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Chiral diphosphites derived from D-glucose in the copper-catalyzed conjugate addition of diethylzinc to cyclohexenone

Montserrat Diéguez,* Aurora Ruiz and Carmen Claver

Departament de Química Física i Inorgànica, Universitat Rovira i Virgili, Pl. Imperial Tàrraco 1, 43005 Tarragona, Spain

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Abstract—A series of diphosphite ligands **1**–**3** derived from readily available D-(+)-glucose and bisphenol or binaphthol derivatives have been applied as ligands in the Cu-catalyzed 1,4-addition of diethylzinc to cyclohexenone. Excellent reaction rates (TOF>1200 h^{-1}) and good enantioselectivities (e.e. of up to 84%) were achieved. The modular nature of these ligands allows easy systematic variation in the configuration of the stereocenters (C(3), C(5)) at the ligand backbone and in the biaryl substituents, so the optimum configuration for maximum enantioselectivity in the asymmetric 1,4-addition can be determined. The results obtained show that the enantioselectivity induced by the ligand depends strongly on the absolute configuration of the C(3) stereogenic centre, while the sense of the enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups of the phosphite moieties. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The enantioselective conjugate addition of organometallic reagents to α,β-unsaturated substrates is still of considerable synthetic interest.[1] In particular, adding organocuprates to enones is an attractive way of forming a C–C bond and simultaneously introducing a new stereogenic center.[2] Diastereoselective additions to chiral Michael acceptors and the use of stoichiometric chiral organometallic reagents are firmly established, but few highly enantioselective catalytic systems have been reported. Excellent enantioselectivities have been obtained in the copper-catalyzed Michael addition of Grignard and diorganozinc reagents to enones and other α,β-unsaturated carbonyl compounds using phosphoroamidites,[3] amido–phosphine,[4] phosphite–oxazolines,[5] diphosphite[6] and Schiff-based[7] ligands. However, further investigations are required in order to understand how to obtain efficient enantiocontrol in this reaction. In this context, the rational design of new readily available ligands continues to be an active field of research.

Carbohydrates are particularly advantageous for this purpose, as they are readily available, highly functionalized compounds with several stereogenic centers. This allows a systematic regio- and stereoselective introduction of different functionalities in the synthesis of a series of chiral ligands that can be screened for high activities and enantioselectivities. At the same time, they can provide useful information about the origin of the stereoselectivity of the reaction.[8] Moreover, carbohydrate-based ligands have demonstrated their potential utility in other types of catalytic reactions.[6d,8,9] Herein, we report the use of a series of 1,2-protected furanoside diphosphite ligands **1**–**3** (Fig. 1), derived from inexpensive D-(+)-glucose, in the enantioselective copper-catalyzed 1,4-addition of diethylzinc to 2-cyclohexenone. The advantage of these types of ligands is that many structural variations can be made, so the optimum configuration for maximum stereoselectivity can be determined. Thus, these ligands allow the systematic variation of the configurations at the C(3) and C(5) stereogenic centers of the ligand backbone and in the biaryl substituents in order to fully study their influence on activity and stereoselectivity.

2. Results and discussion

2.1. Ligand design

Ligands **1**–**3** (Fig. 1) consist of a chiral 1,2-*O*-protected furanoside backbone, which determines their underly-

* Corresponding author. Fax: +34-977559563; e-mail: dieguez@quimica.urv.es

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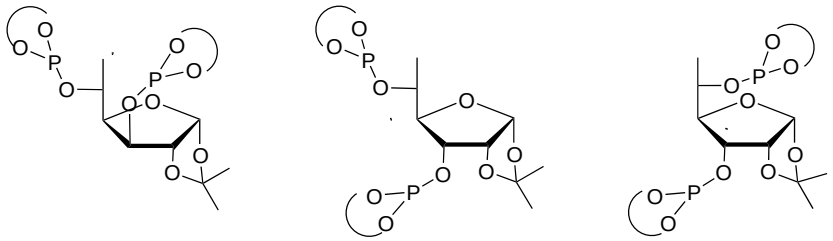
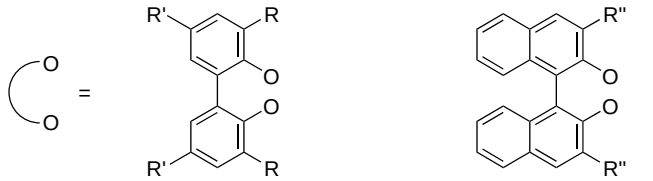


(1*R*,2*R*,3*S*,4*R*,5*R*)-**1** (1*R*,2*R*,3*R*,4*R*,5*R*)-**2** (1*R*,2*R*,3*R*,4*R*,5*S*)-**3**



a R = R' = H
b R = R' = *t*-Bu
c R = *tert*-Bu, R' = OMe
d R = $SiMe_3$, R' = H

e (S^{ax}) R'' = H
f (R^{ax}) R'' = H
g (S^{ax}) R'' = $SiMe_3$
h (R^{ax}) R'' = $SiMe_3$

Figure 1.

ing structure, and two hydroxyl groups at positions C(3) and C(5). To this basic framework several phosphoric acid biaryl esters are attached. The influence of the different groups attached to the *ortho*- and *para*-positions of the bisphenol moieties on the enantioselectivity was investigated using ligands **1a**–**d**, which have the same configurations on the carbon atoms C(3) and C(5). The influence of the configuration of the binaphthol moiety on the enantioselectivity was studied using ligands **1e**–**h**.

We studied the effects of the C(3) stereogenic centre by comparing ligands **2a**–**f** with diastereomeric ligands **1a**–**f**, which have the same substituents in the biphenyl moieties but have opposite configuration at C(3).

The influence of the configuration of the C(5) stereogenic center was studied using ligands **3b**–**c**, whose configuration at C(5) is opposite to that of ligands **2**.

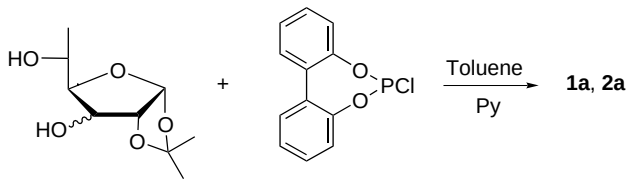
2.2. Ligand synthesis

The new ligands **1a** and **2a** were easily synthesized in one step from the corresponding diols, which are easily prepared on a large scale from D-(+)-glucose using a standard procedure (Scheme 1).[8] The reaction of the corresponding diol with 2 equiv. of the desired in situ formed phosphorochloridite in the presence of base afforded diphosphite ligands **1a** and **2a** in good overall yield. The ^{1}H, ^{13}C and ^{31}P NMR spectra agree with those expected for these C_1 ligands (see Section 4). Rapid ring inversions (atropisomerization) of the seven-membered dioxaphosphepine rings occurred on the NMR timescale, since diastereoisomers were not detected by low temperature ^{31}P NMR.[10]

2.3. Conjugate addition of 2-cyclohexenone

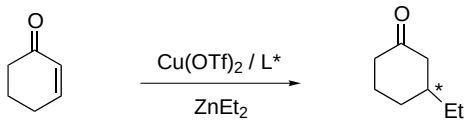
Ligands **1**–**3** were tested in the copper-catalyzed conjugate addition of diethylzinc to 2-cyclohexenone **4**. The catalytic system was generated in situ by adding 1 equiv. of the ligand to a solution of $Cu(OTf)_2$ followed by addition of diethylzinc. In general, good to excellent reaction rates were observed. Moreover, no 1,2-addition product was observed.

The effects of different reaction parameters were investigated for the catalytic precursors containing ligands **1a**. The results are summarized in Table 1.



Scheme 1. Synthesis of diphosphite ligands **1a** and **2a**.

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



4 (*R*)-**5**/(*S*)-**5**

Entry	Ligand	Solvent	*T* (°C)	TOF[b]	Conv.[c] (%)	**5**[d] (%)	*e.e.*[e] (%)
1	**1a**	Toluene	0	876	73	71	58 (*R*)
2	**1a**	CH_2Cl_2	0	900	75	75	60 (*R*)
3	**1a**	THF	0	816	68	65	55 (*R*)
4	**1a**	CH_2Cl_2	25	>1200	100	100	52 (*R*)
5	**1a**	CH_2Cl_2	−20	648	54	54	56 (*R*)
6	**1a**	CH_2Cl_2	−40	456	28	27	43 (*R*)
7[f]	**1a**	CH_2Cl_2	0	888	74	74	60 (*R*)

[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] Determined by GC using undecane as internal standard.
[e] Enantiomeric excess measured by GC using Lipodex A column.
[f] 0.05 mmol of ligand used.

The results showed that the efficiency of the process depended on the nature of the solvent (entries 1–3). Thus, the catalyst performance (activity and selectivity) was best when dichloromethane was used (entry 2).

The effect of the reaction temperature on activity and selectivity was also studied. As expected, conversions were better at high temperature but the best enantioselectivity was found at 0°C. The enantiomeric excess dropped when the temperature was either raised or lowered (entries 2, 4–6). These temperature-dependent results are in line with those reported for other Cu-diphosphite systems.[6d,11]

Varying the ligand-to-copper ratio showed that excess ligand did not affect the product outcome **5** (entries 2 and 7).

For comparative purposes, the rest of the ligands were tested under the conditions that gave the optimum compromise between enantioselectivities and reaction rates i.e. a ligand-to-copper ratio of 1, a temperature of 0°C and dichloromethane as solvent. The results are shown in Table 2.

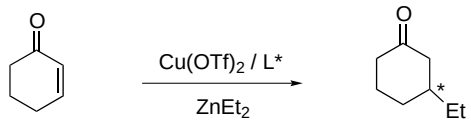
Ligands **1b** and **1d,** which have sterically demanding groups at the *ortho* positions of the biphenyl moieties (*tert*-butyl and trimethylsilyl groups, respectively) resulted in higher reaction rates (entries 2 and 4), but lower enantioselectivities than the less sterically encumbered unsubstituted ligand **1a** (entries 2 and 4 versus 1). The presence of methoxy groups instead of *tert*-butyl groups in the *para* positions of the biphenyl moieties (ligand **1c**) had a negative effect on the activity (entry 3 versus 2).

The results with ligands **1e** and **1f**, which contain stereogenic binaphthyl moieties, show that the different configuration in the binaphthyl moieties has a strong effect on both activity and enantioselectivity (entries 5 and 6). Ligand **1e**, which has an (*S*)-binaphthyl moiety gave (*S*)-**5** with 65% conversion and 35% e.e. after 5 min, whereas diastereomer **1f**, which has an (*R*)-binaphthyl moiety, gave (*R*)-**5** with 99% conversion and 55% e.e. Ligand **1g**, which contains bulky trimethylsilyl groups at the *ortho* positions of the (*S*)-binaphthyl moieties, resulted in a higher reaction rate and a higher enantioselectivity (84% e.e., entry 7) than ligand **1e**. Surprisingly, ligand **1h**, with bulky trimethylsilyl substituents at the *ortho* position of the (*R*)-binaphthyl moieites, showed lower asymmetric induction than the less hindered ligand **1f** (entry 8 versus 6). This unexpectedly low enantioselectivity can be explained by taking into account that the bulky-ligand probably reduces its steric congestion in the species responsible for the catalytic activity by adopting an unfavorable conformation that induces lower enantioselectivities.

Ligands **2a**–**f**, whose configuration at the C(3) stereocenter is opposite to those of ligands **1** (Fig. 1), produced lower enantioselectivities and slightly lower activities (entries 9–14). Ligands **3**, which resulted from changing the configuration of carbon C(5) from (*R*) to (*S*), led to slightly higher activities but similar enantioselectivities compared to the catalytic systems Cu/ligands **2** (entries 10 and 11 versus 15 and 16).

Comparison of entries 2, 10 and 15 clearly shows that the enantiomeric excesses depends strongly on the absolute configuration of C(3) at the ligand backbone.

Table 2. Asymmetric 1,4-addition of diethylzinc to 2-cyclohexenone **4** using diphosphite ligands **1**–**3**[a]



4 (*R*)-**5***I*(*S*)-**5**

Entry	Ligand	TOF[b]	Conv.[c] (%)	**5**[d] (%)	*e.e.*[e] (%)
1	**1a**	900	75	75	60 (*R*)
2	**1b**	>1200	100	99	25 (*R*)
3	**1c**	900	75	75	26 (*R*)
4	**1d**	1080	90	90	20 (*R*)
5	**1e**	780	65	64	35 (*S*)
6	**1f**	1188	99	99	55 (*R*)
7	**1g**	1176	98	98	84 (*S*)
8	**1h**	1044	87	87	8 (*R*)
9	**2a**	720	60	60	3 (*R*)
10	**2b**	816	68	68	3 (*R*)
11	**2c**	480	40	39	4 (*R*)
12	**2d**	>1200	100	99	8 (*R*)
13	**2e**	780	65	64	10 (*S*)
14	**2f**	864	72	70	4 (*R*)
15	**3b**	852	71	71	5 (*S*)
16	**3c**	660	55	54	5 (*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), $T=0$°C.
[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] Determined by GC using undecane as internal standard.
[e] Enantiomeric excess measured by GC using Lipodex A column.

3. Conclusions

A series of diphosphite ligands **1**–**3**, derived from inexpensive D-(+)-glucose, 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 84%). The modular nature of these ligands allow a facile systematic variation in the configuration of the C(3) and C(5) stereogenic centers at the ligand bridge and in the biaryl substituents, so their influence on activity and stereoselectivity can be determined. Systematic variation of the stereocenters at C(3) and C(5) in the ligand backbone revealed that the enantioselectivity depends strongly on the absolute configuration at C(3). The best enantioselectivities were therefore achieved with ligands **1** with (*S*)-configuration at C(3) and (*R*)-configuration at C(5).

Variation in chirality at the axial chiral binaphthyl substituents in ligands **1** indicates that the sense of the enantiodiscrimination is predominantly controlled by the configuration of the biaryl groups at the phosphite moieties. The presence of bulky substituents on the *ortho* positions of the biphenyl moieties has a negative effect on the enantioselectivity, but a positive effect on activity. However, enantioselectivity is strongly dependent on the configuration of the binaphthyl moieties when bulky trimethylsilyl groups are introduced at the *ortho* positions. Thus, the highest enantiomeric excess was found for ligand **1g**, which has *ortho* trimethylsilyl substituents on the (*S*)-binaphthyl moieties. Further research into the application of these ligands in other reactions is therefore underway.

4. Experimental

4.1. General comments

All syntheses were performed using standard Schlenk techniques under argon atmosphere. Solvents were purified by standard procedures. Diphosphites **1b**–**h**, **2b**–**f** and **3b**–**c** were prepared by previously described methods.[8,12] 6-Desoxy-1,2-*O*-isopropylidene-α-D-allofuranose and 6-desoxy-1,2-*O*-isopropylidene-α-D-glucofuranose were synthesized as described in the literature.[8] (1,1′-biphenyl-2,2′-diyl)phosphorochloridite was prepared in analogy with literature procedure.[13] All other reagents were used as commercially available. Elemental analyses were performed on a Carlo Erba EA-1108 instrument. ^1H, $^{13}C\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Varian Gemini 400 MHz spectrometer. Chemical shifts are relative to $SiMe_4$ (^1H 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.

4.1.1. 3,5-Bis[(1,1′-biphenyl-2,2′-diyl)phosphite]-6-deoxy-1,2-*O*-isopropylidene-α-D-glucofuranose 1a. In situ formed phosphorochloridite (2.2 mmol) was dissolved in toluene (5 mL) to which pyridine (0.36 mL, 4.6 mmol) was added. 6-Desoxy-1,2-*O*-isopropylidene-α-D-glucofuranose (0.21 g, 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 the solution of phosphorochloridite at room temperature. The reaction mixture was stirred overnight under reflux and the pyridine salts were removed by filtration. Evaporation of the solvent gave a white foam which was purified by flash chromatography (eluent: toluene) to produce a white powder (0.46 g, 74%). Anal. calcd for $C_{33}H_{30}O_9P_2$: C, 62.66; H, 4.78. Found: C, 62.74; H, 4.82%. ^{31}P NMR: δ 146.8 (d, 1P, $^6J_{P\text{-}P}=16.7$ Hz), 151.8 (d, 1P, $^6J_{P\text{-}P}=16.7$ Hz). ^{1}H NMR: δ 1.28 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 1.55 (d, 3H, H-6, $^3J_{6\text{-}5}=6.4$ Hz), 4.12 (dd, 1H, H-4, $^3J_{4\text{-}5}=8.8$ Hz, $^3J_{4\text{-}3}=2.4$ Hz), 4.63 (d, 1H, H-2, $^3J_{2\text{-}1}=3.6$ Hz), 4.77 (m, 1H, H-5), 4.94 (dd, 1H, H-3, $^3J_{3\text{-}4}=2.4$ Hz, $J_{3\text{-}P}=8.8$ Hz), 5.87 (d, 1H, H-1, $^3J_{1\text{-}2}=3.6$ Hz), 7.0–7.6 (m, 16H, CH=). ^{13}C NMR: δ 21.2 (d, C-6, $J_{C\text{-}P}=2.3$ Hz), 26.5 (CH_3), 26.9 (CH_3), 68.9 (d, C-5, $J_{C\text{-}P}=19.7$ Hz), 76.7 (d, C-3, $J_{C\text{-}P}=12.9$ Hz), 83.0 (t, C-4, $J_{C\text{-}P}=6.8$ Hz), 84.5 (d, C-2, $J_{C\text{-}P}=2.3$ Hz), 105.2 (C-1), 112.4 (CMe_2), 122.2 (CH=), 122.3 (CH=), 122.4 (CH=), 125.3 (CH=), 125.4 (CH=), 125.5 (CH=), 128.4 (CH=), 129.3 (CH=), 129.4 (CH=), 129.5 (CH=), 130.0 (CH=), 130.2 (CH=), 130.3 (CH=), 131.0 (C), 131.1 (C), 131.2 (C), 131.3 (C), 149.3 (C), 149.4 (C), 149.5 (C).

4.1.2. 3,5-Bis[(1,1′-biphenyl-2,2′-diyl)phosphite]-6-deoxy-1,2-*O*-isopropylidene-α-D-allofuranose 2a. Treatment of in situ formed phosphorochloridite (2.2 mmol) and 6-desoxy-1,2-*O*-isopropylidene-α-D-allofuranose (0.21 g, 1 mmol) as described for compound **1a** afforded diphosphite **2a**, which was purified by flash chromatography (eluent: toluene) to produce a white powder (0.41 g, 65%). Anal. calcd for $C_{33}H_{30}O_9P_2$: C, 62.66; H, 4.78. Found: C, 62.85; H, 4.89%. ^{31}P NMR: δ 137.8 (s, 1P), 147.9 (s, 1P). ^{1}H NMR: δ 1.35 (d, 3H, H-6, $^3J_{6\text{-}5}=7.2$ Hz), 1.38 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 4.20 (m, 1H, H-4), 4.44 (dd, 1H, H-2, $^3J_{2\text{-}1}=3.2$ Hz, $^3J_{2\text{-}3}=4.0$ Hz), 4.63 (m, 1H, H-3), 4.78 (m, 1H, H-5), 5.73 (d, 1H, H-1, $^3J_{1\text{-}2}=3.2$ Hz), 7.0–7.5 (m, 16H, CH=). ^{13}C NMR: δ 17.8 (d, C-6, $J_{C\text{-}P}=3.2$ Hz), 26.7 (CH_3), 27.0 (CH_3), 70.5 (d, C-5, $J_{C\text{-}P}=13.6$ Hz), 71.9 (C-3), 79.4 (C-2), 81.2 (t, C-4, $J_{C\text{-}P}=3.0$ Hz), 103.7 (C-1), 113.4 (CMe_2), 122.1 (CH=), 122.2 (CH=), 122.3 (CH=), 124.9 (CH=), 125.0 (CH=), 125.1 (CH=), 125.3 (CH=), 125.4 (CH=), 129.0 (CH=), 129.1 (CH=), 129.2 (CH=), 129.3 (CH=), 129.8 (CH=), 129.9 (CH=), 130.9 (C), 131.0 (C), 131.1 (C), 149.8 (C), 149.9 (C), 150.0 (C), 151.1 (C).

4.2. 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]

Acknowledgements

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