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# New chiral amino-phosphite and phosphite-phosphoroamidite ligands for the copper-catalyzed asymmetric 1,4-addition of diethylzinc to cyclohexenone

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**Abstract**—We have designed a series of amino-phosphite and phosphite-phosphoroamidite ligands **1**–**6** derived from inexpensive D-(+)-xylose. These ligands were screened in the Cu-catalyzed asymmetric 1,4-addition of diethylzinc to cyclohexenone. High reaction rates (TOF >1200 $h^{-1}$) and moderate enantioselectivities (up to 63% e.e.) were obtained. The results showed that the configuration of the stereogenic carbon atom C(3) at the ligand backbone and the different substituents at the amino group had remarkable effects on the activity and enantioselectivity. © 2001 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

Catalytic asymmetric synthesis using organometallic reagents is currently one of the most prominent areas of research in organic chemistry.[1] The 1,4-addition of organometallic reagents to α,β-unsaturated carbonyl compounds is an important process for C–C bond formation in organic synthesis.[2] Although organocuprates and the copper-catalyzed 1,4-additions of Grignard reagents are most frequently employed, a number of alternative reagents, based on other metal catalysts (i.e. Ni and Mn) and other organometallic reagents (i.e. $ZnR_2$ and $AlR_3$), have recently been developed.[3]

Several successful methods for enantioselective 1,4-addition have been described. These have mainly been based on chiral auxiliaries or stoichiometric organometallic reagents, whereas only a few have been based on highly enantioselective catalytic processes.[3] A prominent position in the rapid development of the latter field is occupied by the copper-catalyzed, ligand-accelerated, 1,4-addition of organozinc reagents.[4] Thus, excellent enantioselectivities have been obtained using chiral phosphoroamidites,[4d–f,4k,4p] phosphites,[4c,4h–j,4l,4m] bidentate *P*,*N*-ligands[4b,4g] and Schiff base ligands.[4n,4o] However, further study is needed to understand how efficient enantiocontrol can be achieved. In this context, the rational design of new ligands is still a highly significant field of research. For this purpose, carbohydrates are particularly advantageous because their modular construction means that structural diversity is easy to achieve, so enantioselectivity can be maximized.[5]

Following our interest in using carbohydrates as an available chiral source for preparing ligands[5,6] and encouraged by the success of some bidentate *P*,*N*-[4b,4g] and phosphoroamidite[4d–f,4k,4p] ligands in conjugate 1,4-additions, we have designed a series of amino-phosphite and phosphite-phosphoroamidite ligands **1**–**6** with a furanoside backbone (Fig. 1). We also report the use of these ligands in the enantioselective copper-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone.

The advantage of these ligands is that many structural variations can be made. These variations can provide information about the effects of the different stereogenic centres in the ligand on the enantioselectivity of the reaction. This study may also provide some insight into the origin of the stereochemistry of the reaction. The effect of the amino group was investigated by introducing different substituents at the nitrogen atom. We have also investigated the effects of the configuration of the C(3) stereogenic centre in the ligand backbone and the substituents at the *para* positions of the bisphenol moiety.

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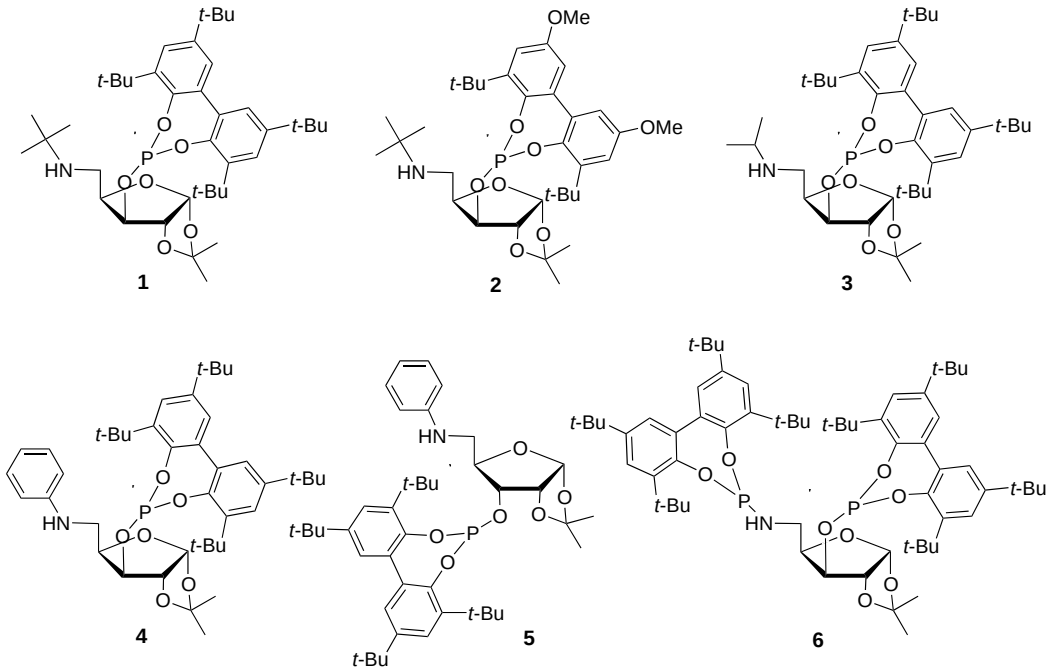


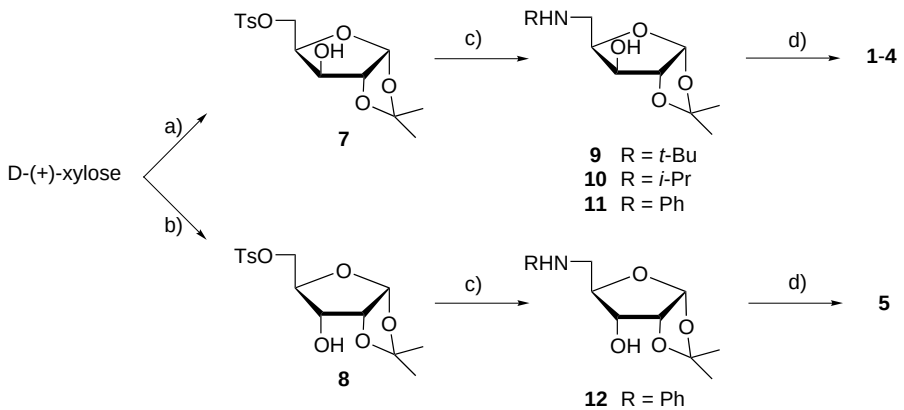

**Figure 1.**

## 2. Results and discussion

### 2.1. Ligand synthesis

The amino-phosphite ligands **1**–**5** were prepared in two steps, starting from the corresponding monotosylates **7**[7] and **8**,[8] which are easily prepared on a large scale from inexpensive D-(+)-xylose (Scheme 1). Treating tosylates **7** and **8** with *tert*-butylamine, aniline and isopropylamine in propan-2-ol at reflux afforded the corresponding amino alcohols **9**, **10**, **11** and **12**, which are stable to air at room temperature. The desired amino-phosphite ligands **1**–**5** were obtained by reaction of the corresponding amino alcohol and either (3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)phosporochloridite[9] or (5,5′-bis-*tert*-butyl-3,3′-bis-methoxy-1,1′-biphenyl-2,2′-diyl)phosporochloridite[9] in the presence of base. Compounds **1**–**5** were isolated in good yields (75–85%) as solids by purification on neutral alumina under an atmosphere of argon. They are stable at room temperature. The $^{1}H$ and $^{13}C$ NMR spectra agree with those expected for these $C_1$ ligands. One singlet was observed in the $^{31}P$ NMR spectrum. Rapid ring inversions (atropisomerization) in the bisphenol moieties occurred on the NMR time scale since the expected diastereoisomers were not detected by low-temperature phosphorus NMR.[10]

Phosphite-phosphoroamidite **6** was synthesized according to our previously reported procedure.[11] The reaction of the tosylate **7** with sodium azide followed by treatment with triphenylphosphine afforded the corresponding amino alcohol. This reacted readily with two equivalents of phosphorochloridite to produce ligand **6** in good yield.




**Scheme 1.** Synthesis of ligands **1**–**5**. (a) Ref. 7. (b) Ref. 8. (c) $RNH_2$, propan-2-ol, reflux. (d) $(RO)_2PCl$, py, toluene, 100°C.

### 2.2. Asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone

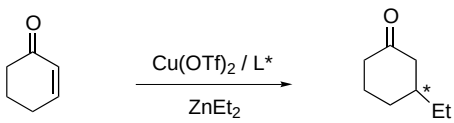
We tested ligands **1**–**6** in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone. The latter was chosen as a substrate because this reaction has been performed with a wide range of ligands having several donor groups enabling the direct comparison of the efficiency of the different ligand systems.[3c–e] The catalytic system was generated in situ by adding the corresponding ligand to a suspension of $Cu(OTf)_2$. The results are shown in Table 1. In general, good reaction rates were found for all ligands. No 1,2-product was observed by gas chromatographic analysis.

In a first set of experiments, we studied the effect of the reaction temperature and solvent using ligand **1**. The results showed that the efficiency of the process depended on the nature of the solvent (entries 1–3). The best catalyst performance (activity and selectivity) was achieved when dichloromethane was used as a solvent (entry 2). As reported for related Cu-diphosphite catalytic systems,[4l,12] the best enantioselectivities were obtained at 0°C (entry 2). These decreased when the reaction temperature was either lowered or raised (entries 2, 4–6). Comparing the results using ligands **1** and **2**, which have different substituents in the *para* positions of the biphenyl moiety, we can conclude that the presence of methoxy groups in the *para* positions of the biphenyl moiety had a negative effect on the activity and enantioselectivity (entry 2 versus 7).

The effect of the ligand aminoalkyl substituent on the performance of the catalyst was investigated by using ligands **1**, **3** and **4**. Our results showed that both the reaction rate and enantioselectivity depended on the nature of the substituent (entries 2, 8 and 9); conversions and enantioselectivities were higher for the catalyst precursor containing ligand **4**, and with a phenyl substituent at the amino group. Interestingly, the sense of enantioselectivity was also affected; ligand **1**, containing a bulky *tert*-butyl substituent in the amino group, gave the (*R*)-product (entry 2), while the less sterically hindered ligands **3** and **4** gave the (*S*)-enantiomer preferentially (entries 8 and 9). Ligand **5**, whose configuration of carbon atom C(3) is opposite to that of ligand **4** (Fig. 1), proceeded at a similar reaction rate, but the enantioselectivity dropped considerably (entry 9 versus 10). Ligand **6**, which contains a bulky phosphoroamidite moiety at carbon atom C(5) rather than the alkylated amino group in ligands **1**–**5**, proceeded at high reaction rates (TOF >1200 $h^{-1}$) but the enantioselectivity was lower (30% e.e., entry 11).

The effect of the ligand-to-copper ratio on the outcome of the reaction was investigated using ligand **4** (entries 9, 12 and 13). Adding a one-fold excess of ligand led to a higher reaction rate and higher enantioselectivity (entry 12). However, the outcome of the reaction was not affected when a greater excess of ligand was added (entry 13). Within the accuracy of these experiments, there was no change in the enantioselectivity over time. This agrees with the presence of the same aggregates

**Table 1.** Asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone[a]




| Entry | Ligand | Solvent | $T$ (°C) | TOF[b] | % Conv.[c] | % e.e.[d] |
|---|---|---|---|---|---|---|
| 1 | **1** | Toluene | 0 | 696 | 58 | 18 (*R*) |
| 2 | **1** | $CH_2Cl_2$ | 0 | 720 | 60 | 20 (*R*) |
| 3 | **1** | THF | 0 | 516 | 43 | 11 (*R*) |
| 4 | **1** | $CH_2Cl_2$ | 25 | 1020 | 85 | 15 (*R*) |
| 5 | **1** | $CH_2Cl_2$ | −20 | 504 | 100[e] | 17 (*R*) |
| 6 | **1** | $CH_2Cl_2$ | −40 | 432 | 92[e] | 12 (*R*) |
| 7 | **2** | $CH_2Cl_2$ | 0 | 660 | 55 | 15 (*R*) |
| 8 | **3** | $CH_2Cl_2$ | 0 | 960 | 80 | 42 (*S*) |
| 9 | **4** | $CH_2Cl_2$ | 0 | 1020 | 85 | 48 (*S*) |
| 10 | **5** | $CH_2Cl_2$ | 0 | 1008 | 84 | 8 (*R*) |
| 11 | **6** | $CH_2Cl_2$ | 0 | >1200 | 100 | 30 (*S*) |
| 12[f] | **4** | $CH_2Cl_2$ | 0 | 1080 | 90 | 63 (*S*) |
| 13[g] | **4** | $CH_2Cl_2$ | 0 | 1092 | 91 | 63 (*S*) |

[a] Reaction conditions: $Cu(OTf)_2$ (0.025 mmol), ligand (0.025 mmol), $ZnEt_2$ (3.5 mmol), **2** (2.5 mmol), solvent (6 mL).
[b] TOF in mol **4**×mol $Cu^{-1}$×$h^{-1}$ determined after 5 min reaction time by GC.
[c] % Conversion determined by GC using undecane as internal standard after 5 min.
[d] Enantiomeric excess measured by GC using Lipodex A column.
[e] After 15 min.
[f] 0.05 mmol of ligand used.
[g] 0.075 mmol of ligand used.

throughout the reaction. It should be noted that under the same reaction conditions the activity and enantioselectivity (e.e. of up to 63%) of reactions with ligand **4** were much higher than those of the corresponding bulky 3,5-bis-[(3,3′,5,5′-tetra-*t*-butyl-1,1′-biphenyl-2,2′-diyl)-phosphite] - 1,2 - *O* - isopropylidene - α - D - xylofuranose diphosphite analogue (which induced e.e. up to 24%).[12]

## 3. Conclusions

A series of amino-phosphite and phosphite-phosphoroamidite ligands **1**–**6**, derived from inexpensive and readily available D-(+)-xylose, were screened in the highly active Cu-catalyzed asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone (TOF >1200 $h^{-1}$ and e.e. of up to 63%). The advantage of these ligands is that their modular nature allows facile systematic variation in the configuration of the C(3) stereocentre, at the ligand bridge and in the amino and biphenyl substituents, so their effects on the stereoselectivity can be studied. The results showed that the configuration of the stereogenic carbon atom C(3) in the ligand backbone and the different substituents at the amino group had very marked effects on the activity and enantioselectivity. The enantioselectivity was best with ligand **4**, which has (*R*)-configuration at C(3) and a phenyl substituent on the amino group. Also, the presence of methoxy groups in the *para* positions of the biphenyl moiety had a negative effect on both the activity and enantioselectivity of the ligand. Exploiting the fact that these sugar ligands can be easily modified, further research is now in progress.

## 4. Experimental

### 4.1. General comments

All syntheses were performed using standard Schlenk techniques under an argon atmosphere. Solvents were purified by standard procedures. 1,2-*O*-Isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-xylofuranose **7**[7] and 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-ribofuranose **8**[8] were prepared by tosylation of the corresponding diols using standards procedures. Compounds **6**,[11] **9**,[13] **10**[13] and phosphorochloridites[9] were prepared by previously described methods. All other reagents were used as commercially available. Elemental analyses were performed on a Carlo Erba EA-1108 instrument. $^{1}H$, $^{13}C\{^{1}H\}$ and $^{31}P\{^{1}H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ ($^{1}H$ and $^{13}C$) as internal standard or $H_3PO_4$ ($^{31}P$) as external standard. All assignments in NMR spectra were determined by COSY and HETCOR spectra. Gas chromatographic analyses were run on a Hewlett–Packard HP 5890A instrument equipped with a Hewlett–Packard HP 3396 series II integrator.

### 4.2. 5-Deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-ribofuranose 12

To a solution of 1,2-*O*-isopropylidene-5-*O*-*p*-tolylsulfonyl-α-D-ribofuranose **8** (689 mg, 2 mmol) in propan-2-ol (4 mL), aniline (0.27 mL, 3 mmol) was added. The mixture was stirred under reflux for 48 h. The solvent was then evaporated and the residue was treated with saturated aqueous $NaHCO_3$ and extracted with dichloromethane (3×20 mL). The organic layers were dried on $Na_2SO_4$ and evaporated. The mixture was purified by flash chromatography to yield as a pale-yellow oil (339 mg, 64%). Anal. calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.56; H, 7.34%. $^{1}H$ NMR, $\delta$: 1.38 (s, 3H, $CH_3$), 1.47 (s, 3H, $CH_3$), 2.21 (b, 1H, NH), 3.34 (dd, 1H, H-5, $^{2}J_{5\text{-}5'}=13.2$ Hz, $^{3}J_{5\text{-}4}=5.6$ Hz), 3.50 (dd, 1H, H-5′, $^{2}J_{5'\text{-}5}=13.2$ Hz, $^{3}J_{5'\text{-}4}=3.6$ Hz), 3.88 (dd, 1H, H-3, $^{3}J_{3\text{-}4}=8.6$ Hz, $^{3}J_{3\text{-}2}=4.8$ Hz), 3.97 (m, 1H, H-4), 4.57 (dd, 1H, H-2, $^{3}J_{2\text{-}1}=3.6$ Hz, $^{3}J_{2\text{-}3}=4.8$ Hz), 5.82 (d, 1H, H-1, $^{3}J_{1\text{-}2}=3.6$ Hz), 6.66 (d, 2H, CH=, $^{3}J_{\text{H-H}}=7.8$ Hz), 6.72 (t, 1H, CH=, $^{3}J_{\text{H-H}}=7.2$ Hz), 7.18 (t, 2H, CH=, $^{3}J_{\text{H-H}}=7.6$ Hz). $^{13}C$ NMR, $\delta$: 26.6 ($CH_3$), 26.8 ($CH_3$), 44.7 (C-5), 73.3 (C-3), 78.8 (C-2), 79.4 (C-4), 104.2 (C-1), 113.0 ($CMe_2$), 113.3 (CH=), 118.0 (CH=), 129.5 (CH=), 148.3 (C).

### 4.3. 5-Deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose 11

Treatment of tosylate **7** (689 mg, 2 mmol) and aniline (0.27 mL, 3 mmol) as described for compound **12** afforded amino alcohol **11**, which was purified by flash chromatography to produce a pale-yellow powder (323 mg, 61%). Anal. calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22. Found: C, 63.17; H, 6.99. $^{1}H$ NMR, $\delta$: 1.34 (s, 3H, $CH_3$), 1.51 (s, 3H, $CH_3$), 3.60 (d, 2H, H-5, H-5′, $^{3}J_{5\text{-}4}=4.2$ Hz), 4.09 (m, 1H, NH), 4.32 (d, 1H, H-3, $^{3}J_{3\text{-}4}=2.6$ Hz), 4.40 (dd, 1H, H-4, $^{3}J_{4\text{-}5}=4.2$ Hz, $^{3}J_{4\text{-}3}=2.6$ Hz), 4.55 (d, 1H, H-2, $^{3}J_{2\text{-}1}=3.6$ Hz), 6.02 (d, 1H, H-1, $^{3}J_{1\text{-}2}=3.6$ Hz), 6.76 (d, 2H, CH=, $^{3}J_{\text{H-H}}=7.8$ Hz), 6.85 (t, 1H, CH=, $^{3}J_{\text{H-H}}=7.2$ Hz), 7.18 (t, 2H, CH=, $^{3}J_{\text{H-H}}=7.6$ Hz). $^{13}C$ NMR, $\delta$: 26.4 ($CH_3$), 27.0 ($CH_3$), 43.9 (C-5), 77.4 (C-3), 77.6 (C-4), 85.8 (C-2), 105.2 (C-1), 111.9 ($CMe_2$), 115.4 (CH=), 120.1 (CH=), 129.5 (CH=), 147.3 (C).

### 4.4. 3-[(3,3′,5,5′-Tetra-*t*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-5-deoxy-5-*N*-*tert*-butylamino-1,2-*O*-isopropylidene-α-D-xylofuranose 1

In situ formed (3,3′,5,5′-tetra-*tert*-butyl-1,1′-biphenyl-2,2′-diyl)-phosphorochloridite (1.2 mmol) was dissolved in toluene (5 mL) to which pyridine (0.36 mL, 4.6 mmol) was added. 1,2-*O*-Isopropylidene-5-desoxy-5-*N*-*tert*-butylamino-α-D-xylofuranose **9** (245.3 mg, 1 mmol) was azeotropically dried with toluene (3×1 mL) and dissolved in toluene (10 mL) to which pyridine (0.18 mL, 2.3 mmol) was added. The diol solution was transferred slowly over 30 min to a solution of phosphorochloridite at room temperature. 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 over alumina (eluent: toluene/$NEt_3$ 100/1, $R_f$ 0.9) to produce a white powder (0.60 g, 88%). Anal. calcd for $C_{40}H_{62}NO_6P$: C, 70.25; H, 9.14. Found: C, 70.01; H, 9.02%. $^{31}P$ NMR, $\delta$: 144.3 (s, 1P). $^{1}H$

NMR, $\delta$: 0.94 (s, 9H, $CH_3$, *t*-Bu-N), 1.21 (s, 3H, $CH_3$), 1.33 (s, 9H, $CH_3$, *t*-Bu), 1.34 (s, 9H, $CH_3$ *t*-Bu), 1.43 (s, 3H, $CH_3$), 1.47 (s, 9H, $CH_3$ *t*-Bu), 1.48 (s, 9H, $CH_3$, *t*-Bu), 2.65 (dd, 1H, H-5, $^2J_{5\text{-}5'}=11.2$ Hz, $^3J_{5\text{-}4}=6.8$ Hz), 2.80 (dd, 1H, H-5′, $^2J_{5'\text{-}5}=11.2$ Hz, $^3J_{5'\text{-}4}=7.6$ Hz), 4.27 (m, 1H, H-4), 4.39 (m, 1H, H-2), 4.66 (dd, 1H, H-3, $^3J_{3\text{-}4}=2.8$ Hz, $J_{3\text{-P}}=9.2$ Hz), 5.75 (d, 1H, H-1, $^3J_{1\text{-}2}=3.2$ Hz), 7.14 (m, 1H, CH=), 7.17 (m, 2H, CH=), 7.43 (m, 1H, CH=). $^{13}$C NMR, $\delta$: 26.3 ($CH_3$), 26.7 ($CH_3$), 28.8 ($CH_3$, *t*-Bu-N), 31.2 ($CH_3$, *t*-Bu), 31.3 ($CH_3$, *t*-Bu), 31.5 ($CH_3$, *t*-Bu), 34.6 (C, *t*-Bu), 34.7 (C, *t*-Bu), 35.4 (C, *t*-Bu), 35.5 (C, *t*-Bu), 41.3 (C-5), 77.3 (m, C-3), 80.3 (d, C-4, $J_{\text{C-P}}=3.8$ Hz), 84.4 (d, C-2, $J_{\text{C-P}}=11.4$ Hz), 104.6 (C-1), 111.7 ($CMe_2$), 124.2 (CH=), 124.3 (CH=), 125.3 (CH=), 133.5 (C), 132.9 (C), 139.9 (C), 140.0 (C), 146.5 (C), 146.8 (C).

### 4.5. 3-[(3,3′-Bis-*tert*-butyl-5,5′-bis-methoxy-1,1′-biphenyl-2,2′-diyl)phosphite]-5-deoxy-5-*N*-*tert*-butylamino-1,2-*O*-isopropylidene-α-D-xylofuranose 2

Treatment of in situ formed (3,3′-bis-*tert*-butyl-5,5′-bis-methoxy - 1,1′ - biphenyl - 2,2′ - diyl)phosphorochloridite (1.2 mmol) and **9** (245.3 mg, 1 mmol) as described for compound **1** afforded amino-phosphite **2**, which was purified by flash chromatography over alumina (eluent: toluene/$NEt_3$ 100/1, $R_f$ 0.9) to produce a white powder (0.47 g, 75%). Anal. calcd for $C_{34}H_{50}NO_8P$: C, 64.64; H, 7.98. Found: C, 64.78; H, 7.92%. $^{31}$P NMR, $\delta$: 146.0 (s, 1P). $^1$H NMR, $\delta$: 0.96 (s, 9H, $CH_3$, *t*-Bu-N), 1.24 (s, 3H, $CH_3$), 1.46 (b, 21H, $CH_3$, $CH_3$ *t*-Bu), 2.65 (dd, 1H, H-5, $^2J_{5\text{-}5'}=11.6$ Hz, $^3J_{5\text{-}4}=5.6$ Hz), 2.77 (dd, 1H, H-5′, $^2J_{5'\text{-}5}=11.6$ Hz, $^3J_{5'\text{-}4}=7.6$ Hz), 3.80 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.28 (m, 1H, H-4), 4.38 (m, 1H, H-2), 4.67 (dd, 1H, H-3, $^3J_{3\text{-}4}=3.2$ Hz, $J_{3\text{-P}}=9.6$ Hz), 5.78 (d, 1H, H-1, $^3J_{1\text{-}2}=3.6$ Hz), 6.69 (d, 1H, CH=, $J_{\text{H-H}}=3.2$ Hz), 6.74 (d, 1H, CH=, $J_{\text{H-H}}=2.8$ Hz), 6.99 (m, 2H, CH=). $^{13}$C NMR, $\delta$: 26.3 ($CH_3$), 26.8 ($CH_3$), 29.0 ($CH_3$, *t*-Bu-N), 31.2 ($CH_3$, *t*-Bu), 31.3 ($CH_3$, *t*-Bu), 35.6 (C, *t*-Bu), 41.4 (C-5), 55.8 (OMe), 76.8 (d, C-3, $J_{\text{C-P}}=3.4$ Hz), 80.7 (d, C-4, $J_{\text{C-P}}=4.1$ Hz), 84.5 (d, C-2, $J_{\text{C-P}}=2.3$ Hz), 104.9 (C-1), 111.9 ($CMe_2$), 113.0 (CH=), 113.2 (CH=), 114.5 (CH=), 133.6 (C), 133.7 (C), 134.1 (C), 142.7 (C), 142.8 (C), 142.9 (C), 155.9 (C), 156.0 (C).

### 4.6. 3-[(3,3′,5,5′-Tetra-*t*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-5-deoxy-5-*N*-isopropylamino-1,2-*O*-isopropylidene-α-D-xylofuranose 3

Treatment of the corresponding in situ formed phosphorochloridite (1.2 mmol) and **10** (231.3 mg, 1 mmol) as described for compound **1** afforded amino-phosphite **3**, which was purified by flash chromatography over alumina (eluent: toluene/$NEt_3$ 100/1, $R_f$ 0.9) to produce of a white powder (0.53 g, 79%). Anal. calcd for $C_{39}H_{60}NO_6P$: C, 69.93; H, 9.03. Found: C, 69.86; H, 8.95%. $^{31}$P NMR, $\delta$: 145.2 (s, 1P). $^1$H NMR, $\delta$: 0.87 (d, 3H, $CH_3$ *i*-Pr, $^3J_{\text{H-H}}=5.6$ Hz), 0.95 (d, 3H, $CH_3$, *i*-Pr, $^3J_{\text{H-H}}=6.4$ Hz), 1.21 (s, 3H, $CH_3$), 1.33 (s, 9H, $CH_3$ *t*-Bu), 1.34 (s, 9H, $CH_3$ *t*-Bu), 1.42 (s, 3H, $CH_3$), 1.46 (s, 9H, $CH_3$ *t*-Bu), 1.47 (s, 9H, $CH_3$ *t*-Bu), 2.58 (m, 1H, H-5), 2.67 (m, 1H, H-5′), 2.75 (m 1H, CH *i*-Pr), 4.27 (m, 1H, H-4), 4.38 (m, 1H, H-2), 4.65 (dd, 1H, H-3, $^3J_{3\text{-}4}=2.8$ Hz, $J_{3\text{-P}}=10.0$ Hz), 5.75 (d, 1H, H-1, $^3J_{1\text{-}2}=3.6$ Hz), 7.1–7.4 (m, 4H, CH=). $^{13}$C NMR, $\delta$: 22.6 ($CH_3$ *i*-Pr), 22.8 ($CH_3$ *i*-Pr), 26.3 ($CH_3$), 26.6 ($CH_3$), 31.1 ($CH_3$, *t*-Bu), 31.2 ($CH_3$, *t*-Bu), 31.4 ($CH_3$, *t*-Bu), 31.5 ($CH_3$, *t*-Bu), 34.6 (C, *t*-Bu), 35.3 (C, *t*-Bu), 35.4 (C, *t*-Bu), 45.9 (CH, *i*-Pr), 48.8 (C-5), 76.9 (d, C-3, $J_{\text{C-P}}=2.0$ Hz), 84.3 (d, C-4, $J_{\text{C-P}}=3.8$ Hz), 84.3 (C-2), 104.6 (C-1), 111.7 ($CMe_2$), 124.1 (CH=), 124.3 (CH=), 125.3 (CH=), 132.4 (C), 132.8 (C), 139.8 (C), 140.0 (C), 146.5 (C), 146.9 (C).

### 4.7. 3-[(3,3′,5,5′-Tetra-*t*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-5-deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-xylofuranose 4

Treatment of the corresponding in situ formed phosphorochloridite (1.2 mmol) and **11** (265.3 mg, 1 mmol) as described for compound **1** afforded amino-phosphite **4**, which was purified by flash chromatography over alumina (eluent: toluene/$NEt_3$ 100/1, $R_f$ 0.9) to produce a white powder (0.57 g, 81%). Anal. calcd for $C_{42}H_{58}NO_6P$: C, 71.67; H, 8.31. Found: C, 71.43; H, 8.40%. $^{31}$P NMR, $\delta$: 145.6 (s, 1P). $^1$H NMR, $\delta$: 1.23 (s, 3H, $CH_3$), 1.31 (s, 9H, $CH_3$ *t*-Bu), 1.36 (s, 9H, $CH_3$ *t*-Bu), 1.42 (s, 3H, $CH_3$), 1.49 (s, 9H, $CH_3$ *t*-Bu), 1.51 (s, 9H, $CH_3$ *t*-Bu), 3.21 (m, 1H, H-5), 3.28 (m, 1H, H-5′), 3.83 (m, 1H, NH), 4.36 (m, 1H, H-4), 4.42 (m, 1H, H-2), 4.70 (dd, 1H, H-3, $^3J_{3\text{-}4}=2.8$ Hz, $J_{3\text{-P}}=9.6$ Hz), 5.79 (d, 1H, H-1, $^3J_{1\text{-}2}=3.6$ Hz), 6.50 (m, 2H, CH=), 6.66 (m, 1H, CH=), 7.2 (m, 4H, CH=), 7.45 (m, 2H, CH=). $^{13}$C NMR, $\delta$: 26.2 ($CH_3$), 26.7 ($CH_3$), 31.1 ($CH_3$, *t*-Bu), 31.2 ($CH_3$, *t*-Bu), 31.4 ($CH_3$, *t*-Bu), 31.5 ($CH_3$, *t*-Bu), 34.6 (C, *t*-Bu), 34.7 (C, *t*-Bu), 35.4 (C, *t*-Bu), 35.5 (C, *t*-Bu), 42.2 (C-5), 76.6 (d, C-3, $J_{\text{C-P}}=2.0$ Hz), 78.4 (d, C-4, $J_{\text{C-P}}=3.8$ Hz), 84.3 (d, C-2, $J_{\text{C-P}}=2.2$ Hz), 104.7 (C-1), 111.8 ($CMe_2$), 112.8 (CH=), 117.4 (CH=), 124.2 (CH=), 124.4 (CH=), 125.2 (CH=), 128.2 (CH=), 129.0 (CH=), 129.1 (CH=), 132.4 (C), 132.9 (C), 137.8 (C), 139.9 (C), 140.0 (C), 146.8 (C), 147.0 (C), 147.7 (C).

### 4.8. 3-[(3,3′,5,5′-Tetra-*t*-butyl-1,1′-biphenyl-2,2′-diyl)phosphite]-5-deoxy-5-*N*-phenylamino-1,2-*O*-isopropylidene-α-D-ribofuranose 5

Treatment of the corresponding in situ formed phosphorochloridite (1.2 mmol) and **12** (265.3 mg, 1 mmol) as described for compound **1** afforded amino-phosphite **5**, which was purified by flash chromatography over alumina (eluent: ethyl acetate, $R_f$ 0.9) to produce a white powder (0.59 g, 84%). Anal. calcd for $C_{42}H_{58}NO_6P$: C, 71.67; H, 8.31. Found: C, 71.52; H, 8.54%. $^{31}$P NMR, $\delta$: 142.3 (s, 1P). $^1$H NMR, $\delta$: 1.31 (s, 3H, $CH_3$), 1.35 (s, 9H, $CH_3$ *t*-Bu), 1.36 (s, 9H, $CH_3$ *t*-Bu), 1.47 (s, 9H, $CH_3$ *t*-Bu), 1.49 (s, 9H, $CH_3$ *t*-Bu), 1.56 (s, 3H, $CH_3$), 3.05 (m, 1H, H-5), 3.42 (dd, 1H, H-5′, $J_{\text{H-P}}=2.8$, $^3J_{5'\text{-}4}=6.0$ Hz, $^2J_{5'\text{-}5}=15.2$ Hz), 3.83 (m, 1H, NH), 4.18 (m, 1H, H-2), 4.28 (m, 2H, H-3, H-4), 5.58 (d, 1H, H-1, $^3J_{1\text{-}2}=3.6$ Hz), 6.54 (d, 2H, CH=, $J_{\text{H-H}}=8.0$ Hz), 6.89 (t, 1H, CH=, $J_{\text{H-H}}=7.2$ Hz), 7.13 (t, 2H, CH=, $J_{\text{H-H}}=7.6$ Hz), 7.16 (d, 1H, $J_{\text{H-H}}=2.4$ Hz), 7.20 (d, 1H, $J_{\text{H-H}}=2.4$ Hz), 7.43 (d, 1H, $J_{\text{H-H}}=2.4$ Hz),

7.45 (d, 1H, $J_{H\text{-}H}=2.4$ Hz). $^{13}C$ NMR, $\delta$: 26.7 ($CH_3$), 26.9 ($CH_3$), 31.3 ($CH_3$, *t*-Bu), 31.4 ($CH_3$, *t*-Bu), 31.5 ($CH_3$, *t*-Bu), 31.7 ($CH_3$, *t*-Bu), 34.9 (C, *t*-Bu), 35.6 (C, *t*-Bu), 44.8 (C-5), 74.8 (C-3), 77.6 (d, C-4, $J_{C\text{-}P}=3.9$ Hz), 78.7 (d, C-2, $J_{C\text{-}P}=2.2$ Hz), 103.8 (C-1), 113.4 ($CMe_2$), 113.5 (CH=), 117.9 (CH=), 124.3 (CH=), 124.5 (CH=), 126.7 (CH=), 127.0 (CH=), 129.3 (CH=), 132.8 (C), 133.0 (C), 140.5 (C), 140.6 (C), 147.0 (C), 148.2 (C).

### 4.9. General procedure for the catalytic conjugate addition of diethylzinc to 2-cyclohexenone

In a typical experiment a solution of $Cu(OTf)_2$ (9 mg, 0.025 mmol) and diphosphite ligand (0.025 mmol) in dichloromethane (3 mL) was stirred for 30 min at room temperature. After cooling to 0°C, diethylzinc (1 M sol. in hexanes, 3.5 mL, 3.5 mmol) was added. A solution of 2-cyclohexenone (0.24 mL, 2.5 mmol) and undecane as GC internal standard (0.25 mL) in dichloromethane (3 mL) was then added. The reaction was monitored by GC. The reaction was quenched with HCl (2 M) and filtered twice through silica flash. The conversion and enantiomeric excesses were obtained by GC using a Lipodex-A column.[14]

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