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Synthesis of novel chiral bidentatephosphite ligands derived from the pyranoside backbone of monosaccharides and their application in the Cu-catalyzed conjugate addition of dialkylzinc to enones

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ABSTRACT

A series of novel bidentatephosphite ligands, derived from methyl 3,6-anhydro-α-D-glucopyranoside and chlorophosphoric acid diaryl ester, were easily synthesized. These ligands were successfully employed in the Cu-catalyzed asymmetric conjugate 1,4-addition of the organozinc reagents diethylzinc and/or dimethylzinc to enones. The stereochemically matched combination of glucopyranoside and (*R*)-H_8-binaphthyl in ligand 2,4-bis{[(*R*)-1,1′-H_8-binaphthyl-2,2′-diyl] phosphite}-methyl 3,6-anhydro-α-D-glucopyranoside was essential to afford 85% ee for 3-ethylcyclohexanone with an (*S*)-configuration in THF, using $Cu(OTf)_2$ as a catalytic precursor. When the reaction was carried out at lower temperatures, changing from −10 to −80 °C, a marginal influence of the temperature on the enantioselectivity of the reaction was observed. The presence of the methyl substituent at the 1-position of the glucopyranoside skeleton had a negative effect on the enantioselectivity in the 1,4-addition of $ZnEt_2$ to acyclic enones.

1. Introduction

The development of highly efficient chiral ligands for homogeneous transition metal catalyzed 1,4-conjugate addition, which is one of the most powerful tools for the synthesis of many biologically active compounds, has been received much attention both from academia and industry. Over the past decades, much effort has been focused on the development of Cu-catalyzed enantioselective 1,4-conjugate additions of organozincs to α,β-unsaturated carbonyl 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 Cu-catalyzed asymmetric conjugate addition reactions, and good results have been obtained. Using carbohydrates (and derivatives) as starting materials for the synthesis of chiral ligands[6] has several advantages: (1) the raw materials are of high enantiomeric purity and are readily available; and (2) the multifunctional properties make it possible to design various structures through a series of modifications. In particular, phosphites, which are derived from carbohydrates, owing to their efficiency, facile preparation, and lower sensitivity to air and moisture, have emerged as efficient ligands for Cu-catalyzed asymmetric conjugate 1,4-addition.[1a,6c–e,7] In recent decades, combinatorial and high-throughput synthetic strategies have been applied to the design and synthesis of new chiral catalysts,[8] and have led to the development of some highly efficient chiral ligands used in transition metal catalytic reactions. It is noteworthy that ligand tuning has allowed the rapid development of efficient catalytic systems.[1a,6c–e,7,9]

In our group, we have reported that bidentatephosphite ligands **1a**–**1d** (Fig. 1), which were derived from a phenyl 3,6-anhydro-β-D-glucopyranoside backbone, were synthesized and employed successfully in Cu-catalyzed asymmetric 1,4-additions of dialkylzinc reagents to enones with up to 93% ee.[10] The stereochemically matched combination of the phenyl 3,6-anhydro-β-D-glucopyranoside backbone and chlorophosphoric acid diaryl ester in ligands **1a** and **1c** was essential in inducing high enantioselectivity for products with an (*R*)-configuration. However, the reaction did have a major problem, in that the use of ligands **1b** and **1d** with the same glucopyranoside backbone as ligands **1a** and **1c**, and (*S*)-binaphthol and/or (*S*)-H_8-binaphthol moieties, gave low enantioselectivities for products with an (*S*)-configuration, which is the desired active pharmaceutical ingredient of erogorgiaene[11a] and ibuprofen.[11b] In an effort to overcome this problem and enhance the enantioselectivity for products with an (*S*)-configuration, we considered tuning ligands **1a**–**1d** to develop novel chiral ligands bearing a D-glucopyranoside scaffold. For ligands **1a**–**1d** based on glucopyranoside derivatives, it is interesting to note that the ^{31}P NMR spectra of ligands **1b** and **1d** showed two singlets (one for each phosphorus moiety), while two doublets for ligands **1a** and **1c** were presented. There were different J_{PP} values in ligands **1a** (J_{PP} = 5.5 Hz) and **1c** (J_{PP} = 6.1 Hz).[10] In view of the ^{31}P NMR spectral analysis of ligands

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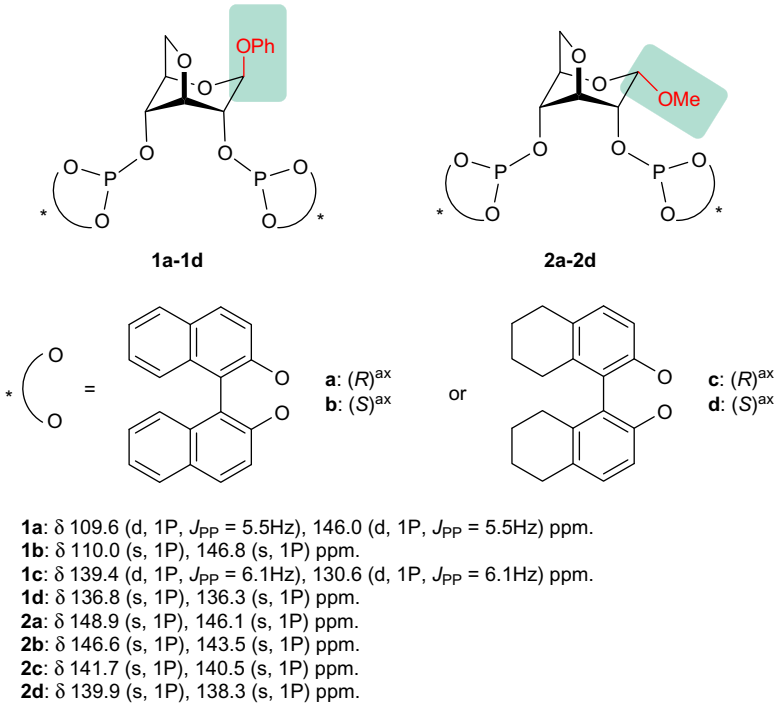


1a: δ 109.6 (d, 1P, J_{PP} = 5.5Hz), 146.0 (d, 1P, J_{PP} = 5.5Hz) ppm.
1b: δ 110.0 (s, 1P), 146.8 (s, 1P) ppm.
1c: δ 139.4 (d, 1P, J_{PP} = 6.1Hz), 130.6 (d, 1P, J_{PP} = 6.1Hz) ppm.
1d: δ 136.8 (s, 1P), 136.3 (s, 1P) ppm.
2a: δ 148.9 (s, 1P), 146.1 (s, 1P) ppm.
2b: δ 146.6 (s, 1P), 143.5 (s, 1P) ppm.
2c: δ 141.7 (s, 1P), 140.5 (s, 1P) ppm.
2d: δ 139.9 (s, 1P), 138.3 (s, 1P) ppm.

Figure 1. Chiral bidentatephosphite ligands derived from glucopyranoside.

1a–**1d**, and, the large difference in reactivity and enantioselectivity, which was induced by ligands **1a**–**1d**, we decided to vary the substituents at the 1-position of the glucopyranoside skeleton in the hope of further improving the performance of the chiral catalyst. Herein we report the synthesis of novel bidentatephosphite ligands **2a**–**2d** (Fig. 1 and Scheme 1) based on methyl 3,6-anhydro-α-D-glucopyranoside, and their application in the Cu-catalyzed asymmetric 1,4-additions of dialkylzincs to enones.

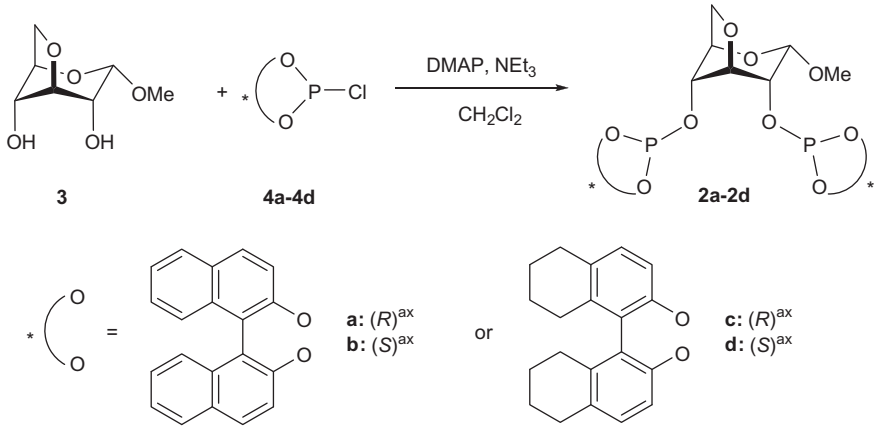
2. Results and discussion

2.1. Synthesis of phosphite ligands 2a–2d

As shown in Scheme 1, bidentatephosphite ligands **2a**–**2d** were synthesized stereospecifically in one step from methyl 3,6-anhydro-α-D-glucopyranoside **3**, and 2,2′-dihydroxy-1,1′-binaphthyl phosphochloridites **4a**–**4b** or 2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl phosphochloridites **4c**–**4d**, by starting from commercially available, enantiopure 2,2′-dihydroxy-1,1′-binaphthol or 2,2′-dihydroxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthol. Compounds **3**[10] and **4a**–**4d**[12] were prepared conveniently according to the literature procedures. All of the ligands were stable during the purification of neutral silica gel under a nitrogen atmosphere with reasonable yields, while the ^{1}H NMR, ^{13}C NMR, and HRMS were consistent with the expectation for them. The ^{31}P NMR spectra of ligands **2a**–**2d** showed two singlets (one for each phosphorus moiety, Fig. 1).

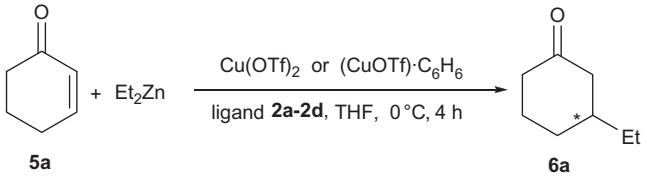
2.2. Asymmetric 1,4-conjugate addition of ZnR_2 to enones

In the first set of experiments, ligands **2a**–**2d** were screened separately in the asymmetric 1,4-addition of $ZnEt_2$ to cyclohexenone **5a** using $Cu(OTf)_2$ as the catalytic precursor in THF (Table 1, entries 1–4). Ligand **2a** gave a 68% yield and 55% ee (*S*) (Table 1, entry 1). In contrast, the use of ligand **2b**, based on the same glucopyranoside as ligand **2a,** but with an opposite configuration of the binaphthyl



Scheme 1. The synthesis of chiral bidentatephosphite ligands **2a**–**2d** derived from methyl 3,6-anhydro-α-D-glucopyranoside.

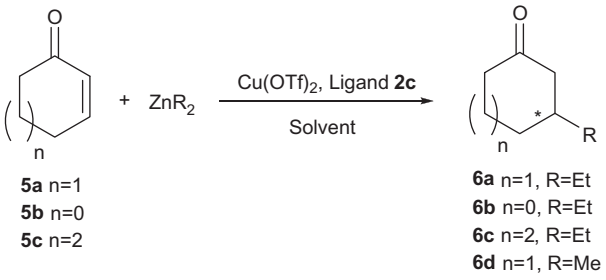
Table 1
Cu-catalyzd asymmetric conjugate 1,4-addition of $ZnEt_2$ to 2-cyclohexenone **5a**[a]



Entry	Cu salts	Ligand	L./Cu	Conv.[b] (%)	Yield [b] (%)	% ee (Conf.) [c]
1	$Cu(OTf)_2$	**2a**	2	91	68	55 (*S*)
2	$Cu(OTf)_2$	**2b**	2	36	27	23 (*R*)
3	$Cu(OTf)_2$	**2c**	2	>99	92	80 (*S*)
4	$Cu(OTf)_2$	**2d**	2	73	52	22 (*R*)
5	$(CuOTf)_2{\cdot}C_6H_6$	**2a**	2	94	74	42 (*S*)
6	$(CuOTf)_2{\cdot}C_6H_6$	**2c**	2	>99	96	60 (*S*)
7	$Cu(OTf)_2$	**2c**	0.5	84	56	77 (*S*)
8	$Cu(OTf)_2$	**2c**	1	99	90	81 (*S*)
9	$Cu(OTf)_2$	**2c**	1.1	99	90	80 (*S*)

[a] Reaction conditions: $Cu(OTf)_2$ (0.005 mmol) or $(CuOTf)_2{\cdot}C_6H_6$ (0.0025 mmol), ligand (0.025–0.015 mmol), $ZnEt_2$ (1.0 M in hexane, 0.6 mmol), **5a** (0.25 mmol), THF (4 mL), 0 °C, 4 h.
[b] The data on conversions and yields were determined by GC using dodecane as an internal standard with an SE-30 column (30 m × 0.32 mm ID).
[c] The enantiomeric excess of **6a** was determined by GC equipped with a Chiraldex A–TA column (50 m × 0.25 mm ID). The absolute configuration of **6a** was determined by comparison with an authentic sample.

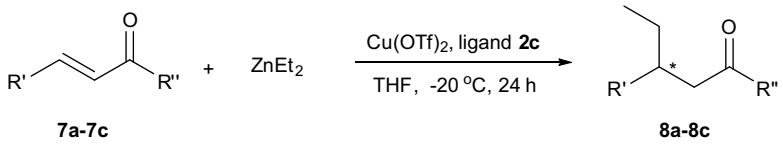
Table 2
Cu-catalyzed asymmetric 1,4-addition of dialkylzinc to cyclic enones[a]



Entry	Sub.	Solvent	*T* (°C)	Time (h)	Conv. [b] (%)	Yield [b] (%)	% ee (Conf.) [b]
1	**5a**	CH_2Cl_2	0	4	>99	62	19 (*S*)
2	**5a**	Toluene	0	4	>99	86	26 (*R*)
3	**5a**	Et_2O	0	4	>99	73	14 (*R*)
4	**5a**	THF	20	4	98	93	73 (*S*)
5	**5a**	THF	−10	4	97	93	80 (S)
6	**5a**	THF	−20	4	85	79	84 (*S*)
7	**5a**	THF	−20	6	92	92	85 (*S*)
8	**5a**	THF	−20	8	96	89	85 (*S*)
9	**5a**	THF	−20	12	98	91	84 (*S*)
10	**5a**	THF	−30	12	95	78	81 (*S*)
11	**5a**	THF	−40	12	90	63	82 (*S*)
12	**5a**	THF	−80	12	14	3	81 (*S*)
13	**5b**	THF	−20	12	>99	32	61 (*S*)
14[c]	**5c**	THF	−20	12	89	67	65 (*S*)
15[c,d]	**5a**	THF	−20	24	62	25	47 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (0.005 mmol), ligand **2c** (0.0055 mmol), $ZnEt_2$ (1.0 M in hexane, 0.6 mmol), cyclic enones (0.25 mmol), solvent (4 mL).
[b] The data on conversions, yields, enantiomeric excesses, and the absolute configuration of products **6b**–**6d** were determined using the same conditions as noted in Table 1.
[c] The enantiomeric excess was determined by GC equipped with a CP-Chirasil-Dex CB column (25 m × 0.25 mm ID).
[d] $ZnMe_2$ (1.1 M in toluene, 0.6 mmol).

moieties, afforded a much lower yield of 27% and an enantioselectivity of 23% (*R*) (Table 1, entry 2). Using ligand **2c**, containing the same glucopyranoside skeleton as ligand **2a** and axially chiral (*R*)-H_8-binaphthyl moieties, the yield and enantioselectivity were enhanced to 92% and 80% ee (*S*), respectively (Table 1, entry 3). However, ligand **2d** bearing the same glucopyranoside skeleton as ligand



8a: R' = Ph, R'' = Ph, 35% yield, 13% ee (*S*)

8b: R' = 4-ClC_6H_4, R'' = Ph, 31% yield, 13% ee (*S*)

8c: R' = 4-$MeOC_6H_4$, R'' = Ph, 33% yield, 11% ee (*R*)

Scheme 2. Cu-catalyzed asymmetric 1,4-addition of $ZnEt_2$ to acyclic enones **7a**–**7c**.

2a and (*S*)-H_8-binaphthyl moieties, gave a 52% yield and 22% ee (*R*) (Table 1, entry 4). The results clearly indicated that the matched combination of methyl 3,6-anhydro-α-D-glucopyranoside and (*R*)-H_8-binaphthyl moieties of ligand **2c** was more favorable with respect to inducing higher enantioselectivity than ligands **2a**, **2b**, and **2d** (Table 1, entries 1 vs 2, and entries 3 vs 4). The reason, why the stereocontrol capability of ligand **2c** was higher than ligand **2a** (Table 1, entries 1 and 3), in our opinion, may be attributed to the wider bite angle of H_8-binaphthol.[13] The enantioselectivities for product **6a** with an (*S*)-configuration can be greatly improved upon by the use of ligand **2c** in the place of ligands **1a**–**1d**.[10]

Next, the influence of the copper precursor as well as the ratio of the molar ligand to copper salts on the catalytic activity and enantioselectivity were examined (Table 1, entries 5–9). The catalysts formed in situ by $(CuOTf)_2{\cdot}C_6H_6$, in the place of $Cu(OTf)_2$, and ligands **2a** and **2c** respectively, gave lower enantioslectivity 42% (*S*) and 60% (*S*) (Table 1, entries 5 and 6). Thus, $Cu(OTf)_2$, owing to its lower sensitivity to air and moisture than $(CuOTf)_2{\cdot}C_6H_6$, was selected as a catalytic precursor in the next cases. An enhancement in enantioselectivity was observed when the ratio of the molar ligand to $Cu(OTf)_2$ ranged from 0.5/1 to 1/1 (Table 1, entries 7 and 8). A further increase of the ratio afforded no obvious change in the catalytic activity and enantioselectivity (Table 1, entries 3 and 9).

Using the catalyst prepared in situ from $Cu(OTf)_2$ and ligand **2c**, the enantioselective 1,4-addition of $ZnEt_2$ to substrate **5a** with a variety of solvents and various temperatures was investigated. The type of solvent had a decisive influence on the performance of the catalysts. The reaction in CH_2Cl_2 afforded low enantioselectivity [19% (*S*)] (Table 2, entry 1). When using toluene and Et_2O as the solvents, ligand **2c** gave 26% (*R*) ee and 14% (*R*) ee, respectively (Table 2, entries 2 and 3). However, in comparison with CH_2Cl_2, the opposite configuration of product **6a** was found. We identified THF as the most appropriate solvent (Table 1, entry 9 vs Table 2, entries 1–3). When the reaction was carried out at lower temperatures, changing from −10 to −80 °C, a marginal influence of the temperature on the enantioselectivity of the reaction was observed (Table 2, entries 5–12). In comparison, at −20 °C, the highest enantioselectivity was achieved with up to 85% ee (*S*) (Table 2, entries 6–9). Under the optimum reaction conditions, we then assessed the 1,4-addition of $ZnEt_2$ to 2-cyclopentenone **5b** and 2-cycloheptenone **5c** in the presence of ligand **2c**/$Cu(OTf)_2$. 3-Ethylcyclopentanone **6b** was obtained in 61% ee (*S*), while 3-ethylcycloheptanone **6c** was obtained in 65% ee (*S*) (Table 2, entries 13 and 14). These results indicated a significant dependence of the enantioselectivity on the ring size of the cyclic enones. The 1,4-addition reaction of $ZnMe_2$ to substrate **5a** gave low enantioselectivity [47% ee (*R*), Table 2, entry 15]. These results indicated a significant dependence of the enantioselectivity on the type of organozinc reagents employed in the reaction.

In our previous work, it had been found that acyclic enones gave lower enantioselectivities in the presence of bidentatephosphite ligands **1c**–**1d** (Fig. 1).[10a] In the presence of ligand **2c**, the asymmetric 1,4-addition of $ZnEt_2$ to acyclic enones was evaluated. However, poor enantioselectivities were observed; 13% ee (*S*) for 1,3-diphenyl-1-pentanone **8a**, 13% ee (*S*) for 3-(4-chlorophenyl)-1-phenylpentanone **8b**, and 11% ee (*R*) for 3-(4-methoxyphenyl)-1-phenylpentanone **8c** (Scheme 2).

This indicated that ligand **2c** was inferior for the reaction of $ZnEt_2$ to acyclic enones **7a**–**7c**. These results suggested that the presence of the methyl substituent at the 1-position of the glucopyranoside skeleton had a negative effect on the enantioselectivity of the 1,4-addition of $ZnEt_2$ to acyclic enones **7a**–**7c**.

3. Conclusion

In conclusion, we have described a new series of chiral bidentatephosphite ligands **2a**–**2d**, which have binaphthol or H_8-binaphthol moieties and a glucopyranoside backbone. The ligands were applied successfully to the Cu-catalyzed asymmetric 1,4-addition of dialkylzincs to enones with good enantioselectivity. The stereogenic centers of the glucopyranoside skeleton and the axially chiral diaryl moieties of ligands **2a**–**2d** had a cooperative effect on the reactivity and enantioselectivity. The combination of carbohydrates and artificial chiral moieties provides an easily accessible tool-box for the fine tuning of efficient ligands. Research concerning other substrates and the use of these ligands in other transition metal-catalyzed reactions is currently underway.

4. Experimental

4.1. General

Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter at 20 °C. Melting points were determined using an X-4 melting point apparatus and were uncorrected. HRMS were recorded on a Bulker micrOTOF-QII mass instrument. NMR spectra were recorded on Bulker spectrometers. ^{31}P NMR spectra were reported in parts per million with 85% H_3PO_4 as an external reference. ^1H NMR and ^{13}C NMR spectra were reported in parts per million with TMS ($\delta = 0.00$ ppm) as an internal standard. Proton chemical shifts (δ) and coupling constants (J) are reported in ppm and Hz, respectively. Spin multiplicities are given as s (singlet), d (doublet), t (triplet), and m (multiplet).

All non-aqueous reactions and manipulations were performed under an N_2 atmosphere with standard Schlenk techniques. All reactions were monitored by thin layer chromatography (TLC, silica gel GF254 plates). Column chromatography separations were conducted on silica gel (200–300 mesh). THF, Et_2O, NEt_3, and toluene were distilled with Na using benzophenone as an indicator, and CH_2Cl_2 was dried over CaH_2 before. H_8-binaphthol was prepared by using a literature procedure.[12a] All other chemicals were obtained commercially and used without further purification.

4.2. Synthesis of ligands 2a–2d

4.2.1. 2,4-Bis{[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphite}-methyl 3,6-anhydro-α-D-glucopyranoside 2a

A solution of (*R*)-H_8-binaphthol (2.0 g) in 10 mL of PCl_3 and 30 mL of toluene was stirred for 24 h at 110 °C under a nitrogen atmosphere in a 100 mL Schlenk flask equipped with a condenser. After removal of the excess PCl_3 and toluene, the residue was dissolved in toluene (20 mL) and then transferred to another Schlenk flask, and toluene was removed *in vacuo* to obtain (*R*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphite **4a** as a white powder, which was used directly in the following reaction without further purification. To a stirred solution of compound **3** (0.6 mmol, 106 mg), **4a** (2.4 mmol, 842 mg), and DMAP (0.12 mmol, 14.6 mg) in CH_2Cl_2 (15 mL), was slowly added anhydrous NEt_3 (0.34 mL) at −15 °C under nitrogen for 0.5 h. The reaction mixture was then stirred at rt for 1 h. Next, CH_2Cl_2 was distilled off in vacuo, and then toluene (20 mL) was added. The solid was removed by filtration through a pad of silica gel, and the solvent was distilled in vacuo. The residue was purified by flash chromatography (toluene, R_f = 0.49), to give ligand **2a** as a white foamy solid (284 mg, 59% yield), mp 123–124 °C; $[\alpha]_D^{20} = -321$ (*c* 0.2, CH_2Cl_2); ^{31}P NMR (162 MHz, DMSO-d_6): δ 148.9 (s, 1P), 146.1 (s, 1P) ppm. ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.04–8.20 (m, 8H), 7.65 (d, *J* = 8.8 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.45–7.56 (m, 6H), 7.35–7.36 (m, 4H), 7.15–7.27 (m, 4H), 5.12 (d, *J* = 4.0 Hz, 1H), 4.70–4.78 (m, 2H), 4.59–4.63 (m, 1H), 4.53 (dd, *J* = 6.0, 4.0 Hz, 1H), 3.94 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.71 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.40 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ 147.3, 146.7, 131.9, 131.7, 131.2, 130.8, 130.7, 130.3, 128.6, 128.5, 126.7, 126.6, 125.9, 125.8, 125.4, 125.1, 123.3, 121.9, 121.7, 121.6, 104.1, 84.9, 77.9, 77.7, 72.7, 70.9, 55.3 ppm. HRMS (ESI) calcd for $C_{47}H_{34}NaO_9P_2$ $(M+Na)^+$ 827.1570, found: 827.1577.

4.2.2. 2,4-Bis{[(*S*)-1,1′-binaphthyl-2,2′-diyl] phosphite}-methyl 3,6-anhydro-α-D-glucopyranoside 2b

(*S*)-1,1′-Binaphthyl-2,2′-diyl-chlorophosphite **4b** was synthesized by the same procedure as that for **4a**, and was used directly without further purification. Treatment of compound **3** (0.6 mmol, 106 mg), **4b** (1.44 mmol, 505 mg) and DMAP (0.12 mmol, 14.6 mg) as described for ligand **2a** afforded ligand **2b**, which was purified by flash chromatography (toluene, R_f = 0.27) to produce a white foamy solid (167 mg, 35% yield), mp 95–96 °C; $[\alpha]_D^{20} = +502$ (*c* 0.2, CH_2Cl_2); ^{31}P NMR (162 MHz, DMSO-d_6): δ 146.6 (s, 1P), 143.5 (s, 1P) ppm. ^{1}HNMR (400 MHz, DMSO-d_6): δ 8.06–8.19 (m, 8H), 7.59–7.66(m, 3H), 7.48–7.54 (m, 5H), 7.32–7.38 (m, 4H), 7.14–7.27 (m, 4H), 5.12 (d, *J* = 3.6 Hz, 1H), 4.51–4.62 (m, 4H), 3.86 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.59 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.48 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 147.4, 146.7, 131.9, 131.6, 131.1, 130.9, 130.8, 130.7, 130.1, 130.0, 128.6, 128.5, 126.7, 126.6, 126.5, 125.9, 125.8, 125.7, 125.3, 125.1, 125.0, 123.3, 122.0, 121.7, 121.6, 103.9, 84.9, 78.6, 77.3, 72.9, 69.6, 55.1 ppm. HRMS (ESI) calcd for $C_{47}H_{34}NaO_9P_2$ $(M+Na)^+$ 827.1570, found: 827.1544.

4.2.3. 2,4-Bis{[(*R*)-1,1′-H_8-binaphthyl-2,2′-diyl] phosphite}-methyl 3,6-anhydro-α-D-glucopyranoside 2c

(*R*)-1,1′-H_8-Binaphthyl-2,2′-diyl-chlorophosphite **4c** was synthesized by the same procedure as that of **4a**, and was used directly without further purification. Treatment of compound **3** (0.6 mmol, 106 mg), **4c** (1.32 mmol, 474 mg) and DMAP (0.12 mmol, 14.6 mg) as described for ligand **2a** afforded ligand **2c**, which was purified by flash chromatography (toluene, R_f = 0.39) to produce a white foamy solid (210 mg, 43% yield), mp 91–92 °C; $[\alpha]_D^{20} = -126$ (*c* 0.2, CH_2Cl_2); ^{31}P NMR (121 MHz, DMSO-d_6): δ 141.7 (s, 1P), 140.5 (s, 1P). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.02–7.28 (m, 6H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.88 (d, *J* = 8.1 Hz, 1H), 5.01 (d, *J* = 3.6 Hz, 1H), 4.59–4.64 (m, 2H), 4.41–4.48 (m, 2H), 4.89–4.94 (m, 1H), 3.62 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.35 (s, 3H), 2.77–2.83 (m, 8H), 2.57–2.64 (m, 4H), 2.09–2.16 (m, 4H), 1.72–1.76 (m, 12H), 1.45–1.53 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 145.5, 145.2, 137.8, 137.0, 134.6, 133.6, 129.4, 129.1, 128.5, 128.4, 127.2, 118.7, 118.5, 103.9, 84.9, 77.7, 77.5, 72.1, 70.4, 55.1, 28.3, 27.2, 27.1, 22.0, 21.9, 21.8 ppm. HRMS (ESI) calcd for $C_{47}H_{51}O_9P_2$ $(M+H)^+$ 821.3003, found: 821.2995.

4.2.4. 2,4-Bis{[(*S*)-1,1′-H_8-binaphthyl-2,2′-diyl]phosphite}-methyl 3,6-anhydro-α-D-glucopyranoside 2d

(*S*)-1,1′-H_8-Binaphthyl-2,2′-diyl-chlorophosphite **4d** was synthesized by the same procedure as that for **4a**, and was used directly without further purification. Treatment of compound **3** (0.6 mmol, 106 mg), **4d** (1.32 mmol, 474 mg) and DMAP (0.12 mmol, 14.6 mg) as described for ligand **2a** afforded ligand **2d**, which was purified by flash chromatography (toluene, R_f = 0.30) to produce a white foamy solid (154 mg, 31% yield), mp 106–108 °C; $[\alpha]_D^{20} = +309$ (*c* 0.2, CH_2Cl_2); ^{31}P NMR (162 MHz, DMSO-d_6): δ 139.9 (s, 1P), 138.3 (s, 1P) ppm. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.03–7.27(m, 6H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 4.0 Hz, 1H), 4.55 (t, *J* = 5.6 Hz, 1H), 4.45–4.50 (m, 2H), 4.37–4.41 (m, 1H), 3.80–3.85 (m, 1H), 3.54 (dd, *J* = 8.8, 6.4 Hz, 1H), 3.40 (s, 3H), 2.77–2.83 (m, 8H), 2.59–2.63 (m, 4H), 2.11–2.15 (m, 4H), 1.72 (m, 12H), 1.47–1.49 (m, 4H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ 145.6, 145.4, 137.9, 136.9, 134.7, 133.6, 129.5, 129.1, 128.6, 127.1, 119.1, 118.8, 103.9, 84.9, 78.4, 77.3, 72.7, 69.7, 55.0, 28.4, 27.2, 22.1, 22.0, 21.9, 21.8 ppm. HRMS (ESI) calcd for $C_{47}H_{50}NaO_9P_2$ $(M+Na)^+$ 843.2822, found: 847.2790.

4.3. Typical procedure for the asymmetric conjugate addition of dialkylzinc to enones

A solution of $Cu(OTf)_2$ (0.005 mmol, 1.8 mg) and ligand **2c** (0.0055 mmol, 4.5 mg) in THF (4 mL) was stirred for 1 h at rt under nitrogen. After the solution was cooled down to 0 °C, 2-cyclohexenone (0.25 mmol, 0.024 mL) was added, and the solution was stirred for 10 min at 0 °C. Then $ZnEt_2$ (0.6 mmol, 0.6 mL of 1.0 M solution in hexane) was added dropwise using a syringe within 2 min. After 4 h., the reaction was quenched by H_2O (2 mL) and 2 M HCl (2 mL), and extracted with ethyl acetate (5 mL × 3). The combined extracts were washed using a saturated $NaHCO_3$ solution, brine, and then dried over anhydrous Na_2SO_4, filtered, and concentrated to afford the crude product. The conversion and the yield were determined by GC equipped with a SE-30 column (30 m × 0.32 mm ID) using dodecane as an internal standard. The enantiomeric excess was determined by GC with a Chiraldex A-TA column (50 m × 0.25 mm ID) or a CP-Chirasil-Dex CB column (25 m × 0.25 mm ID). The absolute configuration was determined by comparison with authentic samples.

The 1,4-addition of $ZnEt_2$ to acyclic enone substrates was the same as for the cyclic substrate enones. However, the 1,4-adducts were separated by column chromatography on silica gel (200–300 mesh) and eluted with Petroleum ether/EtOAc (40/1–20/1), and the enantiomeric excess was determined by HPLC (Daicel Chiralcel AD-H 25 cm × 4.6 mm ID). The analytical conditions for the 1,4-adducts are as follows.

4.3.1. 3-Ethylcyclohexanone 6a

Chiral GC, Chiraldex A–TA column (50 m × 0.25 mm ID), *T*: 120 °C, Rt_1 = 11.55 min (*R*), Rt_2 = 11.93 min (*S*).

4.3.2. 3-Ethylcyclopentanone 6b

Chiral GC, Chiraldex A–TA column (50 m × 0.25 mm ID), *T*: 110 °C, Rt_1 = 14.39 min (*R*), Rt_2 = 13.73 min (*S*).

4.3.3. 3-Ethylcycloheptanone 6c

Chiral GC, CP-Chirasil-Dex CB (25 m × 0.25 mm ID), *T*: 120 °C, Rt_1 = 13.68 min (*R*), Rt_2 = 13.20 min (*S*).

4.3.4. 3-Methylcyclohexanone 6d

Chiral GC, CP-Chirasil-Dex CB (25 m × 0.25 mm ID), *T*: 70 °C, Rt_1 = 37.84 min (*R*), Rt_2 = 38.69 min (*S*).

4.3.5. 1,3-Diphenyl-1-pentanone 8a

Chiral-HPLC, Daicel Chiralcel AD-H (25 cm × 4.6 mm ID), hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min at 25 °C, detected at 254 nm. Rt_1 = 15.41 min (*R*), Rt_2 = 13.19 min (*S*).

4.3.6. 3-(4-Chlorophenyl)-1-phenylpentanone 8b

Chiral-HPLC, Daicel Chiralcel AD-H (25 cm × 4.6 mm ID), hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min at 25 °C, detected at 254 nm. Rt_1 = 18.04 min (*R*), Rt_2 = 14.28 min (*S*).

4.3.7. 3-(4-Methoxyphenyl)-1-phenylpentanone 8c

Chiral-HPLC, Daicel Chiralcel AD-H (25 cm × 4.6 mm ID), hexane/*i*-PrOH = 95/5, flow rate = 0.5 mL/min at 25 °C, detected at 254 nm. Rt_1 = 23.39 min (*R*), Rt_2 = 16.65 min (*S*).

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