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Cu-catalyzed enantioselective conjugate addition of diethylzinc to cyclic enones with chiral phosphite ligands derived from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol

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Abstract—A new and readily in situ prepared catalytic system of copper salts with chiral P,N-ligands or aryl diphosphite ligand, which derived from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol, 1,1′-binaphthol, and phenyl isocyanate derivatives, were successfully employed in the enantioselective conjugate additions of diethylzinc to cyclic enones with up to 71% ee. Two notable cooperative effects of the stereochemistry of the ligands on the enantioselectivity were observed in the reactions: one between the phenylcarbamate substituent and the axially chiral binaphthyl moiety; another between the stereogenic centers of mannitol and the chiral binaphthol substituents. A significant dependence of the product yield and stereoselectivity on the ring size of the substrate using the ligand 1,2:5,6-di-*O*-cyclohexylidene-3,4-bis [(*S*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol was also observed: 71% ee for 2-cyclopentenone, 62% ee for 2-cyclohexenone, and 40% ee for 2-cycloheptenone.

1. Introduction

The conjugate addition of nucleophiles to α,β-unsaturated compounds catalyzed by organometallic complexes is an important means for carbon–carbon bond formation in organic synthesis.[1] In recent years, asymmetric conjugate 1,4-additions of nucleophiles to cyclic enones have been extensively investigated, since the products are desirable for the synthesis of biologically active compounds.[2] Several successful chiral phosphorus donor ligands such as P,N-ligands,[3] P,O-ligands,[4] phosphoramidite,[5] phosphite ligands,[6] and other ligands[7] have been employed in the Cu-catalyzed asymmetric conjugate addition of organozinc reagents to cyclic enones, and good results have been obtained. However, one of the problematic issues revealed in these investigations is the dynamic behavior of the equilibria between several species of organocopper compounds in solution. If the more reactive cuprates lead to the racemic product, the loss of enantioselectivity is unavoidable. Thus, it is desirable to design and synthesize new chiral catalysts, which can react rapidly with the substrate, and which suppress the formation of undesired competing reactions.

There are several advantages in using carbohydrates (and derivatives) as starting materials for the synthesis of chiral phosphine ligands: (1) the raw materials are of high enantiomeric purity and are readily available; (2) their multifunctional property makes it possible to design an array of ligand structures through a series of modifications.[6a,8] In recent years, several versatile chiral ligands derived from D-mannitol were synthesized and successfully applied in the asymmetric addition reaction of diethylzinc to benzaldehyde with a high enantioselectivity of 82% ee,[9] as well as in the Rh-catalyzed asymmetric hydrogenation of amidoacrylic acid and its derivatives with a product of 97% ee.[10] More recently, we reported that several new chiral P,N-ligands were efficiently synthesized from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol, 1,1′-binaphthol, and phenyl isocyanate derivatives. Their Rh(I) complexes were applied as catalyst precursors in the asymmetric hydroformylation of vinylarenes, and hydroformylation of the styrene to give

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the product in 75% ee when 1,2:5,6-di-*O*-cyclohexylidene-3,4-bis[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol was used as the chiral ligand.[11]

In an effort to expand upon the application of these chiral phosphite ligands and also to develop an efficient catalytic system for the asymmetric conjugate addition of dialkylzinc to cyclic enones, we herein report the utility of a new catalytic system, which is prepared in situ from such chiral phosphite ligands and copper salts for the enantioselective conjugate additions of diethylzinc to cyclic enones. The results clearly show the synergistic effects of different chiral elements within ligands on the enantioselectivity of the reactions: one between the phenylcarbamate substituent and the axially chiral binaphthyl moiety; another between the stereogenic centers of mannitol and the chiral binaphthol substituents.

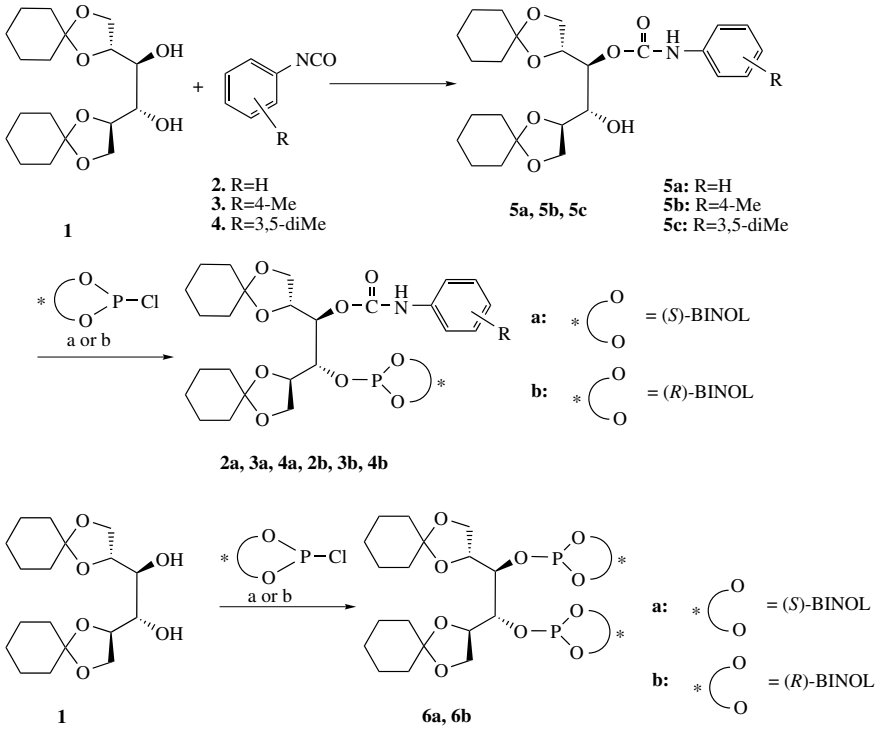
2. Results and discussion

Chiral P,N-ligands **2a**–**4a** and **2b**–**4b**, and chiral diphosphite ligands **6a** and **6b**, which derived from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol **1**, were prepared according to a reported procedure.[11] As shown in Scheme 1, the treatment of compound **1** with phenyl isocyanate derivatives **2**–**4** gave the expected compounds **5a**–**5c** in moderate yield.

Mixing of compound **5** with 1.1 equiv of in situ prepared phosphorochloride,[12] afforded the corresponding chiral P,N-ligands **2a**–**4a** and **2b**–**4b**, respectively. Chiral diphosphite ligands **6a** and **6b** were directly synthesized from compound **1** with the appropriate phosphorochloride (Scheme 1). All ligands were found to be stable on silica gel during the purification procedure under a nitrogen atmosphere, and were white solids and air-stable at room temperature.

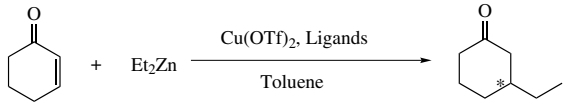
Based on our experience from previous studies, $Cu(OTf)_2$ was chosen as the Cu source for the preparation of the optically active catalysts. In the first set of experiments, 2-cyclohexenone was treated with diethylzinc in the presence of $Cu(OTf)_2$ and ligands **2a**–**6a** and **2b**–**6b** in toluene, respectively. The results are summarized in Table 1. In all cases, no 1,2-addition products were detected by GC–MS analysis.

Ligand **2a** gave moderate yield (63%) and low enantioselectivity (31% ee) (Table 1, entry 1). In contrast, the use of ligand **2b** (in which the phenylcarbamate substituent was the same as ligand **2a**, and the chirality of the binaphthyl moiety was opposite to that of ligand **2a**) gave a similar yield (66%) and much lower enantioselectivity (6.1% ee) (Table 1, entry 2). Ligand **3a**, bearing a 4-methyl phenylcarbamate substituent, gave a high yield (84%) and 8.9% ee (Table 1, entry 3). Ligand **3b**, bearing the same phenylcarbamate substituent and axially chiral binaphthyl with a configuration opposite to that of ligand **3a**, gave excellent yield (96%) and racemic product (Table 1, entry 4). Ligand **4a** bearing a 3,5-dimethyl phenylcarbamate substituent gave a low yield (5.8%) and low enantioselectivity (only 7% ee) (Table 1, entry 5). When ligand **4b** bearing a 3,5-dimethyl phenylcarbamate substituent and an axially chiral binaphthyl with a configuration opposite to that of **4a** was applied, a higher yield (84%) and racemic products were obtained (Table 2, entry 6). The comparison of these results clearly indicated that the steric and electronic prop-



Scheme 1. The synthesis of chiral phosphite ligands.

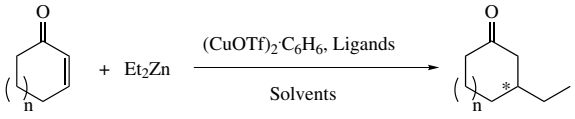
Table 1. Cu-catalyzed enantioselective conjugate addition of diethylzinc reagents to 2-cyclohexenone[a]



Entry	L.	T (°C)	Time (h)	Conv.[b] (%)	Y.[b] (%)	% ee[c] (conf.)
1	**2a**	−30	4	95	63	31 (*S*)
2	**2b**	−20	16	>99	66	6.1 (*S*)
3	**3a**	−40	15.5	90	84	8.9 (*S*)
4	**3b**	−40	15.5	96	96	Racemic
5	**4a**	−20	13	57	5.8	7 (*S*)
6	**4b**	−20	13	>99	84	Racemic
7	**6a**	−30	4	64	74	32 (*S*)
8	**6b**	−30	4	76	44	7.9 (*R*)

[a] Reaction conditions: $Cu(OTf)_2$ (0.01 mmol), ligand (0.02 mmol), $ZnEt_2$ (1.2 mmol), 2-cyclohexenone (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.).
[c] 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.

Table 2. Cu-catalyzed enantioselective conjugate addition of diethylzinc reagents to cyclic enones[a]



n= 0, **7a**
1, **7b**
2, **7c**

n= 0, **8a**
1, **8b**
2, **8c**

Entry	Substrate	L.	Sol.	T (°C)	t (h)	Conv.[b] (%)	Y.[b] (%)	% ee[b] (conf.)
1	**7b**	**2a**	Toluene	−44	16.5	98	99.5	19 (*S*)
2	**7b**	**6a**	Toluene	−44	16.5	88	82	62 (*S*)
3	**7a**	**6a**	Toluene	−44	16.5	>99	18	71 (*S*)
4	**7c**	**6a**	Toluene	−44	16.5	90	93	40 (*S*)
5	**7a**	**6a**	Ether	−44	17	>99	65	48 (*S*)
6	**7a**	**6a**	THF	−44	17	97	59	69 (*S*)
7	**7a**	**6a**	CH_2Cl_2	−44	17	>99	59	61 (*S*)

[a] Reaction conditions: $(CuOTf)_2{\cdot}C_6H_6$ (0.01 mmol), ligand (0.02 mmol), $ZnEt_2$ (1.2 mmol), substrate (0.5 mmol), solvent (4 mL).
[b] The date on conversion, yield, enantiomeric excess, and the absolute configuration of the chiral product were determined using the same conditions as noted in Table 1.

erties of the phenylcarbamate substituent and the axially chiral binaphthyl moiety had a synergistic effect on the enantioselectivity of the reaction (Scheme 1). The matching combination of phenylcarbamate and binaphthyl moieties of ligand 1,2:5,6-di-*O*-cyclohexylidene-3-phenylcarbamate-4-[(*S*)-1,1′-binaphthyl-2,2′-diyl]-phosphate-D-mannitol gave a moderate yield 63% and 31% ee. The same sense of enantioselectivity (Table 1, entries 1–3 and 5) indicated that the configuration of the desired product was mainly controlled by the stereogenic centers of mannitol of ligands **2a**–**4a** and **2b**–**4b**.

Ligand **6a** with two (*S*)-BINOL moieties afforded 74% yield and 32% ee (Table 1, entry 7). However, the use of ligand **6b** bearing two (*R*)-BINOL moieties gave a lower yield (44%) and the opposite sense of enantioselectivity with 7.9% ee (Table 1, entry 8). These results clearly indicated the existence of a synergic effect between the stereogenic centers of mannitol and the chiral binaphthol substituents (Scheme 1). It is interesting to note that the sense of enantioselectivity was mainly determined by the configuration of the binaphthol group of ligands **6a** and **6b**.

The copper precursor plays an essential role in accounting for high catalytic activity and enantioselectivity.[13] Using the catalytic precursor $(CuOTf)_2{\cdot}C_6H_6$, ligand **2a** gave excellent yield (99.5%) and 19% ee (Table 2, entry 1). It is noteworthy that a good yield (82%) and moderate enantioselectivity (62%) were obtained when $Cu(OTf)_2$ was replaced by $(CuOTf)_2{\cdot}C_6H_6$ in the presence of ligand **6a** (Table 2, entry 2). The results suggested that the matched combination of $(CuOTf)_2{\cdot}C_6H_6$, and ligand **6a** under the reaction conditions gave a moderate enantioselectivity and chemical yield of the product **8b**.

2-Cyclopentenone **7a** and 2-cycloheptenone **7c** were also treated with diethylzinc in the presence of $(CuOTf)_2{\cdot}C_6H_6$

and ligand **6a**, respectively. A significant dependence of the yield and stereoselectivity on the ring size of the substrate was observed: 71% ee for 2-cyclopentenone (Table 2, entry 3), 62% ee for 2-cyclohexenone (Table 2, entry 2), and 40% ee for 2-cycloheptenone (Table 2, entry 4).

Alexakis et al.[14] and Chan et al.[15] found that the asymmetric conjugate addition of diethylzinc to enones gave higher ee values using coordinating solvents when compared to other reaction media. In addition to toluene, other solvents such as ether, THF, and dichloromethane were tested in our case while a solvent effect on the enantioselectivity was also observed. In non-coordinating solvents, toluene and dichloromethane, 71% ee and 61% ee were obtained, respectively (Table 2, entries 3 and 7). In contrast, using the coordinating solvents ether and THF as medium 48% ee and 69% ee were obtained, respectively (Table 2, entries 5 and 6). Although the ether solvent THF lead to slightly higher ee value than CH_2Cl_2, toluene is still the best one in our case.

3. Conclusion

In conclusion, we have demonstrated six chiral P,N-ligands and two chiral diphosphite ligands, which were derived from 1,2:5,6-di-*O*-cyclohexylidene-D-mannitol, in the application of Cu-catalyzed asymmetric conjugate addition of diethylzinc to cyclic enones. Two cooperative effects of the stereochemistry of the ligands on the enantioselectivity were observed in the reactions: one between the phenylcarbamate substituent and the axially chiral binaphthyl moiety; another between the stereogenic centers of mannitol and the chiral binaphthol substituents. The value of the enantiomeric excess is controlled by the cooperative effect between the stereocenters of ligand backbone (C-3 and C-4) and the configuration of binaphthol phosphite moiety. When using ligand **6a** up to 71% ee was obtained.

4. Experimental

4.1. Reagents and materials

All experiments were carried out under a nitrogen atmosphere. Phenyl isocyanate, 4-methylphenyl isocyanate, and 3,5-dimethylphenyl isocyanate were purchased from Acros and used without further purification. $(CuOTf)_2{\cdot}C_6H_6$, $Cu(OTf)_2$, and Et_2Zn (neat) were purchased from Aldrich and used without further purification. 2-Cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone were dried with anhydrous sodium sulfate, 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 were reported in parts per million with TMS as an internal standard ($\delta = 0$ ppm). ^{31}P NMR spectra were reported in parts per million with 85% H_3PO_4 as an external reference.

4.2. 1,2:5,6-Di-*O*-cyclohexylidene-3-phenylcarbamate-D-mannitol 5a, 1,2:5,6-di-*O*-cyclohexylidene-3-[(4-methyl)phenylcarbamate]-D-mannitol 5b, and 1,2:5,6-di-*O*-cyclohexylidene-3-[(3,5-dimethyl)phenylcarbamate]-D-mannitol 5c

1,2:5,6-Di-*O*-cyclohexylidene-D-mannitol **1** (1.0 g, 2.92 mmol) was dissolved in 20 mL of dichloromethane, and mixed at room temperature with 4-*N*,*N*-dimethylaminopyridine (DMAP, 0.025 g, 0.205 mmol) and phenyl isocyanate (0.35 g, 2.92 mmol). The reaction mixture was stirred for 12 h at room temperature, after which the dichloromethane was distilled off under reduced pressure at room temperature. The residue was purified by column chromatography (eluent: CH_2Cl_2/EA = 10) to produce **5a** as a white powder (0.51 g, 39%). ^{1}H NMR ($CDCl_3$): $\delta = 1.53$–1.66 (m, 20H), 2.8 (d, 1H), 3.93 (dd, 1H), 4.05 (m, 2H), 4.13 (m, 2H) ppm, 4.47 (dd, $J = 6.5$ and 12.5 Hz, 1H), 5.10 (d, $J = 5.5$ Hz, 1H), 6.81 (s, 1H), 7.26–7.27 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 19.7$, 22.7, 23.8, 24.1, 25.0, 30.8, 34.4, 34.6, 35.8, 36.5, 65.4, 66.1, 71.9, 74.1, 75.7, 76.0, 76.3, 76.5, 109.0, 110.8, 118.0, 128.9, 133.6, 134.2, 150.9 ppm.

Treatment of compound **1** and 4-methylphenyl isocyanate, as described for compound **5a**, yielded compound **5b** as a white powder (0.62 g, 45%). ^{1}H NMR ($CDCl_3$): $\delta = 1.38$–1.66 (m, 20H), 2.30 (s, 3H), 3.90–4.14 (m, 6H), 4.44 (dd, $J = 6.0$ and 12.0 Hz, 1H), 5.07 (d, $J = 5.0$ Hz, 1H), 6.84 (s, NH), 7.26–7.27 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 20.7$, 23.7, 23.9, 24.0, 25.0, 25.1, 30.9, 34.5, 34.6, 36.1, 36.5, 65.5, 66.0, 70.9, 75.1, 76.7, 77.0, 77.3, 77.5, 110.0, 110.7, 119.0, 129.9, 133.6, 135.2, 152.9 ppm.

Treatment of compound **1** and 3,5-dimethylphenyl isocyanate, as described for compound **5a**, yielded compound **5c** as a white powder (0.805 g, 58%). ^{1}H NMR ($CDCl_3$): $\delta = 1.30$–1.59 (m, 20H), 2.21 (s, 6H), 3.85 (m, 1H), 3.96 (m, 3H), 4.06 (m, 2H), 4.37 (dd, $J = 6.5$ and 12.0 Hz, 1H), 5.00 (d, $J = 5.5$ Hz, 1H), 6.65 (s, NH), 6.90–6.94 (m, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$, 23.9, 24.1, 24.2, 25.1, 25.2, 34.7, 34.8, 36.3, 36.7, 65.6, 66.2, 71.0, 73.4, 75.0, 75.3, 77.0, 77.2, 77.4, 77.5, 109.9, 110.6, 116.5, 125.6, 137.6, 139.0, 152.8 ppm.

4.3. 1,2:5,6-Di-*O*-cyclohexylidene-3-phenylcarbamate-4-[(*S*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 2a and 1,2:5,6-di-*O*-cyclohexylidene-3-phenylcarbamate-4-[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 2b

Treatment of the in situ formed[12] (*S*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphine (0.87 mmol) and compound **5a** afforded ligand **2a**, which was purified by flash chromatography (CH_2Cl_2/Et_2O, 9/1, $R_f = 0.87$) to produce a white powder (0.26 g, 43%). ^{31}P NMR (202 MHz, $CDCl_3$), $\delta =$ 154.5 ppm. ^{1}H NMR ($CDCl_3$): $\delta = 1.32$–1.74 (m, 20H), 2.23 (s, 3H), 3.86 (m, 1H), 3.95 (m, 1H), 4.13 (m, 3H), 4.40 (d, $J = 6.5$ Hz, 1H), 4.78 (d, $J = 7.0$ Hz, 1H), 5.08 (d, $J = 8.0$ Hz, 1H), 6.49 (s, NH), 6.91–7.91 (m, 16H, Ar–H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 24.1$, 24.2,

24.7, 25.3, 25.6, 33.9, 35.2, 35.6, 36.7, 64.0, 66.3, 72.7, 75.0, 77.0, 77.3, 77.5, 109.0, 110.6, 113.3, 118.0, 118.4, 122.1, 122.8, 123.7, 124.0, 124.5, 124.6, 124.9, 125.6, 126.6, 127.0, 127.1, 127.7, 128.0, 128.9, 129.0, 129.3, 129.5, 130.0, 130.6, 131.6, 132.8, 133.1, 133.8, 152.6 ppm.

Treatment of the in situ formed[12] (*R*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphine (0.87 mmol) and compound **5a** afforded ligand **2b**, which was purified by flash chromatography (CH_2Cl_2/Et_2O, 9/1, $R_f = 0.84$) to produce a white powder (0.28 g, 46%). ^{31}P NMR (202 MHz, $CDCl_3$), $\delta =$ 156.1 ppm. ^1H NMR ($CDCl_3$): $\delta = 1.17$–1.83 (m, 20H), 3.71 (s, 1H), 3.87 (s, 1H), 3.93 (s, 1H), 4.08 (s, 1H), 4.18 (d, $J = 6.5$ Hz, 1H), 4.31 (s, 1H), 4.90 (d, $J = 7.5$ Hz, 1H), 5.01 (d, $J = 7.0$ Hz, 1H), 6.51 (s, NH), 6.94–7.84 (m, 17H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta =$ 24.0, 24.2, 24.3, 25.5, 25.6, 34.0, 35.2, 35.9, 36.8, 64.1, 66.9, 72.9, 75.6, 77.1, 77.3, 77.6, 110.0, 110.6, 111.3, 118.1, 118.8, 122.0, 122.3, 123.2, 124.3, 124.5, 124.6, 124.7, 125.6, 126.6, 127.2, 127.3, 127.7, 128.5, 128.6, 129.1, 129.3, 129.7, 130.2, 130.6, 131.8, 132.9, 133.1, 133.7, 152.3 ppm.

4.4. 1,2:5,6-Di-*O*-cyclohexylidene-3-[(4-methylphenylcarbamate)]-4-[(*S*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 3a and 1,2:5,6-di-*O*-cyclohexylidene-3-[(4-methylphenylcarbamate)-4-[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 3b

Treatment of the in situ formed[12] (*S*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphine (0.87 mmol) and compound **5b** afforded ligand **3a**, which was purified by flash chromatography (CH_2Cl_2/Et_2O, 9/1, $R_f = 0.85$) to produce a white powder (0.25 g, 40%). ^{31}P NMR (202 MHz, $CDCl_3$), $\delta =$ 154.5 ppm. ^1H NMR ($CDCl_3$): $\delta = 1.32$–1.74 (m, 20H), 2.23 (s, 3H), 3.86 (m, 1H), 3.95 (m, 1H), 4.13 (m, 3H), 4.40 (d, $J = 6.0$ Hz, 1H), 4.78 (d, $J = 12.5$ Hz, 1H), 5.08 (d, $J = 7.0$ Hz, 1H), 6.49 (s, NH), 6.91–7.91 (m, 16H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.5$, 23.9, 24.3, 25.6, 33.0, 35.5, 35.8, 36.6, 64.7, 65.9, 71.9, 76.6, 76.9, 77.0, 77.9, 109.0, 110.8, 117.9, 121.0, 122.1, 122.2, 123.2, 124.6, 124.7, 125.0, 125.1, 125.3, 126.3, 126.5, 127.0, 127.2, 128.3, 128.6, 129.8, 130.1, 130.5, 131.2, 131.8, 132.9, 133.1, 133.6, 134.8, 147.6, 148.3, 148.6, 151.3 ppm.

Treatment of the in situ formed[12] (*R*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphine (0.87 mmol) and compound **5b** afforded ligand **3b**, which was purified by flash chromatography (CH_2Cl_2/Et_2O, 9/1, $R_f = 0.83$) to produce a white powder (0.27 g, 43%). ^{31}P NMR (202 MHz, $CDCl_3$), $\delta =$ 157.6 ppm. ^1H NMR ($CDCl_3$): $\delta = 1.33$–1.84 (m, 20H), 2.20 (s, 3H), 3.73 (s, 1H), 3.94 (m, 2H), 4.07 (m, 1H), 4.18 (d, $J = 8.0$ Hz, 1H), 4.32 (s, 1H), 4.91 (d, $J =$ 7.5 Hz, 1H), 5.01 (d, $J = 6.5$ Hz, 1H), 6.46 (s, NH), 6.99–7.88 (m, 16H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.0$, 24.0, 24.3, 25.5, 33.9, 35.2, 35.9, 36.7, 64.0, 66.9, 72.9, 75.6, 77.0, 77.3, 77.5, 109.9, 110.5, 118.9, 122.0, 122.1, 122.2, 123.1, 124.6, 124.7, 125.0, 125.1, 125.3, 126.2, 126.5, 127.2, 127.3, 128.5, 128.6, 129.8, 130.2, 130.5, 131.4, 131.8, 132.9, 133.1, 133.7, 134.9, 147.6, 148.5, 148.6, 150.8 ppm.

4.5. 1,2:5,6-Di-*O*-cyclohexylidene-3-[(3,5-dimethyl)phenylcarbamate]-4-[(*S*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 4a and 1,2:5,6-di-*O*-cyclohexylidene-3-[(3,5-dimethyl)phenylcarbamate]-4-[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 4b

(*S*)-1,1′-Binaphthyl-2,2′-diyl-chlorophosphine (0.87 mmol) was synthesized in situ[12] and dissolved in toluene (10 mL). Compound **5c** (0.381 g, 0.8 mmol) was azeotropically dried with toluene (3×10 mL) and then dissolved in triethylamine (4 mL) to which DMAP (0.01 g, 0.083 mmol) had been added. A solution of phosphorochloridite was transferred slowly to a solution of compound **5c** at 0 °C. The reaction mixture was stirred overnight at room temperature, and the formed triethylamine salts were removed by filtration. Evaporation of the solvent gave a white foam, which was purified by flash chromatography (CH_2Cl_2/Et_2O, 9/1, $R_f = 0.86$) to produce **4a** as a white powder (0.42 g, 66%). ^{31}P NMR (202 MHz, $CDCl_3$), $\delta =$ 153.7 ppm. ^1H NMR ($CDCl_3$): $\delta = 1.61$–1.86 (m, 20H), 2.30 (s, 6H), 3.94–4.14 (m, 3H), 4.29 (s, 2H), 4.53 (d, $J = 7.0$ Hz, 1H), 4.92 (s, 1H), 5.22 (d, $J = 7.5$ Hz, 1H), 6.74 (s, NH), 7.01–8.02 (m, 15H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.6$, 21.7, 24.0, 24.3, 25.5, 33.9, 35.3, 35.9, 36.8, 64.1, 66.9, 72.9, 74.3, 75.1, 75.6, 77.1, 77.3, 77.6, 110.0, 110.6, 116.6, 122.0, 122.3, 123.2, 124.7, 125.3, 125.6, 125.9, 126.3, 126.5, 127.3, 128.5, 128.6, 129.3, 130.2, 130.6, 131.4, 131.8, 132.9, 133.1, 137.3, 138.1, 139.1, 147.3, 147.6, 148.6, 152.3 ppm.

Treatment of the in situ formed[12] (*R*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphine (0.87 mmol) and compound **5c** afforded ligand **4b**, which was purified by flash chromatography (CH_2Cl_2/Et_2O, 9/1, $R_f = 0.87$) to produce a white powder (0.30 g, 47%). ^{31}P NMR (202 MHz, $CDCl_3$), $\delta =$ 156.6 ppm. ^1H NMR ($CDCl_3$): $\delta = 1.32$–1.71 (m, 20H), 2.31 (s, 6H), 3.87 (s, 1H), 4.08 (d, $J = 22$ Hz, 2H), 4.23 (s, 1H), 4.34 (d, $J = 4.5$ Hz, 1H), 4.46 (s, 1H), 5.06 (d, $J = 7.0$ Hz, 1H), 5.15 (d, $J = 6.5$ Hz, 1H), 6.56 (s, NH), 6.75–8.01 (m, 15 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 21.0$, 21.7, 24.0, 24.3, 26.5, 33.9, 35.3, 36.8, 64.1, 66.9, 73.9, 74.3, 75.1, 75.3, 75.9, 77.1, 77.3, 77.6, 110.0, 110.6, 116.6, 122.0, 122.8, 123.2, 124.7, 125.1, 125.3, 125.6, 125.9, 126.4, 126.5, 127.3, 128.5, 128.6, 129.3, 130.2, 130.6, 131.1, 131.8, 132.9, 133.1, 137.3, 138.1, 139.1, 147.2, 147.6, 148.9 ppm.

4.6. 1,2:5,6-Di-*O*-cyclohexylidene-3,4-bis[(*S*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 6a and 1,2:5,6-di-*O*-cyclohexylidene-3,4-bis[(*R*)-1,1′-binaphthyl-2,2′-diyl]phosphite-D-mannitol 6b

Compound **1** (0.206 g, 0.6 mmol) and DMAP (0.015 g, 0.123 mmol) were put in a 50 mL round-bottomed flask. Toluene (5 mL) and dry triethylamine (0.2 mL) were added under dry nitrogen. The mixture was cooled to 0 °C. with an ice-bath. (*S*)-1,1′-Binaphthyl-2,2′-diyl-chlorophosphine (1.2 mmol) synthesized in situ[12] in toluene (5 mL) was added dropwise in the solution and stirred for 30 min at 0 °C, then left at room temperature overnight. The solvent was removed in vacuo and the residues were purified by flash chromatography (toluene, $R_f = 0.33$) to produce **6a**

as white powder (0.47 g, 81%). ^{31}P NMR (202 MHz, CD_2Cl_2), $\delta = 153.4$ ppm. ^{1}H NMR (CD_2Cl_2): $\delta = 1.49$–1.79 (m, 20H), 4.22–4.27 (m, 4H), 4.61–4.65 (m, 2H), 4.80–4.84 (m, 2H), 7.23–8.06 (m, 12H) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 24.1$, 24.5, 25.5, 35.1, 37.0, 67.2, 73.9, 76.4, 110.9, 122.0, 122.3, 125.3, 125.5, 125.6, 126.6, 126.7, 127.1, 127.2, 128.5, 128.8, 129.3, 130.1, 130.8, 131.5, 132.0, 132.8, 133.1, 147.5, 148.3 ppm.

Treatment of the in situ formed[12] (*R*)-1,1′-binaphthyl-2,2′-diyl-chlorophosphine (1.2 mmol) and compound **1** afforded ligand **6b**, which was purified by flash chromatography (toluene, $R_f = 0.34$) to produce a white powder (0.49 g, 84%). ^{31}P NMR (202 MHz, CD_2Cl_2), $\delta = 155.1$ ppm. ^{1}H NMR (CD_2Cl_2): $\delta = 1.52$–1.58 (m, 4H), 1.78–1.86 (m, 16H), 4.15–4.18 (m, 2H), 4.28–4.31 (m, 2H), 4.49–4.52 (m, 2H), 4.79–4.82 (m, 2H), 7.30–7.56 (m, 8H), 7.89–8.05 (m, 4H) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): $\delta = 24.3$, 24.4, 25.6, 34.7, 36.6, 66.5, 74.3, 76.9, 77.1, 110.5, 121.8, 121.9, 122.9, 124.6, 125.2, 125.4, 125.6, 126.4, 126.6, 127.1, 128.5, 128.7, 129.3, 130.3, 130.7, 131.4, 131.9, 132.7, 133.1, 147.5, 148.1 ppm.

4.7. General procedure for the conjugate addition of diethylzinc to 2-cyclohexenone

All experiments were carried out under a nitrogen atmosphere. A solution of $Cu(OTf)_2$ (0.01 mmol) and ligand **2a** (0.02 mmol) in 4 mL toluene was stirred for 1 h. The solution was cooled to −30 °C, and 2-cyclohexenone (0.5 mmol) and diethylzinc (1.2 mmol) were added. After stirring for 4 h at −30 °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 sulfate. Most of the solvent were 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.

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