. L. Feringa, M. Pineschi, L. A. Arnold, R. Imbos, A. H. M. de Vries, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2620–2623.

[4] a) A. Alexakis, J. Burton, J. Vastra, C. Benhaim, X. Fournioux, A. van den Heuvel, J. M. Leveque, F. Maze, S. Rosset, *Eur. J. Org. Chem.* **2000**, 4011–4027; b) A. Alexakis, J. Vastra, J. Burton, C. Benhaim, P. Mangency, *Terahedron Lett.* **1998**, *39*, 7869–7872.

[5] a) M.Yan, L. W. Yang, A. S. C. Chan, *Chem. Commun.* **1999**, 11–12; b) M. Yan, A. S. C. Chan, *Tetrahedron Lett.* **1999**, *40*, 6645–6648; c) M. Yan, A. S. C. Chan, *Chem. Commun.* **2000**, 115–116.

[6] M. Spescha, *Helv. Chim. Acta* **1993**, *76*, 1832–1846.

[7] a) R. Selke, H. Pracejus, *J. Mol. Catal.* **1986**, *37*, 213–225; b) A. Kumar, G. Oehme, J. P. Roque, M. Schwartze, R. Selke, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2197–2199.

[8] O. Pamies, S. Van, P. F. Gino, M. Dieguez, S. Deeerenberg, G. Net, T. V. Rajanbabu, T. A. Ayers, G. A. Halliday, K. K. You, J. C. Calabrese, *J. Org. Chem.* **1997**, *62*, 6012–6028.

[9] M. Dieguez, O. Pamies, A. Ruiz, C. Claver, *New J. Chem.* **2002**, *26*, 827–833.

[10] E. Guiu, B. Munoz, S. Castillon, C. Claver, *Adv. Synth. Catal.* **2003**, *345*, 169–171.

[11] O. Pamies, G. P. F. van Strijdonck, M. Diegzeez, S. Deerenberg, G. Net, A. Ruiz, C. Claver, P. C. J. Kamer, P. W. N. M. van Leeuwen, *J. Org. Chem.* **2001**, *66*, 8867–8871.

[12] a) M. Dieguez, A. Ruiz, C. Claver, *Tetrahedron: Asymmetry* **2001**, *12*, 2861–2866; b) O. Pamies, G. Net, A. Ruiz, C. Claver, *Tetrahedron: Asymmetry* **1999**, *10*, 2007–2014.

[13] J. L. Frahn, J. A. Mills, *Aust. J. Chem.* **1965**, *18*, 1303.

[14] A. B. Foster, W. G. Overend, G. Vaughan, *J. Chem. Soc.* **1954**, 3625.

[15] a) G. J. H. Buisman, L. A. van der Veen, A. Klootwijk, A.; W. G. J. der Lange, P. C. J. Kamer, P. W. N. M. van - Leeuwen, D. Vogt, *Organometallics* **1997**, *16*, 2929–29 39; b) D. D. Pastor, S. P. Shum, R. K. Rodebaugh, A. D. Debellis, F. H. Clarke, *Helv. Chim. Acta* **1993**, *76*, 900–914.

[16] a) A. H. M. de Vries, A. Meetsma, B. L. Feringa, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2374–2376; b) A. Alexakis, J. Frutos, P. Mangeney, *Tetrahedron: Asymmetry* 1993, *4*, 2427–2430.

[17] S. Cserepi-Szucs, G. Huttner, L. Zsolnai, A. Szolosy, C. Hegedüs, J. Bakos, *Inorg. Chim. Acta* **1999**, #33#*296*, 222–230.

[18] A. Alexakis, C. Benhaim, S. Rosset, M. Humam, *J. Am. Chem. Soc.* **2002**, *124*, 5262–5263.

